The National Institute on Aging (NIA), part of the National Institutes of Health at the U.S. Department of Health and Human Services, was established to help improve the health and well-being of older people through research. NIA conducts and supports research on the medical, social, and behavioral aspects of aging. This mission is carried out through NIA’s Intramural Research Program composed of staff scientists in Baltimore and Bethesda, Maryland, and through its Extramural Research Program, which funds researchers at major institutions across the United States and internationally. *Biology of Aging: Research Today for a Healthier Tomorrow* describes some of NIA’s exciting findings about the basic biology of aging and points to directions for future investigation.
We marvel at the 90-year-old who still gets up every day and goes to work. And, it is a genuine thrill to celebrate a relative’s 100th birthday. Yet our feelings about aging are complex.

We may want to live forever, but who looks forward to getting old? We hope we’re vigorous right up until the very end. Still, day-to-day, many of us make unhealthy choices that could put our future at risk.

From the beginning of time, people have tried to understand aging. Almost every culture has a mythology to explain it. As we grow up, tales of eternal youth pique our curiosity. And, it is these musings that may provide just the spark needed to ignite a budding scientist. There’s the little girl, excited to visit her grandmother, who asks her parents how someone so spunky and fun could be so old. Or, the 3rd grader who, after watching in awe as a caterpillar spins a cocoon and then days later emerges as a butterfly, peppers the teacher with questions about this magical transformation. These are the types of questions and kinds of experiences that could stimulate a lifelong quest to explore what happens as we age.

Since the National Institute on Aging (NIA) was established at the National Institutes of Health (NIH) in 1974, scientists asking just such questions have learned a great deal about the processes associated with the biology of aging. For scientists who study aging—called gerontologists—this is an exciting time. Technology today supports research that years ago would have seemed possible only in a science fiction novel. And, a scientific community that values active collaboration as well as individual scientific achievement has helped to move research forward faster than ever before.
Over centuries, theories about aging have emerged and faded, but the true nature of the aging process is still uncertain. The fact is—aging is a part of everyone’s life. But the facts of aging—what is happening on a biochemical, genetic, and physiological level—remain rich for exploration.

This booklet introduces some key areas of research into the biology of aging. Each area is a part of a larger field of scientific inquiry. You can look at each topic individually, or you can step back to see how they fit together in a lattice-work, interwoven to help us better understand aging processes. Research on aging is dynamic, constantly evolving based on new discoveries, and so this booklet also keeps an open eye on the future, as today’s research provides the strongest hints of things to come.

What is aging?

In the broadest sense, aging reflects all the changes that occur over the course of life. You grow. You develop. You reach maturity. To the young, aging is exciting—it leads to later bedtimes and curfews, and more independence. By middle age, another candle seems to fill up the top of the birthday cake. It’s hard not to notice some harmless cosmetic changes like gray hair and wrinkles. Middle age also is the time when people begin to notice a fair amount of physical decline. Even the most athletically fit cannot escape these changes. Take marathon runners, for example. An NIA-funded study found that their record times increased with age—aging literally slowed down the runners. Although some physical decline may be a normal result of aging, the reasons for these changes are of particular interest to gerontologists.

Gerontologists look for what distinguishes normal aging from disease, as well as explore why older adults are increasingly vulnerable to disease and disability. They also try to understand why these health threats take a higher toll on older bodies. Since 1958, NIA’s Baltimore Longitudinal Study of Aging (BLSA) has been observing and reporting on these kinds of questions. As with any longitudinal study, the BLSA repeatedly evaluates people over time rather than comparing a group of young people to a group of old people, as in a cross-sectional study. Using this approach, BLSA scientists have observed, for example, that people who have no evidence of ear problems or noise-induced hearing loss still lose some of their hearing with age—that’s normal. Using brain scans to learn if cognitive changes can be related to structural changes in the brain, BLSA scientists discovered that even people who remain healthy and maintain good brain function late in life lose a significant amount of brain volume during normal aging.

However, some changes that we have long thought of as normal aging can be, in fact, the signs of a potential disease. Take, for example, sudden changes in personality. A common belief is that people become cranky, depressed, and withdrawn as they get older. But an analysis of long-term data from the BLSA showed that an adult’s personality...
To answer questions about why and how we age, some scientists look for mechanisms or pathways in the body that lead to aging. Our cells constantly receive cues from both inside and outside the body, prompted by such things as injury, infection, stress, or even food. To react and adjust to these cues, cells send and receive signals through biological pathways. Some of the most common are involved in metabolism, the regulation of genes, and the transmission of signals. These pathways may also be important to aging.
generally does not change much after age 30. People who are cheerful and assertive when they are younger will likely be the same when they are age 80. The BLSA finding suggests that significant changes in personality are not due to normal aging, but instead may be early signs of disease or dementia.

The rate and progression of cellular aging can vary greatly from person to person. But generally, over time, aging affects the cells of every major organ of the body. Changes can start early. Some impact our health and function more seriously than others. For instance, around the age of 20, lung tissue starts to lose elasticity, and the muscles of the rib cage slowly begin to shrink. As a result, the maximum amount of air you can inhale decreases. In the gut, production of digestive enzymes diminishes, affecting your ability to absorb foods properly and maintain a nutritional balance. Blood vessels in your heart accumulate fatty deposits and lose flexibility to varying degrees, resulting in what used to be called “hardening of the arteries” or atherosclerosis. Over time, women's vaginal fluid production decreases, and sexual tissues atrophy. In men, aging decreases sperm production, and the prostate can become enlarged.

Scientists are increasingly successful at detailing these age-related differences because of studies like the BLSA. Yet studies that observe aging do not identify the reasons for age-related changes, and, therefore, can only go so far toward explaining aging. Questions remain at the most basic level about what triggers aging in our tissues and cells, why it occurs, and what are the biological processes underlying these changes. Scientists look deep into our cells and the cells of laboratory animals to find answers. What they learn today about aging at the cellular and molecular levels may, ultimately, lead to new and better ways to live a longer, healthier life.

Living long and well: Can we do both? Are they the same?

