infoaging guides

BIOLOGY OF AGING

THEORIES OF AGING

An introduction to aging science brought to you by the American Federation for Aging Research

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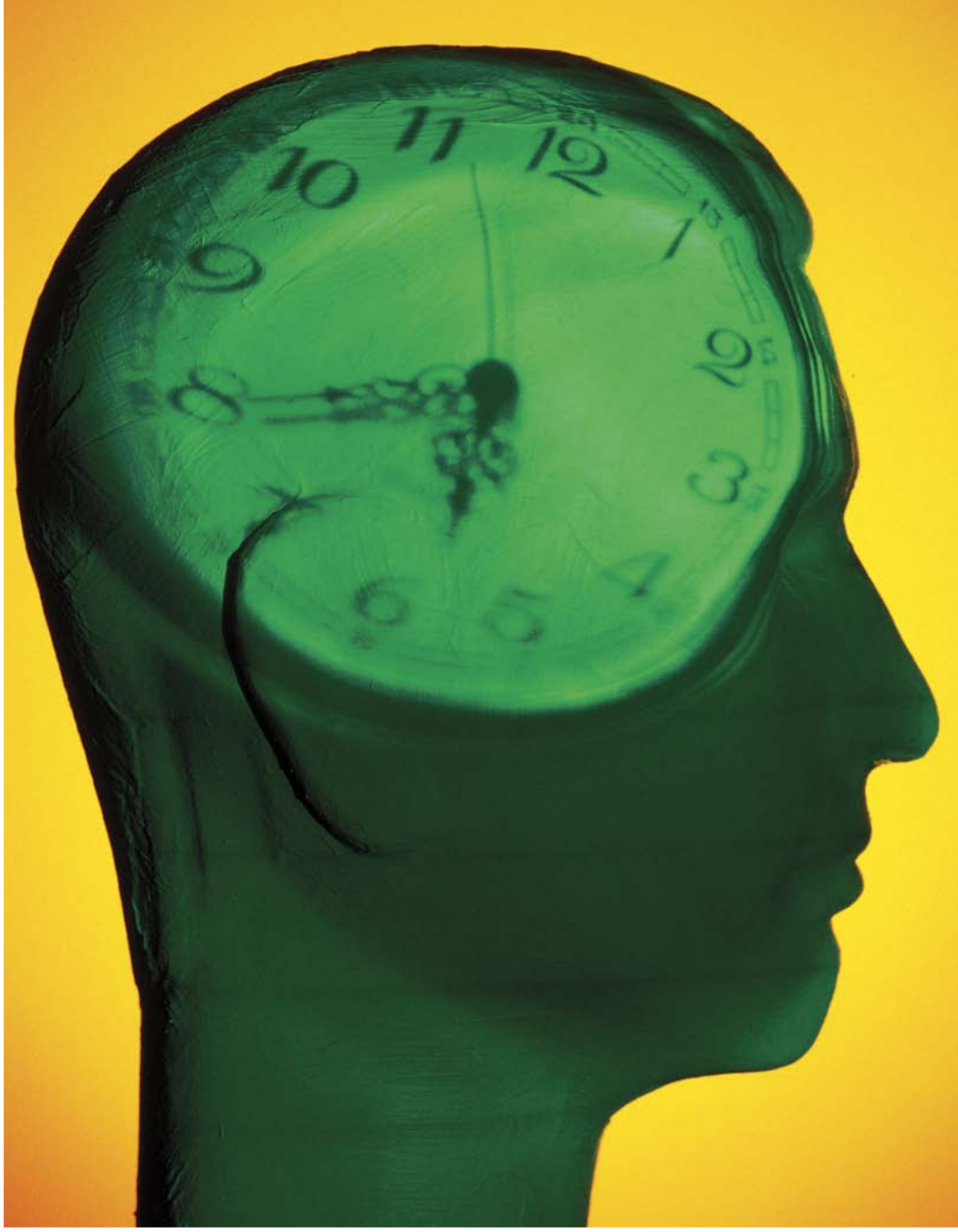
WHAT IS A THEORY OF AGING?

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 that 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.

MODIFYING THE COURSE 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 could ever hope to devise a way of slowing down how we age or even understand why aging happens at all.



