

theories of aging

- What is a theory of aging?
- How do theories of aging affect aging research?

Why and how do we age?

Scientists have been trying to develop a theory or theories of aging for centuries. Today, there is a growing consensus among experts about how and why we age — questions that may be answered by just a few complementary hypotheses.

Theories of aging can be divided into two categories:

- **Those that answer the question “Why do we age?”**
- **And those that address the question “How do we age?”**

Only a few broad, overarching theories attempt to explain why we and nearly all living organisms age. These theories compete with each other, making it unlikely that more than one of them could be true. Over time, some theories have fallen out of favor as others have become more widely accepted.

Other theories, more properly called hypotheses, are smaller in scope and address the question, “How do we age?” They attempt to explain the mechanisms that affect how we and other species age, and it is likely that a number of them are simultaneously true.

Testing these hypotheses is the current pursuit of most aging research. Identification of the mechanisms that affect aging could lead to interventions to slow or alter aging. Recent research implies that there may be a limited number of these mechanisms, giving scientists hope that their efforts may one day lead to strategies that could help us lead longer, healthier lives.



The Infoaging Guide to Theories of Aging is a publication of the American Federation for Aging Research (AFAR). Since 1981, AFAR has provided grant, scholarship, and fellowship support worth \$93 million to 2,200 talented researchers, helping them begin and further their careers in aging research and geriatric medicine.

AFAR is also committed to the dissemination of scientific knowledge about aging, both within the scientific community and to the public. Infoaging.org, AFAR’s web site for consumers, is a critical tool in that outreach effort.

How do theories of aging affect aging research?

Theories of aging help scientists formulate the questions that drive research. Asking why we age can help scientists investigate the nature of aging itself, and asking how we age can lead scientists to discoveries that could potentially alter the nature of aging.

A critical issue in aging research is whether aging is affected by one, several, or a multitude of underlying processes. If there are hundreds of different biological pathways that affect aging, then odds are slim that science will find a way to slow down how we age or even understand why aging happens at all.

Thankfully, evidence seems to be pointing to several fundamental processes as being the primary culprits affecting aging. The best evidence for this belief is the existence of single-gene mutations that affect lifespan in experimental animals, as well as a well-known environmental intervention called caloric restriction.

Caloric restriction, in which laboratory animals are maintained on nutritionally balanced but sparse diets containing 30-40% fewer calories than a normal diet, has been shown to increase the average and maximum life spans of a range of organisms, including worms, insects, and rodents. It is currently under investigation in primates. By itself, caloric restriction retards almost all age-related changes mice normally undergo, including the onset of age-related diseases.

Single-gene mutations that extend lifespan, discovered so far in roundworms, fruit flies, and mice, are also a powerful argument that a finite number of pathways influence aging. Interestingly, the genes all seem to affect one of a few biochemical pathways, such as energy consumption, stress resistance, or regulation of the insulin/IGF-1 neuroendocrine pathway.

These findings offer hope that researchers may eventually be able to



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modify the course of aging in humans. However, there is a caveat. Animals modified to live longer often show inherent defects. Some mutant roundworms have reduced fertility and a reduced ability to enter a dormant state. Mutant Ames dwarf mice live a long time but are sterile and inactive. Rodents maintained on calorically restricted diets are thin, cold, stunted, and sometimes sterile. It is likely that such animals, although they survive to hale old age in the laboratory, would never stand a chance in the wild.

“Due to antagonistic pleiotropy,” says Steven Austad, PhD, aging researcher, zoologist, and top expert on the theories that underlie aging research, “all the life-extending genes . . . investigated in detail have turned out to manifest side effects. As we move toward the development of interventions in the aging process in the not-too-distant future, we must not forget this.”

Why do we age?

The evolutionary senescence theory of aging

The most widely accepted overall theory of aging is currently the evolutionary senescence theory of aging. Unlike the earlier programmed theory of evolution and aging, which tried to find reasons why evolution might favor aging, evolutionary senescence theory focuses on the failure of natural selection to be able to affect late-life traits.