You can hardly turn on your computer these days without being bombarded with advertisements that pop up trying to convince you of the power of a pill that will make you live longer or a cream that will help to revive your youthful vigor and appearance. The search for
ways to stop or reverse the aging process is a near-obsession in popular culture. The likelihood of discovering a scientifically proven “anti-aging” elixir is slim, but researchers believe their work will reveal ways to improve a person’s ability to live a longer, healthier life. They express these goals in terms of “lifespan” and “health span,” respectively.

Lifespan is the length of life for an organism. For instance, if you live to age 99, that would be your lifespan. Maximal lifespan is the maximum number of years of life observed in a specific population. It differs from species to species. The maximum recorded lifespan for humans, reported in 2010, was 122.5 years for females and 116 years for males.

Lifespan is a common measurement in aging research. That’s because it is clear-cut and easy to measure—an organism is either alive or dead. Scientists look for factors such as genes, environment, and behavioral traits (including diet) that may contribute to an organism’s lifespan. Altering a factor to see if it changes lifespan can provide evidence about whether or not that specific factor is important for aging. For instance, when researchers suspect that a specific gene has an effect on lifespan, they may test their hypothesis by modifying the activity of that gene (perhaps lower its activity by deleting the gene or increase its activity by adding an extra copy of it). If the life of the animal with the modified gene activity is longer or shorter, then the gene probably does play a role in lifespan.

Researchers are finding that lifespan may be influenced by external factors, as well. This has been demonstrated in animal studies. NIA’s Interventions Testing Program (ITP) examines a variety of compounds for their effects on the lifespan of mice. Compounds studied include dietary supplements, hormones, and anti-inflammatory drugs. In one ITP study, male mice treated with aspirin, an anti-inflammatory drug, displayed a moderately increased lifespan. In another ITP study, masoprocol, an anti-inflammatory drug that has antioxidant properties, was found to increase longevity of male, but not female, mice. These and other findings may help scientists identify compounds to test in...
humans for their effects on aging. While some of the compounds tested in the ITP already have a clinical use for humans, scientists are clear: These compounds should be used only as prescribed and not for lifespan extension at this time.

The ability to withstand disease could also be central to lifespan. Studies of exceptionally long-lived people are helping to establish patterns of health decline and increased disease (called morbidity) with old age. For example, do health problems start around the same age in all people and expand over extra years of life for the long-lived, or are the problems delayed, occurring closer to the end of life among exceptional agers? Evidence from a Danish longitudinal study of 92- to 100-year-olds found that health problems seem to be delayed, appearing closer to the end of life. This is not a certain outcome, but in many studies, the average centenarian seems to be in better health than the average 80-year-old. However, living to 100 does not mean never having any health issues. In the New England Centenarian Study, researchers have developed three categories for their long-lived participants. They are characterized as “survivors,” “delayers,” or “escapers,” depending on whether they have survived a life-threatening disease, delayed a serious health problem until much later in life, and/or escaped any serious health events.

Scientists used to think that long life was a good indicator of health span, or years of good health and function. However, some experiments, particularly in mice, demonstrate significant improvements in health, without actually increasing lifespan. For example, NIA scientists and grantees (that is, scientists at a university or other institution whose research is funded by NIA) examining the effects of the wine-derived compound resveratrol in mice on a normal diet found the
A compound positively influenced the health of the mice—resveratrol-treated mice had better bone health, heart function, strength, vision, coordination, and cholesterol than the control group. But, resveratrol did not increase lifespan. (Lifespan was increased, however, in mice on a high-fat diet supplemented with resveratrol.)

Understanding how to extend health span—apart from its impact on longevity—is a growing focus of many studies, and for good reason. Imagine a society where a majority of people live to be 100, but along with the added years comes considerably more physical decline. While there is still a place for lifespan research, health span research holds promise for revealing ways to delay or prevent disease and disability so that we can live healthier longer.

**Is what’s good for mice good for men?**

A lot of research findings seem to tell us what is good—or bad—for yeast, mice, roundworms (*C. elegans*), or fruit flies (*Drosophila melanogaster*). Does that mean it will work for you? Animal models are essential to research in the biology of aging. Fruit flies and roundworms, along with more complex organisms like mice, rats, and nonhuman primates, have many biological mechanisms and genes that are similar to humans. They also experience many of the same physiological changes (changes in the body) with aging. Therefore, these animals can be used as models of human aging and human physiology, despite the obvious differences in appearance. Scientists can use some exploratory approaches (like modifying a gene to measure its effects on health or longevity) in animal models such as worms, flies, and mice that would not be possible in humans. They also can better isolate the variable...
they want to investigate because animal studies are conducted in tightly controlled environments. The animals typically have a very structured daily regimen with limited exposure to pollutants, stressors, or other elements that could otherwise affect lifespan and health span.

Different types of studies use different animal models. Animal models with a short lifespan take less time and fewer resources to study from birth to death and to test interventions that might affect the aging process. Scientists might favor a fruit fly when studying a possible genetic target for an intervention to increase longevity, for example, because their average lifespan is only 30 days. This allows researchers to measure the effects in about a month. The roundworm’s 2- to 3-week lifespan makes it another ideal model for identifying and studying genes that might affect longevity. In a landmark study, NIA-funded researchers found that reducing the activity of a set of genes, called *daf*, increased roundworm lifespan by three- or even fourfold. *Daf* genes are involved in the roundworm’s ability to enter a type of hibernation stage, called diapause, to survive periods of food scarcity. This research would not have been as feasible if conducted using an animal model with an average lifespan of 10 or 20 years.

After scientists establish a possible intervention in one animal model, they then apply the intervention to increasingly complex organisms. They might work their way up from worms or flies to mice and then to larger mammals, such as nonhuman primates. At each step, researchers carefully study if the intervention has the same effect on the comparable biological pathway. Sometimes it does not. Part of the reason might be that while mice, for example, have only a slightly larger number of genes than worms, and the genes in mice and worms serve similar functions, the activity of mouse genes is different and somewhat more complex than that of worms. As a result, a genetic intervention that increases a worm’s lifespan by fourfold might have a significantly less impressive effect on a mouse’s lifespan. For similar reasons, an intervention might be promising in mice, but that does not mean it will work the same way or at all in humans.

