**Cell Aging and Death**

*By Kirstie Saltsman*



Elderly man holding a child.  
UN/DPI PHOTOS

Have you ever wondered why we age? What exactly is happening inside our bodies to bring on the wrinkles, gray hair, and the other changes seen in older people? Considering the universality of the process, you might be surprised to know that there remain many unanswered questions about how aging happens at the cellular level. However, theories abound, and the roles played by various suspects in the aging process are beginning to take shape.

Cell death, on the other hand, is an area in which scientists have made great leaps in understanding in recent years. Far from being strictly harmful, scientists have found that cell death, when carefully controlled, is critical to life as we know it. Without it, you wouldn't have your fingers and toes or the proper brain cell connections to be able to read the words on this page.

**Aging: A World of Theories**



*Beautiful*. This image of a woman’s eye was photographed and titled by her 15-year-old granddaughter.  
JENNA KARLSBERG

Most scientists now agree that aging is, at least in part, the result of accumulating damage to the molecules—such as proteins, lipids, and nucleic acids (DNA and RNA)—that make up our cells. If enough molecules are damaged, our cells will function less well, our tissues and organs will begin to deteriorate, and eventually, our health will decline. So in many respects, we appear to age much like a car does: Our parts start to wear out, and we gradually lose the ability to function.

The question is, where does the damage come from? It turns out that damage can come from many different sources, both internal and external.

**Thieving Oxygen**

Take a deep breath. Oxygen in the air you just breathed entered your lungs, passed into the tiny blood vessels that line them, and then went on a wild ride through the creeks, rivers, and cascades of your bloodstream. Thanks to your rich network of blood vessels, oxygen gets carried to every cell in every corner of your body. Once delivered to a cell, oxygen heads for the mitochondria, where it slurps up the electrons coming off the end of the energy-production assembly line. Mitochondria need oxygen to generate cellular energy, and humans need a constant supply of that energy to survive. That's why people die within a few minutes if deprived of oxygen.

But oxygen has a darker side, and it has attracted the attention of scientists who study aging. Normally, an oxygen molecule (O2) absorbs four electrons and is eventually safely converted into water. But if an oxygen molecule only takes up one or two electrons, the result is one of a group of highly unstable molecules called [**reactive oxygen species**](https://publications.nigms.nih.gov/insidethecell/glossary.html#reactiveoxygenspecies) that can damage many kinds of biological molecules by stealing their electrons. These renegade oxygen-containing species can mutate your genes, damage the lipids that make up your cellular membranes, and break the proteins that do much of the cell's work, thereby causing cellular injury in multiple and overlapping ways.

**Growing Old Is Fairly New**



When she died at the verified age of 122, Jeanne Calment (1875–1997) had lived longer than any other human on record.  
AP/WIDE WORLD PHOTOS

It's important to realize that growing old is a relatively new phenomenon in humans. For more than 99.9 percent of the time humans have roamed the Earth, average life expectancies have topped out at 30 or 40 years. The most dramatic leap in life expectancy occurred in the past century, with the advent of improved sanitation and medical care in developed countries. For example, in 1900, the average lifespan in the United States was 47 years, while just a century later, it had skyrocketed to 77 years.

In contrast to the average life expectancy, the maximum human life expectancy has always hovered around 115 to 120 years. These apparent inborn maximum intrigues scientists who study aging. Does there have to be a maximum? What determines it? Why is it about 120 years?

Studies of centenarians (people who live 100 years or more) have indicated that a positive and inquisitive outlook, healthy eating habits, moderate exercise, close ties to family and friends, and genetic factors are associated with long life. Some centenarians have their own theories. Jeanne Calment, a French woman who died at age 122, claimed olive oil, port wine, and chocolate were the keys to her long life!

**Damage, Yes. But Aging?**

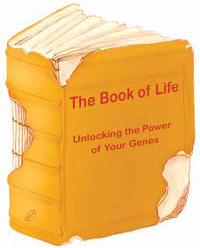


Vividly colored fruits and vegetables such as these are rich in antioxidants. Although their role in the aging process is still unknown, antioxidants are believed to reduce the risk of certain cancers.