Natural selection, because it operates via reproduction, can have little effect on later life. In the wild, predation and accidents guarantee that there are always more younger individuals reproducing than older ones. Genes and mutations that have harmful effects that appear only after reproduction is over do not affect reproductive success and therefore can be passed on to future generations. In 1952, Peter Medawar proposed that the inability of natural selection to influence late-life traits could mean that genes with detrimental late-life effects could continue to be passed from generation to generation. This theory is called the mutation accumulation theory.

A few years later, George Williams extrapolated on this idea by formulating the theory of “antagonistic pleiotropy.” Antagonistic pleiotropy means that some genes that increase the odds of successful reproduction early in life may have deleterious effects later in life. Because the gene’s harmful effects do not appear until after reproduction is over, they cannot be eliminated through natural selection. An example of antagonistic pleiotropy in humans is p53, a gene that directs damaged cells to stop reproducing or die. The gene helps prevent cancer in younger people, but may be partly responsible for aging by impairing the body’s ability to renew deteriorating tissues. Because of antagonistic

pleiotropy, it is likely that tinkering with genes to improve late-life fitness could have a detrimental effect on health at younger ages.

Much experimental evidence exists to support the basic premises of the evolutionary senescence theory of aging. For example, the theory predicts that delaying the age of reproduction should delay aging, as it would increase the power of natural selection later in life. Experiments with fruit flies in which younger flies were prevented from mating, allowing only older flies to reproduce, confirmed this prediction. Aging in the fruit fly population was delayed. However, these long-lived flies were less fertile in early life than normal flies, giving support to the idea of antagonistic pleiotropy. In experiments with roundworms given a gene mutation that extended their life span, scientists found that these long-lived worms exhibited defects, such as reduced ability to enter a protective dauer stage, delayed development, and impaired reproduction.

In the 1970s, Thomas Kirkwood added to the evolutionary biology theory of aging with his “disposable soma” theory. He believed that organisms have to balance the demands of maintaining their body, or soma, cells and reproducing. Because an organism invests resources into reproduction, over time mutations and other cellular damage accumulate in the soma because the body cannot repair all of it. This idea explains some of the disparity in life span between different types of organisms. Species that are likely to die to predation, such as mice, invest more energy in reproduction than in maintaining health because an individual is unlikely to live long anyway. Humans, on the other hand, have few



Figure 1. Studying opossums in Virginia, Steven Austad found that animals living on a predator-free island aged more slowly.

predators and can therefore allocate more resources to repairing physical damage since they can reproduce over a longer period of time.

Research conducted by Steven Austad in the early 1990s provides interesting proof of this idea, namely, that hazardous environments favor early reproduction and short life spans, whereas safer environments favor the opposite. Studying opossums in Virginia, he found that animals living on a predator-free island aged much more slowly and reproduced later than opossums on the more dangerous mainland.

The disposable soma theory may also explain why some organisms, like salmon or certain kinds of spiders, reproduce only once and then die. If the animal is likely to die anyway before the next breeding season, then natural selection would favor allocating all an animal’s resources to reproduction, leaving nothing for somatic maintenance.

Although many scientists believe the evolutionary theory of aging needs further refinement, most agree that it is currently the best explanation for why we and other organisms age.

Go Online!

Check out the Theories of Aging Information Center on the Infoaging web site (www.infoaging.org) to read about other theories that could explain why humans and other organisms age.

How do we age?