Studies in animal models closer to humans, such as monkeys or other nonhuman primates, can be key to understanding how basic discoveries might apply to humans. They are essential for pre-clinical studies, an intermediary step between research in animal models like mice and clinical studies in humans. Studies in nonhuman primates, for example, have demonstrated to NIA researchers how normal age-related changes in the heart influence risk of heart disease. They have also been important for testing interventions to lower risks of heart disease, such as drugs to decrease blood vessel stiffness.

So, if something works to slow aging in mice, worms, fruit flies, or monkeys, does that mean it will definitely work for you? The answer is no. Certainly, data from animal studies provide critical insights to the aging process and can form the basis for testing potential interventions. But direct testing in humans is essential before an intervention can be considered safe and effective.
One approach to aging biology research is called “comparative biology.” It involves comparing two or more similar species that have very different lifespans—one lives much longer than the other—to understand how the longer-lived species has, as one NIA-funded researcher puts it, “exceptional resistance to basic aging processes.” Comparative biology studies generally focus on species that live at least twice as long as their close relatives.

A few possible theories explain what may be taking place among these longer-lived animals:

- They experience a slower rate of age-related decline.
- They can survive even when their organs and/or systems break down and have minimal function.
- They are better able to tolerate cellular damage or diseases.

The naked mole rat, a mouse-size rodent that lives underground, has been widely used in comparative research. It lives approximately 17 years in the wild and more than 28 years in captivity. Its relative, the mouse, lives a maximum of 4 years. What accounts for this startling difference? Naked mole rats have lower metabolic rates and body temperature, meaning that they require less energy to survive. They have low concentrations of blood glucose (blood sugar), insulin, and thyroid hormone, so they are less susceptible to certain diseases. Naked mole rats are better able to withstand some types of biological stress and, at this point, there has never been a case of cancer reported in these animals. All these factors and likely others yet to be determined contribute to their healthier and longer life.
Is aging in our genes?

You may get your hair color from your father’s side of the family and your great math skills from your mother. These traits are “in the genes,” so to speak. Likewise, longevity tends to “run in families”—your genetic make-up plays an important role in how you age. You can see evidence of this genetic connection in families with siblings who live into their 90s or families that have generation after generation of centenarians. These long-lived families are the basis for many genetic studies.

Identifying the genes associated with any trait is difficult. First, just locating the gene requires a detailed understanding of the trait, including knowledge of most, if not all, of the contributing factors and pathways related to that trait. Second, scientists must have clear ways of determining whether the gene suspected to have a relationship with the trait has a direct, indirect, or even no effect on that trait.
Identifying longevity genes is even more complex than determining genes for height or hair color, for example. Scientists do not know all the factors and pathways that contribute to longevity, and measuring a gene’s effect on long-lived animals, including humans, would literally take a lifetime! Instead, scientists have identified hundreds of genes that affect longevity in short-lived animal models, like worms and flies. Not all of these genes promote long life. Sometimes mutating or eliminating a gene increases lifespan, suggesting that the normal function of the gene limits longevity. Findings in animal models point to places for scientists to look for the genes that may influence longevity in humans.

How can we find aging genes in humans?

The human genetic blueprint, or genome, consists of approximately 25,000 genes made up of approximately 3 billion letters (base pairs) of DNA. Small deviations in the base pairs naturally occur about once in every 1,000 letters of DNA code, generating small genetic variants. Scientists are finding that some of these variants (polymorphisms) are actually associated with particular traits or chance of developing a specific disease. People with a certain trait, for example, those living past age 100, may be more likely to have one variant of a gene, while people without the same trait may be more likely to have another variant. While it is very difficult to prove that a gene influences aging in humans, a relationship, or “association,” may be inferred based upon whether a genetic variant is found more frequently among successful agers, such as centenarians, compared with groups of people who have an average or short lifespan and health span.

Several approaches are used to identify possible genes associated with longevity in humans. In the candidate gene approach, scientists look for genes in humans that serve similar functions in the body as genes already associated with aging in animal models, so-called “homologs” or “orthologs” to animal genes. For instance, after finding longevity genes involved in the insulin/IGF-1 pathway of animal models, researchers look for the comparable genes in the insulin/IGF-1 pathway of humans. Scientists then determine whether the genes are linked to longevity in humans by looking to see if a variant of the genes is prevalent among people who live healthy, long lives but not for people who have an average health span and lifespan.

In one NIA-funded project, researchers studied 30 genes associated with the insulin/IGF-1 pathway in humans to see if any variants of those genes were more common in women over 92 years old compared to women who were less than 80 years old. Variants of certain genes—like the FOXO3a gene—predominated among long-lived individuals, suggesting a possible role with longer lifespan. This finding provides evidence that, like in animal models, the insulin/IGF-1 pathway has
The human genetic blueprint, or genome, consists of approximately 25,000 genes made up of approximately 3 billion letters (base pairs) of DNA. Base pair sequences: guanine (G) pairs with cytosine (C); adenine (A) pairs with thymine (T).
Most longevity genes identified thus far influence one of three pathways in a cell: insulin/IGF-1, sirtuins, or mTOR.

In the 1980s, scientists discovered the first gene shown to limit lifespan in roundworms, which they named age-1. Further investigation revealed that the effects of age-1 are involved with the insulin/IGF-1 pathway. When scientists “silenced” the age-1 gene’s activity, the insulin/IGF-1 pathway’s activity also decreased and the worms lived longer. Since then, many other genes associated with the insulin/IGF-1 pathway have been found to affect the lifespan of fruit flies and mice, strengthening the hypothesis that the insulin/IGF-1 pathway plays an important role in the aging process. More research is needed to determine if inhibiting this pathway could increase longevity in humans or create insulin–related health problems like diabetes. A recent report suggests that people with a mutation related to the insulin/IGF-1 pathway may have less risk of developing diabetes and cancer.