Scientists have already uncovered clear links between reactive oxygen compounds and aging. Fruit flies genetically engineered to produce high levels of enzymes that destroy reactive oxygen species lived almost 50 percent longer than normal flies. The same enzymes also made the microscopic roundworm *C. elegans* live significantly longer than normal.

Long-lived flies and worms are one thing, but are reactive oxygen species a factor in human aging as well? The answer is that we don't know yet. Large-scale clinical studies are under way to examine the link between aging and [**antioxidants**](https://publications.nigms.nih.gov/insidethecell/glossary.html#antioxidant)—compounds, such as vitamins E and C, found in fruits and vegetables as well as within our own bodies. Antioxidants are less potent than the enzymes that quash reactive oxygen species, but like the enzymes, they can disarm dangerous reactive oxygen compounds.

**Telomeres: Cellular Timekeepers**



Damage to each person’s genome, often called the "Book of Life," accumulates with time. Such DNA mutations arise from errors in the DNA copying process, as well as from external sources, such as sunlight and cigarette smoke. DNA mutations are known to cause cancer and also may contribute to cellular aging.



The 46 human chromosomes are shown in blue, with the telomeres appearing as white pinpoints. And, no you’re not seeing double—the DNA has already been copied, so each chromosome is actually made up of two identical lengths of DNA, each with its own two telomeres.  
HESED PADILLA–NASH AND THOMAS RIED

Many scientists speculate that another contributor to the aging process is the accumulation of cellular retirees. After cells divide about 50 times, they quit the hard work of dividing and enter a phase in which they no longer behave as they did in their youth.

How do our cells know when to retire? Do cellular clocks have a big hand and a little hand and go, "Tick, tock?" Not exactly. It turns out that each cell has 92 internal clocks—one at each end of its 46 chromosomes. Before a cell divides, it copies its chromosomes so that each daughter cell will get a complete set. But because of how the copying is done, the very ends of our long, slender chromosomes don't get copied. It's as if a photocopier cut off the first and last lines of each page.

As a result, our chromosomes shorten with each cell division. Fortunately, the regions at the ends of our chromosomes—called [**telomeres**](https://publications.nigms.nih.gov/insidethecell/glossary.html#telomere)—spell out the genetic equivalent of gibberish, so no harm comes from leaving parts of them behind. But once a cell's telomeres shrink to a critical minimum size, the cell takes notice and stops dividing.



In 1985, scientists discovered [**telomerase**](https://publications.nigms.nih.gov/insidethecell/glossary.html#telomere). This enzyme extends telomeres, rebuilding them to their former lengths. In most of our cells, the enzyme is turned off before we're born and stays inactive throughout our lives. But theoretically, if turned back on, telomerase could pull cellular retirees back into the workforce. Using genetic engineering, scientists reactivated the enzyme in human cells grown in the laboratory. As hoped, the cells multiplied with abandon, continuing well beyond the time when their telomerase-lacking counterparts had stopped.

**Aging in Fast-Forward: Werner Syndrome**



At age 15, this Japanese-American woman looked healthy, but by age 48, she had clearly developed symptoms of Werner syndrome.  
INTERNATIONAL REGISTRY OF WERNER SYNDROME

Mary was diagnosed with Werner syndrome at age 26, when she was referred to an ophthalmologist for cataracts in both eyes, a condition most commonly found in the elderly. She had developed normally until she'd reached her teens, at which point she failed to undergo the growth spurt typical of adolescents. She remembers being of normal height in elementary school, but reports having been the shortest person in her high school graduating class, and she had slender limbs relative to the size of her trunk. In her early 20s, she noticed her hair graying and falling out, and her skin became unusually wrinkled for someone her age. Soon after the diagnosis, she developed diabetes.

Although hypothetical, Mary's case is a classic example of Werner syndrome, a rare inherited disease that in many respects resembles premature aging. People with Werner syndrome are particularly prone to cancer, cardiovascular disease, and diabetes, and they die at a young age—typically in their 40s. At a genetic level, their DNA is marked by many mutations. These characteristics support the theory that accumulating DNA mutations is a significant factor in normal human aging.