The cross-linking/glycation hypothesis of aging

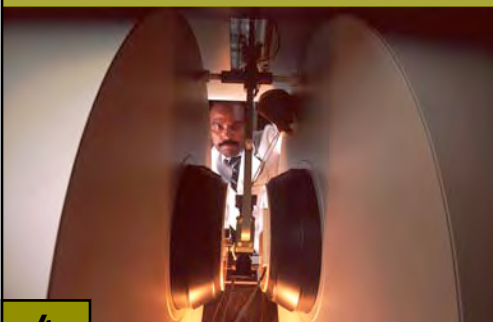
The cross-linking hypothesis is based on the observation that with age, our proteins, DNA, and other structural molecules develop inappropriate attachments or cross-links to one another. These unnecessary links or bonds decrease the mobility or elasticity of proteins and other molecules. Proteins that are damaged or no longer needed are normally broken down by enzymes called proteases, and the presence of cross-linkages inhibits the activity of proteases. These damaged and unneeded proteins, therefore, stick around and can cause problems.

The oxidative-damage/free-radical hypothesis of aging

Oxygen free radicals are one of the toxic byproducts of normal cell metabolism. Natural substances within our cells called antioxidants sop up and neutralize these dangerous free radicals. But those that escape this cleanup process can damage DNA, proteins, and mitochondria. And that damage, called oxidative damage, accumulates over time. Some fruit fly studies suggest that oxidative damage is one of the direct causes of aging.

Proponents of the free-radical hypothesis of aging note that free radicals can cause DNA damage, the

Figure 2. Researchers use electron spin resonance spectroscopy to study how free radicals contribute to the aging process.



cross-linking of proteins, and the formation of age pigments. Oxidative damage contributes to many age-related diseases, such as cancer, heart disease, diabetes, and Alzheimer's disease.

The genome maintenance hypothesis of aging

Damage to our DNA happens throughout our lives: it can be caused by oxidative damage, mistakes in replication, or outside environmental factors such as radiation or toxins. Mutations or spontaneous changes in the structure of our genes that occur in our egg or sperm cells will be passed on to our future generations, if those mutations are not so potentially disruptive as to be fatal to our offspring. Mutations that occur in the rest of the cells of the body will only affect that individual and cannot be passed on to future generations. Most of those body cell, or somatic, mutations will be corrected and eliminated, but some will not. Those will accumulate, eventually causing the cells to malfunction and die. This process, it has been suggested, is a crucial component in the aging process. This theory also encompasses a role for mitochondria, the cellular powerhouses, as important factors in aging. Somatic mutations in the DNA of the mitochondria accumulate with age, and are associated with an age-related decline in the functioning of mitochondria. Many scientists believe that mitochondrial aging is an important contributor to aging in general.

The replicative senescence hypothesis of aging

Many human cells have a limited capacity to reproduce themselves in culture by dividing. Most scientists today believe that what determines the Hayflick Limit for dividing human cells is the length of cells' telomeres. Telomeres can be pictured as caps on the ends of chromosomes. Each time a cell divides, it must first double its chromosomes, so that each daughter cell receives a full complement of genetic material. But each time a

For Further Reading

Why We Age: What Science Is Discovering about the Body's Journey Through Life by Steven Austad, Wiley 1999

"Why Does Aging Occur?" by Thomas BL Kirkwood in *Focus on Modern Topics in the Biology of Aging*, Springer Publishing Company 2001

chromosome reproduces itself, it loses a small bit of its telomeres. When a cell's telomeres have reached a critically short length, after 40 to 60 population doublings in young human cells, the cell can no longer replicate its chromosomes and thus will stop dividing. These cells with shortened telomeres that can no longer divide become what is called "senescent."

For quite a while, scientists believed that telomere shortening held the answer to human aging. They thought that it was a sort of "cellular clock" that might govern aging. Scientists have concluded that while telomeres and senescence may contribute to human aging, they do not govern it.

The neuroendocrine hypothesis of aging

For a time, aging researchers working in neuroendocrinology—the study of hormones regulated by the brain—thought that later-life reduction of hormones, such as the reduction of estrogen that accompanies menopause, was responsible for aging. However, although some late-life functional changes may be linked to reduced hormone levels, experimental evidence in mice from as early as the 1960s and continuing today shows the opposite: reduction in hormones can lengthen life. Studies in mice whose pituitary glands were removed showed the mice lived longer with a delay in age-related changes.