There is also a great deal of interest in the sirtuin pathway. Sirtuin genes are present in all species and regulate metabolism in the cell. They are crucial for cell activity and cell life. In the 1990s, scientists at the Massachusetts Institute of Technology found that inserting an extra copy of a sirtuin equivalent, called Sir2, increased the lifespan of yeast. Extension of lifespan has been replicated in other organisms, including flies and worms. However, studies in mice have yielded conflicting results.

The mTOR pathway—an abbreviation of “mammalian target of rapamycin”—plays a role in aging of yeast, worms, flies, and mice. This pathway controls the cell’s rate of protein synthesis, which is important for proper cell function. Researchers have found that inhibiting the pathway in mice genetically or pharmacologically (using rapamycin) leads to increased longevity and improved health span.

Another approach, the genome-wide association study, or GWAS, is particularly productive in finding genes involved in diseases and conditions associated with aging. In this approach, scientists scan the entire genome looking for variants that occur more often among a group with a particular health issue or trait. In one GWAS study, NIH-funded researchers identified genes possibly associated with high and low blood fat levels, cholesterol, and, therefore, risk for coronary artery disease. The data analyzed were collected from Sardinians, a small genetically alike population living off the coast of Italy in the Mediterranean, and from two other international studies. The findings revealed more than 25 genetic variants in 18 genes connected to cholesterol and lipid levels. Seven of the genes were not previously connected to cholesterol/lipid levels, suggesting that there are possibly other pathways associated with risk for coronary artery disease. Heart disease is a major health issue facing older people. Finding a way to eliminate or lower risk for heart disease could have important ramifications for reducing disability and death from this particular age-related condition.

Scientists are also currently using GWAS to find genes directly associated with aging and longevity. Because the
At the center of this research is the epigenome—chemical modifications, or marks, on our DNA, or in proteins that interact with DNA, that tell it what to do, where to do it, and when to do it. The marks that make up the epigenome are affected by your lifestyle and environment and may change, for example, based on what you eat and drink, if you smoke, what medicines you take, and what pollutants you encounter. Changes in the epigenome can cause changes in gene activity. Most epigenetic changes are likely harmless, but some could trigger or exacerbate a disease or condition, such as your risk for age-related diseases. In some cases, scientists find that these epigenetic changes driven by the environment can be inherited by the offspring.

Identical, maternal twins are ideal for epigenetic research. At birth, twins have nearly the same genetic blueprint; however, over time, they may have fewer identical traits. Careful study of these changes may help scientists better understand environmental and lifestyle’s influence on genes.

Epigenetics might also explain variations in lifespan among laboratory mice that are genetically identical and seemingly raised in the exact same environment. Scientists theorize that the difference in their lifespans may result from a disparity in the amount of nurturing they received when very young. The mice with the shorter lifespan might have been less adept at feeding and, therefore, got less of their mother’s milk, or their mother may have licked them less, or they may have slept farther away from the center of the litter. Receiving less nurturing may have influenced their epigenetics, marking the genes that control aging.

As epigenetic research moves forward, scientists hope to answer three key questions:

• How do changes in the epigenome translate into long-term differences in health and aging?
• Do single events influence the epigenome?
• If single events can change the epigenome, does the organism’s age (or stage of development) at the time of the change matter?
GWAS approach does not require previous knowledge of the function of the gene or its potential relationship with longevity, it could possibly uncover genes involved in cellular processes and pathways that were not previously thought to play roles in aging. Since no single approach can precisely identify each and every gene involved in aging, scientists will use multiple methods, including a combination of the GWAS and candidate gene approaches to identify genes involved in aging.

As scientists continue to explore the genetics of aging, its complexity becomes increasingly evident. Further studies could illustrate the varying ways genes influence longevity. For example, some people who live to a very old age may have genes that better equip them to survive a disease; others may have genes that help them resist getting a disease in the first place. Some genes may accelerate the rate of aging, others may slow it down. Scientists investigating the genetics of aging do not foresee a “Eureka!” moment when one gene is discovered as the principal factor affecting health and lifespan. It is more likely that we will identify several combinations of many genes that affect aging, each to a small degree.

What happens when DNA becomes damaged?

The impact of age, of course, is not limited to organisms. You drive a brand new car off the lot, and ideally it’s in perfect working condition. But by the time it reaches the 100,000 mile mark, the car doesn’t run quite like it used to. Or, that lovely walking path you discovered when you first moved into your home has now become weathered, the weeds are overgrown, and some of the asphalt has buckled.

Like the car and the walking path, over time your DNA accumulates damage. That’s normal. Our DNA suffers millions of damaging events each day. Fortunately, our cells have powerful mechanisms to repair damage and, by and large, these mechanisms remain active and functional through old age. However, over time, some damage will fail to be repaired and will stay in our DNA. Scientists think this damage—and a decrease in the body’s ability to fix itself—may be an important component of aging. Most DNA damage is harmless—for example, small errors in DNA code, called mutations, are harmless. Other types of DNA damage, for example, when a DNA strand breaks, can have more serious ramifications. Fixing a break in a DNA strand is a complex operation and it is more likely the body will make mistakes when attempting this repair—mistakes that could shorten lifespan.

Another kind of DNA damage build-up occurs when a cell divides and passes its genetic information on to its two daughter cells. During cell division, the telomere, a stretch of DNA at each end of a chromosome that doesn't encode any proteins but instead protects the protein-encoding part of the DNA, becomes shorter. When the telomere
becomes too short, it can no longer protect the cell’s DNA, leaving the cell at risk for serious damage. In most cells, telomere length cannot be restored. Extreme telomere shortening triggers an SOS response, and the cell will do one of three things: stop replicating by turning itself off, becoming what is known as senescent; stop replicating by dying, called apoptosis; or continue to divide, becoming abnormal and potentially dangerous (for example, leading to cancer).

Scientists are interested in senescent cells because, although they are turned off, they still work on many levels. For instance, they continue to interact with other cells by both sending and receiving signals. However, senescent cells are different from their earlier selves. They cannot die, and they release molecules that lead to an increased risk for diseases, particularly cancer.