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However, evidence seems to be pointing to just a few fundamental processes as the primary culprits in the scenario of aging. The best evidence lies in 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 to 40 percent fewer calories than a normal diet, has been shown to reliably increase the average and maximum lifespans of a range of organisms, including worms, insects, and rodents. It is currently under investigation in primates. By itself, caloric restriction retards almost all of the 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 what is called the insulin/IGF-1 neuroendocrine pathway. IGF stands for insulin-like growth factor.

These findings offer hope that researchers may eventually be able to 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 a ripe old age in the laboratory, would never stand a chance in the wild.

AGING IS NOT A PROGRAMMED ASPECT OF DEVELOPMENT

Aging is not a programmed aspect of development. It is the deterioration of what might be thought of as a survival program. Not long after Charles Darwin published his groundbreaking theory of evolution by natural selection in *On the Origin of Species* in 1859, scientists began to try to use Darwin's theory to explain aging. One of the first was August Weismann, who published his hypothesis in 1891. He proposed that aging evolved to benefit species or groups by eliminating unfit animals to make room for the next generation. Although this idea was popular for decades, Weismann later rejected it, as do modern biologists. Evidence overwhelmingly shows that natural selection operates to affect the reproductive success of individuals, not the overall survival of groups.

Further argument against aging as a programmed aspect of development, ordered by a genetic blueprint, lies in its variability. Although members of a species develop into adults in the same way, even genetically similar or identical individuals, raised in identical conditions and eating identical food, age differently. Whereas one person (or mouse) may die of heart failure, another may succumb to cancer with his or her heart functioning perfectly.

When scientists discovered that changing just one gene in the roundworm, *C. elegans*, could significantly extend its lifespan, some researchers argued that this showed aging was genetically programmed. However, most scientists now believe that overstated the case: just because a gene happens to affect the rate of aging does not mean that it was designed by nature to do so. The majority of scientists now prefer other theories.

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 are no longer needed are normally broken down by enzymes called proteases. However, the presence of cross-linkages inhibits the activity of proteases. These damaged and unneeded proteins, therefore, stick around and can cause problems.

One of the main ways cross-linking occurs is through a process called glycosylation or glycation. Glucose molecules can stick to proteins, then transform into brownish molecules called advanced glycosylation endproducts, or AGEs. When both of the sticky ends of AGEs adhere to neighboring proteins, they form permanent cross-links that disable the proteins' functions. This is the same process that causes food to brown when it is cooked.

Some research supports the hypothesis that cross-linking contributes to aging. Cross-linking of the skin protein collagen, for example, has proven at least partly responsible for wrinkling and other age-related dermal changes. Cross-linking of proteins in the lens of the eye is also believed to play a role in age-related cataract formation. Researchers speculate that cross-linking of proteins in the walls of arteries or the filtering systems of the kidney account for at least some of the atherosclerosis (hardening of the arteries) and age-related decline in kidney function observed in older adults. Another study conducted at the Bjorksten Institute in Wisconsin treated brain tissue from young animals with known cross-link-inducing compounds. That brain tissue soon looked quite similar to older brain tissue, with its naturally cross-linked brain proteins, adding evidence in support of this theory of aging.

Recently, scientists have found evidence that glycation contributes to the formation of beta-amyloid,

the protein that clumps together in the brains of Alzheimer's patients.

Somewhat indirect experimental evidence in support of the cross-linking theory of aging appears in studies that look at drugs that prevent cross-linking, and the impact of taking those drugs on the various components of the aging process. Studies done in China and in the United Kingdom on the molecule carnosine are provocative. Carnosine occurs in very low concentrations in the brain and other tissues. In the laboratory, carnosine has been shown to delay the senescence or aging of human cells called fibroblasts. Carnosine works by preventing cross-linking of proteins. The more recent Chinese studies suggest carnosine might be of benefit in delaying the formation of cataracts, in which cross-linking is thought to play a part.

Although many scientists agree that cross-linking of proteins, and perhaps the cross-linking of DNA molecules as well, is a component of aging, it is likely only one of several mechanisms that contributes to aging.