The gene involved in Werner syndrome was identified in 1996 and was found to encode what appears to be an enzyme involved in DNA repair. This suggests that people with Werner syndrome accumulate excessive DNA mutations because this repair enzyme is either missing or not working properly.

A few years after the discovery of the human Werner syndrome gene, scientists identified a corresponding gene in yeast. Deleting the gene from yeast cells shortened their lifespan and led to other signs of accelerated aging. This supports a link between this gene and aging, and it provides scientists a model with which to study Werner syndrome and aging in general.

**Cells That Never Die Can Kill You**



Could reactivating telomerase in our cells extend the human lifespan? Unfortunately, the exact opposite—an untimely death from cancer—could occur. Cancer cells resurrect telomerase, and by maintaining the ends of the cell's chromosomes, the enzyme enables the runaway cell division that typifies cancer. It may, therefore, be a good thing that shrinking telomeres mark most of our cells for eventual retirement.

Nonetheless, scientists still have high hopes for harnessing telomerase. For instance, the enzyme could be used as a tool for diagnosing cancer, alerting doctors to the presence of a malignancy. Another possibility is to use chemicals that block telomerase to put the brakes on cell division in cancer cells. The search for such chemicals is on, and several candidates already have shown promise in preliminary studies.

According to most scientists, aging is caused by the interplay of many factors, such as reactive oxygen species, DNA mutations, and cellular retirement. Unfortunately, as a result, there is probably no such thing as a simple anti-aging remedy.

**Death of a Cell**



As you read this, millions of your cells are dying. Don't panic—you won't miss them. Most of them are either superfluous or potentially harmful, so you're better off without them. In fact, your health depends on the judicious use of a certain kind of cell death—[**apoptosis**](https://publications.nigms.nih.gov/insidethecell/glossary.html#apoptosis).

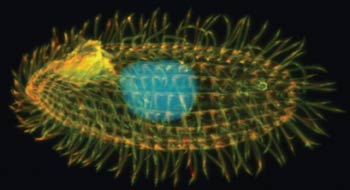
Apoptosis is so carefully planned out that it is often called programmed cell death. During apoptosis, the cell shrinks and pulls away from its neighbors. Then, the surface of the cell appears to boil, with fragments breaking away and escaping like bubbles from a pot of boiling water. The DNA in the nucleus condenses and breaks into regular-sized fragments, and soon the nucleus itself, followed by the entire cell, disintegrates. A cellular cleanup crew rapidly mops up the remains.

Cells come primed for apoptosis, equipped with the instructions and instruments necessary for their own self-destruction. They keep these tools carefully tucked away, like a set of sheathed knives, until some signal—either from within or outside the cell—triggers their release. This initiates a cascade of carefully coordinated events that culminate in the efficient, pain-free excision of unneeded cells.

There is another kind of cell death, called [**necrosis**](https://publications.nigms.nih.gov/insidethecell/glossary.html#necrosis), that is unplanned. Necrosis can result from a sudden traumatic injury, infection, or exposure to a toxic chemical. During necrosis, the cell's outer membrane loses its ability to control the flow of liquid into and out of the cell. The cell swells up and eventually bursts, releasing its contents into the surrounding tissue. A cleanup crew composed of immune cells then moves in and mops up the mess, but the chemicals the cells use cause the area to become inflamed and sensitive. Think of the redness and pain in your finger after you accidentally touch a hot stove.

Many different kinds of injuries can cause cells to die via necrosis. It's what happens to heart cells during a heart attack, to cells in severely frostbitten fingers and toes, and to lung cells during a bout of pneumonia.

**Pond-Dwelling Creature Led Scientists to Telomerase**



RUPAL THAZHATH AND JACEK GAERTIG

Elizabeth Blackburn, a molecular biologist at the University of California, San Francisco, has been studying telomeres since the 1970s. She says that we can think of telomeres as the plastic caps at the ends of our shoelaces—the aglets of our genome. Her work has propelled our understanding of telomeres, in particular as they relate to aging and cancer.