The relationship among cell senescence, cancer, and aging is an area of ongoing investigation. When we are young, cell senescence may be critical in helping to suppress cancer. Senescence makes the cell stop replicating when its telomeres become too short, or when the cell cannot repair other damage to its DNA. Thus, senescence prevents severely damaged cells from producing abnormal and perhaps cancerous daughter cells. However, later in life, cell senescence may actually raise the risk of cancer by releasing certain molecules that make the cells more vulnerable to abnormal function.

Consider fibroblasts, cells that divide about 60 times before turning off. Normally, fibroblasts hold skin and other tissues together via an underlying structure, a scaffold outside the cell, called the extracellular matrix. The extracellular matrix also helps to control the growth of other cells. When fibroblasts turn off, they
emit molecules that can change the extracellular matrix and cause inflammation. This disturbs the tissue’s function and contributes to aging. At the same time, the breakdown of the extracellular matrix may contribute to increased risk of cancer with age.

Learning why—on a biological level—cell senescence goes from being beneficial early in life to having detrimental effects later in life may reveal some important clues about aging.

TELOMERE LENGTH: HEALTH SPAN VS. LIFESPAN?

Aging biologists are investigating whether humans’ telomere length is associated with lifespan, health span, or both. In one study of people age 85 years and older, researchers found telomere length was not associated with longevity, at least not in the oldest-old. In another study, researchers analyzing DNA samples from centenarians found that telomeres of healthy centenarians were significantly longer than those of unhealthy centenarians, suggesting that telomere length may be associated with health span.
Stem cells can come from a variety of sources. Adult stem cells are candidates for regenerative medicine approaches for several reasons—doctors can use the patient’s own stem cells; stem cells can develop into nearly any type of cell based on where they are inserted and other factors; and stem cells continue to function normally during an almost infinite number of cell divisions, making them essentially immortal. Therefore, in theory, if stem cells were inserted in a damaged part of the body, they could develop into area-specific cells that could potentially restore function. But does that work? That’s what researchers are trying to find out.

Findings from early research on regenerative medicine, primarily in animal models, show potential for stem cell treatment. For example, inserting mouse ovarian cells created from a female donor’s stem cells into infertile mice restored the mice’s ability to reproduce. Another study in mice found that function could be restored to injured muscle tissue by reactivating existing stem cells rather than transplanting new ones. The ability to reactivate dormant adult stem cells continues to be investigated. In a 2010 Italian study with human participants, researchers restored vision to some people with severe burns on the outmost layer of their eyes (the cornea) by using stem cells grown in the laboratory.

Researchers are also looking for alternatives to stem cells that have similar healing abilities and can be used in regenerative medicine. It appears that certain cells, like skin cells, can be reprogrammed to act as artificial stem cells, called induced pluripotent cells.

Many questions about stem cell (and induced pluripotent cell) therapy need to be answered: Do older adults have enough stem cells for this type of therapy or do they need to be donated from someone else? Would creating stem cells from an older person’s skin cells work? Would stem cell therapy restore health and vigor to an older person or only work in a younger person? How would stem cell therapy work on the cellular level—would stem cells replace the non-functioning cells or would they reactivate and repair the damaged cells? Would stem cell therapy work in all areas of the body, or only in some areas?

While many questions remain, the prospect of regenerative medicine could have important implications for the treatment of many degenerative diseases.
Does stress really shorten your life?

Have you ever looked at side-by-side photos of a person before and after a particularly trying time in his or her life, for instance, before and a few years after starting a highly demanding job? The person likely appears much older in the later photo. The stress of the job is thought to contribute to the prematurely aged appearance. You might feel stress from work or other aspects of your daily life, too. Stress is everywhere. Even when you feel relaxed, your body is still experiencing considerable stress—biological stress. And, it is this type of stress that is widely studied by gerontologists for its effects on aging and longevity.

Biological stress begins with the very basic processes in the body that produce and use energy. We eat foods and we breathe, and our body uses those two vital elements (glucose from food and oxygen from the air) to produce energy, in a process known as metabolism. You may already think of metabolism as it pertains to eating—“My metabolism is fast, so I can eat dessert,” or “My metabolism has slowed down over the years, so I’m gaining weight.” Since metabolism is all about energy, it also encompasses breathing, circulating blood, eliminating waste, controlling body temperature, contracting muscles, operating the brain and nerves, and just about every other activity associated with living.
These everyday metabolic activities that sustain life also create “metabolic stress,” which, over time, results in damage to our bodies. Take breathing—obviously, we could not survive without oxygen, but oxygen is a catalyst for much of the damage associated with aging because of the way it is metabolized inside our cells. Tiny parts of the cell, called mitochondria, use oxygen to convert food into energy. While mitochondria are extremely efficient in doing this, they produce potentially harmful by-products called oxygen free radicals. A variety of environmental factors, including tobacco smoke and sun exposure, can produce them, too. The oxygen free radicals react with and create instability in surrounding molecules. This process, called oxidation, occurs as a chain reaction: the oxygen free radical reacts with molecule “A” causing molecule “A” to become unstable; molecule “A” attempts to stabilize itself by reacting with neighboring molecule “B”; then molecule “B” is unstable and attempts to become stable by reacting with neighboring molecule “C”; and so on. This process repeats itself until one of the molecules becomes stable by breaking or rearranging itself, instead of passing the instability on to another molecule.

Some free radicals are beneficial. The immune system, for instance, uses oxygen free radicals to destroy bacteria and other harmful organisms. Oxidation and its by-products also help nerve cells in the brain communicate. But, in general, the outcome of free radicals is damage (breaks or rearrangements) to other molecules, including proteins and DNA. Because mitochondria metabolize oxygen,
they are particularly prone to free radical damage. As damage mounts, mitochondria may become less efficient, progressively generating less energy and more free radicals.

Scientists study whether the accumulation of oxidative (free radical) damage in our cells and tissues over time might be responsible for many of the changes we associate with aging. Free radicals are already implicated in many disorders linked with advancing age, including cancer, atherosclerosis, cataracts, and neurodegeneration.

Fortunately, free radicals in the body do not go unchecked. Cells use substances called antioxidants to counteract them. Antioxidants include nutrients, such as vitamins C and E, as well as enzyme proteins produced naturally in the cell, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase.

Many scientists are taking the idea that antioxidants counter the negative effects of oxygen free radicals a step further. Studies have tested whether altering the antioxidant defenses of the cell can affect the lifespan of animal models. These experiments have had conflicting results. NIA-supported researchers found that inserting extra copies of the SOD gene into fruit flies extended the fruit flies’ average lifespan by as much as 30 percent. Other researchers found that immersing roundworms in a synthetic form of SOD and catalase extended their lifespan by 44 percent. However, in a comprehensive set of experiments, increasing or decreasing antioxidant enzymes in laboratory mice had no effect on lifespan. Results from a

HEAT SHOCK PROTEINS

In the early 1960s, scientists discovered that fruit flies exposed to a burst of heat produced proteins that helped their cells survive the temperature change. Over the years, scientists have found these “heat shock proteins” in virtually every living organism, including plants, bacteria, worms, mice, and even humans. Scientists have learned that, despite their name, heat shock proteins are produced when cells are exposed to a variety of stresses, not just heat. The proteins can be triggered by oxidative stress and by exposure to toxic substances (for example, some chemicals). When heat shock proteins are produced, they help cells dismantle and dispose of damaged proteins and help other proteins keep their structure and not become unraveled by stress. They also facilitate making and transporting new proteins in the body.

Heat shock response to stress changes with age. Older animals have a higher everyday level of heat shock proteins, indicating that their bodies are under more biological stress than younger animals. On the other hand, older animals are unable to produce an adequate amount of heat shock proteins to cope with fleeting bouts of stress from the environment.

Heat shock proteins are being considered as a possible aging biomarker—something that could predict lifespan or development of age-related problems—in animal models like worms and fruit flies. However, the exact role heat shock proteins play in the human aging process is not yet clear.
Scientists also found that age-related damage to DNA and proteins is often reversible and does not cause problems until the damage evokes a stress response. This suggests that the stress response, rather than the damage itself, is partially responsible for age-related deterioration.

Some biologists have started looking at stress resistance when choosing animal models to study as examples of successful aging. Researchers can test stress resistance in young animals and then continue studying only those animals demonstrating high resistance. Ongoing studies will determine if there is a direct cause-effect relationship between stress resistance and longevity, and if these longer-lived animals are resistant to all or only certain sources of stress.

In addition, researchers are studying the relationship between psychological stress and aging. In one study, mothers of severely and chronically sick children had shorter telomeres, relative to other women. In other research, caregivers of people with Alzheimer’s disease were found to have shortened telomeres. These findings could suggest that emotional or psychological stress might affect the aging process. More research on the mechanisms involved is needed before scientists can make any conclusions about clinical implications.

THE FUTURE OF AGING RESEARCH

STRESS

The first C. elegans worm genetically manipulated to have a longer lifespan was resistant to stress caused by heat. Subsequently, researchers learned that a common thread among all long-lived animals is that their cells (and in some cases the animals as a whole) are more resistant to a variety of stresses, compared to animals with an average or shorter lifespan.

limited number of human clinical trials involving antioxidants generally have not supported the premise that adding antioxidants to the diet will support longer life. Antioxidant supplementation remains a topic of continuing investigation.
Does how much you eat affect how long you live?

Your body needs food to survive. However, the very process of extracting energy from food—metabolizing food—creates stress on your body. Overeating creates even more stress on the body. That’s part of the reason why it can lead to a shorter lifespan and serious health problems common among older people, including cardiovascular disease and type 2 diabetes.

Calorie restriction, an approach primarily (but not exclusively) used in a research setting, is more tightly controlled than normal healthy eating or dieting. It is commonly defined by at least a 30 percent decrease in calorie consumption from the normal diet with a balanced amount of protein, fat, vitamins, and minerals. In the 1930s, investigators found that laboratory rats and mice lived up to 40 percent longer when fed a calorie-restricted diet, compared to mice fed a normal diet. Since that time, scientists observed that calorie restriction increased the lifespan of many other animal models, including yeast, worms, flies, some (but not all) strains of mice, and maybe even nonhuman primates. In addition, when started at an early age or as a young adult, calorie restriction was found to increase the health span of many animal models by delaying onset of age-related disease and delaying normal age-related decline.

Two studies of calorie restriction in nonhuman primates (the animals most closely related to humans) have had intriguing results. In a study conducted at NIA, monkeys fed a calorie-restricted diet had a notably decreased and/or delayed onset of age-related diseases, compared to the control group of “normal” eaters. In a University of Wisconsin study supported by NIA, calorie-restricted rhesus monkeys had three times fewer age-related diseases compared to the control group. The Wisconsin study also found that rhesus monkeys on a restricted diet had fewer age-related deaths compared to their normal fed controls. In 2007, when the findings from the study conducted at NIA were published, it was too early to determine whether calorie restriction had any effects on lifespan. Research in primates continues.
Despite its apparent widespread acceptance, calorie restriction does not increase lifespan in all animals. In studies of non-laboratory (wild) mice, researchers found that on average, calorie restriction did not have any effect on lifespan. Some of the calorie-restricted mice actually lived shorter than average lives. This may be due to differences in the genetics of the wild mice. A 2010 NIA-funded study provides further evidence that genetics may play a role in whether or not calorie restriction will have a positive effect on longevity. Looking at 42 closely related strains of laboratory mice, researchers found that only about a third of the strains on a calorie-restricted diet had an increase in longevity. One-third of the strains of mice on a calorie-restricted diet had a shortened lifespan, and the other third had no significant difference in lifespan compared to mice on a normal diet.

While animal studies are ongoing, researchers are also exploring calorie restriction in humans to test its safety and practicality, as well as to see if it will have positive effects on health. Participants in a 2002 pilot of the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) study had, after 1 year, lowered their fasting glucose, total cholesterol, core body temperature, body weight, and fat. At the cellular level, they had better functioning mitochondria and reduced DNA damage. However, in terms of practicality, scientists observed that adapting and adhering to the regimen could be difficult. A longer-term trial is underway.