Prior to her work, scientists knew telomeres existed but knew little else about them. Blackburn probed the genetic aglets through studies of a pond-dwelling microorganism called *Tetrahymena*. It may seem like a strange choice, but *Tetrahymena* has the distinct advantage of having roughly 20,000 chromosomes (humans have 46), so it's a rich source of telomeres. In a 1978 paper, Blackburn described the structure of telomeres in detail for the first time.

Seven years later, Blackburn and her then-graduate student, Carol Greider, discovered telomerase. Without it, single-celled organisms like *Tetrahymena* would die out after a limited number of generations, when their telomeres were worn down. Greider and her colleagues later observed that human telomeres become progressively shorter with each cell division, and the scientists suggested that this could eventually destabilize the chromosomes and lead to cell aging and death. Subsequent studies proved this prediction to be correct.

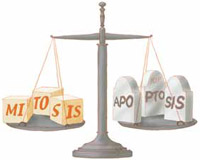
Since then, Blackburn has made inroads into understanding exactly how telomerase works—in particular, how the functions of the enzyme are split between its RNA and protein components. She is currently testing the application of her findings to anticancer strategies in human breast, prostate, and bladder cells.

Greider, now a molecular biologist at Johns Hopkins University School of Medicine, is studying another connection between telomerase and disease. Defects in telomerase have been linked to a rare genetic disorder called dyskeratosis congenita, in which limited telomerase activity causes progressive bone marrow failure, typically leading to death by the mid-teens. Greider has recently developed a mouse model of the disease, which should lead to a deeper understanding of the ailment and lay the foundation for the development of new treatments.

**Apoptosis and Mitosis: Life in Balance**



Before being diagnosed with an incurable muscle-wasting disease that now bears his name, Lou Gehrig proved himself to be one of the most talented baseball players of all time.  
ESTATE OF LOU GEHRIG, C/O CMG WORLDWIDE





Apoptosis removes excess cells to help shape fingers and toes.  
WOODY MACHALEK

Mitosis creates cells and apoptosis kills them. Although these processes oppose one another, they often work together to keep us healthy. For example, our skin and hair cells are renewed via a continuous cycle of apoptosis and mitosis. So are the cells lining our intestines. Because new cells replace old, worn-out ones, our tissues remain healthy.

As you can well imagine, loss of the balance between apoptosis and mitosis can have hazardous consequences. If apoptosis is triggered when it shouldn't be, our bodies squander perfectly good cells. Scientists believe that too much apoptosis is at least partly to blame for some neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Lou Gehrig's. On the other hand, unchecked mitosis can lead to cancer.

**Apoptosis: Nature's Sculptor**



*C. elegans* is a transparent, 1-millimeter-long roundworm commonly used to study the genetics of development, nerve function, behavior, and aging. In this developing *C. elegans* worm, cell nuclei appear pink. The green stain serves as a control to indicate that the staining procedure and microscope are working as they should.  
EWA M. DAVISON

Death is part of life. And at the cellular level, it's essential for life. Like a sculptor carving away unneeded pieces of stone, cell death—apoptosis—shapes our physical features and organs before we are born.

How do we know the way apoptosis works in embryos? In the 1970s, H. Robert Horvitz, a geneticist at Massachusetts Institute of Technology in Cambridge, began looking for a genetic program that controls apoptosis in the tiny roundworm *C. elegans*. During development of the worm, cell division generates 1,090 cells, and exactly 131 of those cells die before the worm becomes an adult.

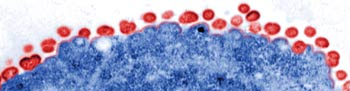
In a landmark paper published in 1986, Horvitz and his then-graduate student Hilary Ellis unearthed two death genes in the worm that are necessary for apoptosis. He later helped identify a gene that protects against apoptosis, as well as genes that direct how the body removes dead cells. He also identified the human counterparts of the worm death genes. Other scientists confirmed the roles of the human genes in apoptosis. Horvitz's research, which won a Nobel Prize in physiology or medicine in 2002, proved that apoptosis is directed from within—by our very own genes.