Given that ample studies have demonstrated mostly positive effects of calorie restriction in many organisms, today’s scientific studies focus on finding the mechanisms and pathways by which calorie restriction works. Researchers are also studying compounds that might act the same way in the body, mimicking the benefits of calorie restriction.

A wide range of possible mechanisms for calorie restriction are being investigated. Some scientists are exploring the possibility that metabolizing fewer calories results in less oxidative damage to the cells. Other scientists are looking at how the relative scarcity of nutrients caused by calorie restriction might induce heat shock proteins and other defense mechanisms that allow the body to better withstand other stresses and health problems. Some researchers wonder if the effects of calorie restriction are controlled by the brain and nervous system. In one NIA-conducted study, calorie restriction increased the production of brain-derived neurotrophic factor, or BDNF, a protein that protects the brain from dysfunction and degeneration, and supports increased regulation of blood sugar and heart function in animal models. Still other studies indicate calorie restriction may influence hormonal balance, cell senescence, or gene expression. It is likely that calorie restriction works through a combination of these mechanisms, and others yet to be identified.

There is an intriguing overlap between the pathways that control normal aging and
those that scientists think may be pertinent to calorie restriction. The most relevant are the sirtuins and mTOR (mammalian target of rapamycin) pathways as discussed on page 16. In several, but not all cases, disrupting these pathways means the organism no longer responds positively to calorie restriction. These two pathways have been important for identifying at least two compounds that may mimic the effects of calorie restriction: resveratrol and rapamycin.

Resveratrol, found naturally in grapes, wine, and nuts, activates the sirtuin pathway. It has been shown to increase the lifespan of yeast, flies, worms, and fish. In 2006, NIA researchers, in collaboration with university scientists funded by NIA, reported on a study comparing mice fed a standard diet, a high fat-and-calorie diet, or a high fat-and-calorie diet supplemented with resveratrol beginning at middle age. Resveratrol appeared to lessen the negative effects of the high fat-and-calorie diet, both in terms of lifespan and disease. In a 2008 follow-up study, investigators found that resveratrol improved the health of aging mice fed a standard diet. It prevented age- and obesity-related decline in heart function. Mice on resveratrol had better bone health, reduced cataract formation, and enhanced balance and motor coordination compared to non-treated mice. In addition, resveratrol was found to partially mimic the effects of calorie restriction on gene expression profiles of liver, skeletal muscle, and adipose (fatty) tissue in the mice. However, the compound did not have an impact on the mice’s overall survival or maximum lifespan. These findings suggest that resveratrol does not affect all aspects of the basic aging process and that there may be different mechanisms for health versus lifespan. Research on resveratrol continues in mice, along with studies in nonhuman primates and people.

Rapamycin, another possible calorie restriction mimetic, acts on the mTOR pathway. This compound’s main clinical use is to help suppress the immune system of people who have had an organ transplant so that the transplant can succeed. A study by NIA’s Interventions Testing Program, as discussed on page 7, reported in 2009 that rapamycin extended the median and maximum lifespan of mice, likely by inhibiting the mTOR pathway. Rapamycin had these positive effects even when fed to the mice beginning at early-old age (20 months), suggesting that an intervention started later in life may still be able to increase longevity. Researchers are now looking at rapamycin’s effects on health span and if there are other compounds that may have similar effects as rapamycin on the mTOR pathway.

Scientists do not yet know how resveratrol, rapamycin, and other compounds that demonstrate effects similar to calorie restriction will influence human aging. Learning more about these calorie restriction mimetics, and the mechanisms and pathways underlying calorie restriction, may point the way to future healthy aging therapies.
Can your immune system still defend you as you age?

Elementary schools are breeding grounds for the common cold. Kids pass their germs around as often as they share their lunch. For children, catching a cold may not be a big deal. They might take it easy for a few days while their immune system kicks into action and fights off infection. But for their older teachers and grandparents, each cold can be more of a challenge. It may take a week or longer to get back to feeling 100 percent. Does that mean that the immune system gets weaker as we age? That’s what gerontologists are trying to figure out.

Our immune system is a complicated network of cells, tissues, and organs to keep us healthy and fight off disease and infection. The immune system is composed of two major parts: the innate immune system and the adaptive immune system. Both change as people get older. Studies to better understand these changes may lead to ways of supporting the aging immune system.
Innate immunity is our first line of defense. It is made up of barriers and certain cells that keep harmful germs from entering the body. These include our skin, the cough reflex, mucous membranes, and stomach acid. If germs are able to pass these physical barriers, they encounter a second line of innate defense, composed of specialized cells that alert the body of the impending danger. Research has shown that, with age, innate immune cells lose some of their ability to communicate with each other. This makes it difficult for the cells to react adequately to potentially harmful germs called pathogens, including viruses and bacteria.

Inflammation is an important part of our innate immune system. In a young person, bouts of inflammation are vital for fighting off disease. But as people age, they tend to have mild, chronic inflammation, which is associated with an increased risk for heart disease, arthritis, frailty, type 2 diabetes, physical disability, and dementia, among other problems. Researchers have yet to determine whether inflammation leads to disease, disease leads to inflammation, or if both scenarios are true. Interestingly, centenarians and other people who have grown old in relatively good health generally have less inflammation and a more efficient recovery from infection and inflammation when compared to people who are unhealthy or have average health. Understanding the underlying causes of chronic inflammation in older individuals—and why some older people do not have this problem—may help gerontologists find ways to temper its associated diseases.

The adaptive immune system is more complex than the innate immune system and includes the thymus, spleen, tonsils, bone marrow, circulatory system, and lymphatic system. These different parts of the body work together to produce, store, and transport specific types of cells and substances to combat health threats. T cells, a type of white blood cell (called lymphocytes) that fights invading bacteria, viruses, and other foreign cells, are of particular interest to gerontologists.

T cells attack infected or damaged cells directly or produce powerful chemicals that mobilize an army of other immune system substances and cells. Before a T cell gets programmed to recognize a specific harmful germ, it is in a “naïve” state. After a T cell is assigned to fight off a particular infection, it becomes a “memory” cell. Because these cells remember how to resist a specific germ, they help you fight a second round of infection faster and more effectively. Memory T cells remain in your system for many decades.