The pioneering work of Horvitz and his collaborators touched off rapid advances in our understanding of apoptosis. Scientists are making fast-paced discoveries about the genes, proteins, and organelles involved in the process. Pharmaceutical scientists are now testing human apoptosis genes as potential drug targets for ailments as diverse as neurodegenerative diseases, liver diseases, and cancer.

**Getting Rid of Troublemakers**

During an infection, apoptosis can serve a protective function by killing off virus-contaminated cells before they spill over with virus particles. This act of self-sacrifice hampers the spread of infection and can save the whole organism.

Unfortunately, our viral assailants are not so easily done in. They come armed with a box full of tools designed to defuse the apoptotic response. Because viruses depend upon their cellular hosts for survival, it's in their best interest to keep cells alive until the viruses are ready to move on.



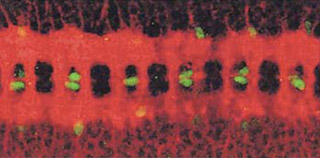
HIV particles (red) budding off an infected cell (blue).  
UTA VON SCHWEDLER AND WES SUNDQUIST

The tools viruses use to forestall the cell's suicide attempt are remarkable in their diversity and ingenuity. Some viruses, such as a type that causes common colds, make proteins that mimic "off" switches of the cellular apoptotic pathway, fooling cells into thinking their own sensors have put the brakes on suicide. Others, such as HIV, have an enzyme that can disable a key component of the pathway, bringing the death march to a screeching halt.

Still other viruses, such as smallpox, inhibit apoptosis by throwing up a smokescreen in front of external triggers of the pathway. Normally, immune cells recognize virally infected cells and release alarm chemicals that stick to receptors on the infected cell surface, triggering apoptosis. But smallpox and other related viruses release proteins that specifically recognize and capture the alarm chemicals before they can do their job. Other kinds of viruses target the executioners themselves, the enzymes that, once activated, shred the cell contents and lead to its demise.

Although these evasion tactics can allow viruses to gain the upper hand and make us sick, they've also guided scientists toward a deeper understanding of apoptosis. Key insights into the process have emerged from studies about how viruses evade apoptosis, and clinical benefits are likely not far behind.

**The SPITZ of Life**



Glial cells (stained green) in the developing fly embryo have survived thanks to chemical messages sent by neighboring nerve cells (stained red).  
ANDREAS BERGMANN AND HERMANN STELLER

Nature has its harsh realities, even at the cellular level. Nowhere is this more true than in the developing nervous system, where the prevailing canon seems to be "make yourself useful or die." Scientists have found that some cells automatically die by apoptosis when they are poorly positioned and unlikely to play a useful role in the nervous system. So if the default is death, how do the survivors stay alive? Scientists have speculated about this for some time, but only recently have they identified the exact mechanisms.

Hermann Steller, a developmental biologist at Rockefeller University in New York City, investigates the signals that control cell death in the developing fruit fly embryo. He and his colleagues were the first to identify all of the molecular messengers that direct the survival of certain glial cells in the nervous system.

It turns out that the signal for glial cells to survive originates from nearby nerve cells. So glial cells have their neighbors to thank for their continued existence.

Physical contact between glial and nerve cells triggers nerve cells to release a chemical messenger called SPITZ, which sticks to and activates molecular receptors on the glial cell surface. The activated receptors then trigger a cascade of enzymatic reactions inside the glial cells that ultimately blocks apoptosis. This process ensures that the only glial cells to survive are those that come close enough to a nerve cell to compete for SPITZ. If a glial cell is close enough to a nerve cell to be SPITZed upon, it's probably also close enough to nurture the SPITZing nerve cell. Thus, like self-serving neighbors, nerve cells only extend a lifesaving hand to those in a position to return the favor.

These findings could help scientists better understand cell death and survival in the human brain and possibly in other parts of the body. The work also might point the way to new treatments for diseases resulting from the premature death of brain cells, such as Parkinson's and Alzheimer's.