A healthy young person’s body is like a T cell producing engine, able to fight off infections and building a lifetime storehouse of memory T cells. With age, however, people produce fewer naïve T cells, which makes them less able to combat new health threats. This also makes older people less responsive to vaccines, because vaccines generally require naïve T cells to produce a protective immune response. One exception is the shingles vaccine. Since shingles is the reactivation
ORGANS OF THE IMMUNE SYSTEM

- Barriers — Nose, Mucous
- Thymus
- Bone Marrow
- Tonsils
- Lymph Nodes
- Lymphatic Vessels
- Spleen
of the chickenpox virus, this particular vaccine relies on existing memory T cells and has been particularly effective in older people. Researchers are investigating ways to develop other vaccines that are adjusted for the changes that happen in an older person’s immune system.

Negative, age-related changes in our innate and adaptive immune systems are known collectively as immunosenescence. A lifetime of stress on our bodies is thought to contribute to immunosenescence. Radiation, chemical exposure, and exposure to certain diseases can also speed up the deterioration of the immune system. Studying the intricacies of the immune system helps researchers better understand immunosenescence and determine which areas of the immune system are most vulnerable to aging. Ongoing research may shed light on whether or not there is any way to reverse the decline and boost immune protection in older individuals.


do not hallucinate.

THE FUTURE OF AGING RESEARCH
ALTERING OLDER ADULTS' IMMUNITY

Our ability to survive the germs around us is based on a tightly controlled immune system. Too little of an immune response makes us susceptible to infection, including life-threatening pneumonia. Conversely, an overactive immune response is at the root of autoimmune diseases common among older people and may contribute to age-related chronic diseases like Alzheimer’s disease, osteoarthritis, diabetes, and heart disease. So, should scientists try to change the immune response in older people, or is immunosenescence somehow beneficial within the context of the aging body?

Given the delicate balance of the immune system, gerontologists suspect that, along with its more obvious negative consequences, immunosenescence might have a protective role in seniors. More research is needed before scientists fully understand the aging immune system and determine whether changing an immune response would lead to an increase or a decrease in health span and lifespan in humans.
So, in the end, what causes aging? Clearly this question has fascinated medical researchers, philosophers, anthropologists, and the general public for centuries. This booklet offers you just a glimpse of the journey to understand the science of aging.

In a sense, we are all aging experts—every day we get older. It’s true that most of us cannot explain what’s happening under the microscope, but the little girl can still be curious about her vivacious grandmother without knowing that the grandmother’s good health may be a sign of what to expect during her own golden years. And, the man in middle age can know that he looks and feels better when making healthy food choices and staying physically active without understanding the intricacies of metabolism and biological stress. Aging is part of us, it’s part of life.

As the field of gerontology matures, scientists will continue to learn about what happens deep inside our bodies during our passage from child to older adult. Experiments involving animal models that on the surface seem so different from us—yeast, fruit flies, worms, and mice—will yield insights into aspects of aging that could one day lead to important clinical, pharmacological, or behavioral interventions for humans.

What is the future of biology of aging research? It is not likely that we will see a modern-day fountain of youth, that mythical elixir promised to restore people to their younger selves. But research may very well offer us the means to a healthier, longer life. And, with that, we may have the opportunity to spend more time with our loved ones, the opportunity to meet our great-great-grandchildren, and the opportunity to enjoy more life experiences.
Antioxidants – Compounds that may protect cells from oxygen free radicals by preventing or slowing the process of oxidation. Some antioxidants are enzyme proteins like superoxide dismutase (SOD) and catalase, while others are nutrients, such as vitamin C.

Calorie restriction – A diet that is lower by a specific percent of calories than the normal diet, but includes all essential nutrients. At this time calorie restriction is an experimental intervention being studied to determine its impact on health and longevity.

Cell senescence – A process in which a cell turns off its capacity to produce new cells, stops dividing, and has limited function. Cell senescence may contribute to aging, but it may also be a protective mechanism against cancer (a disease state in which cells continue to divide without control).

Centenarian – A person who has lived at least 100 years.

Chromosome – A structure inside cells containing DNA, which carries our genetic information and is responsible for heritable traits.

DNA – Abbreviation for deoxyribonucleic acid; DNA contains the genetic code for all animals and plants, from single-cell organisms to humans.

Enzyme – A protein that increases the rate of a specific chemical reaction.

Fibroblast – One of the major cell types found in skin and other tissues. Fibroblasts secrete molecules that have important structural properties for tissues and organs, and they change with age.

Free radicals – Unstable molecules that react readily with other molecules to try to become stable. Oxygen free radicals are produced normally when food is metabolized and may cause damage to cells. Over a lifetime, this damage may contribute to aging.

Gene – A region of DNA containing code that can be read to make proteins in the cell. Genes are responsible for many heritable traits.

Immunosenescence – The age-related decline in functions of the immune system.

Life expectancy – The average number of years that members of a population (or species) live; also known as average lifespan.

Lymphocytes – 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 population (or species).
Mitochondria – Cell organelles that produce energy necessary for life from the foods we eat. Mitochondria contain DNA, which may be damaged by oxygen free radicals produced during this process. Damage of mitochondrial DNA may contribute to aging. Mitochondria also are involved in controlling cell death.

Proteins – Molecules arranged in a specific order determined by DNA. Proteins are essential for all life processes. Certain proteins, such as those protecting against free radicals and those produced by the immune system, are studied extensively by gerontologists.

Stem Cells – Cells with the potential to become many different types of cells found in the body. Stem cells are also able to replicate almost indefinitely without becoming abnormal.

Telomerase – An enzyme that restores telomeres to the ends of chromosomes in certain cells, such as egg and sperm cells. This telomere lengthening insures that the cells can continue to divide and multiply.

Telomeres – Repeated short, non-coding sequences of DNA at each end of a chromosome. Telomeres protect the chromosome from damage and shorten each time a cell divides.