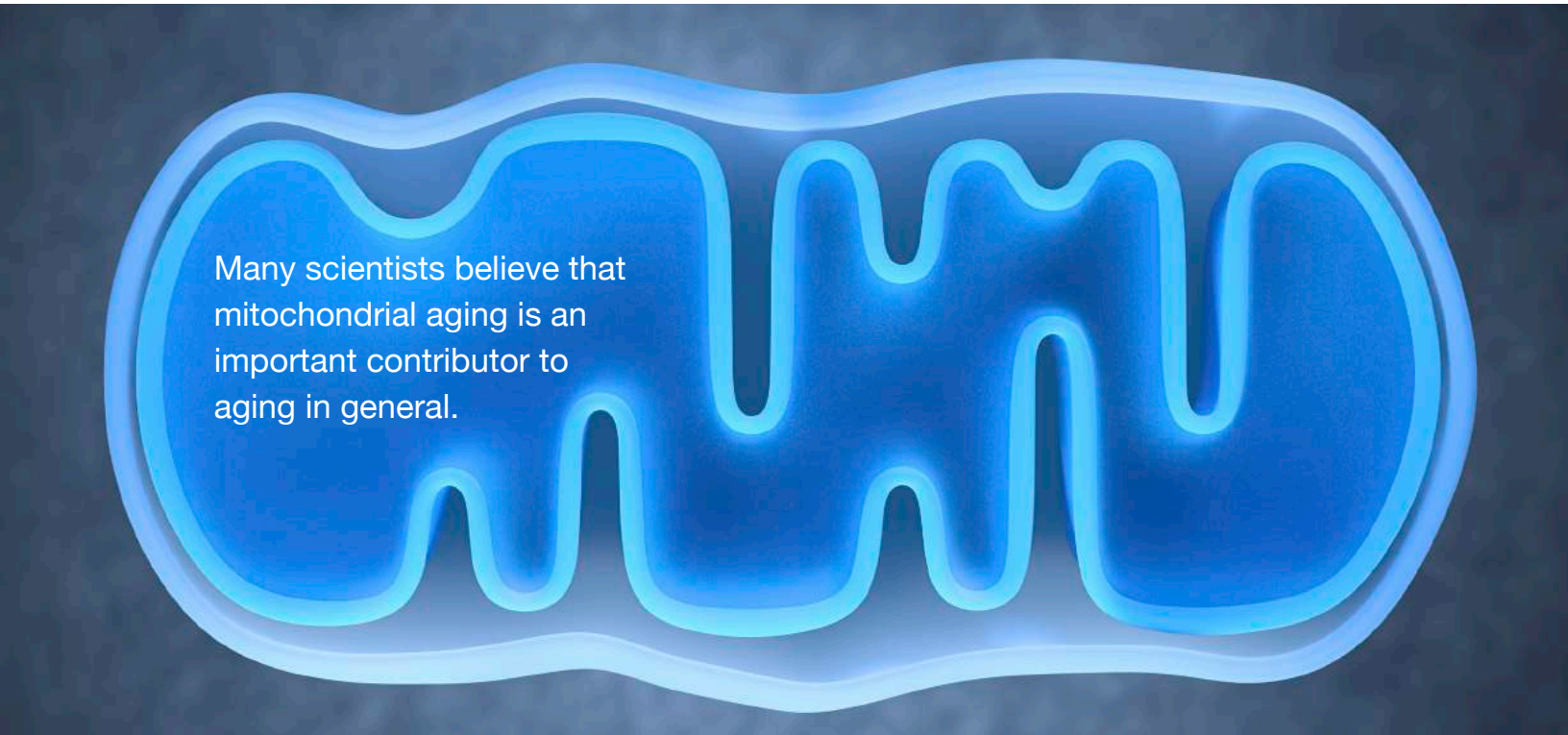
THE EVOLUTIONARY SENESCENCE THEORY OF AGING

The most widely accepted overall theory of aging is 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 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 but 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



Many scientists believe that mitochondrial aging is an important contributor to aging in general.

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 lifespan, scientists found that these long-lived worms exhibited defects, such as reduced ability to enter a protective dauer stage (a developmental state in which worm larvae can better survive harsh conditions), 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 cells, or soma, 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 lifespan between different types of organisms. Species that are likely to die due 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 predators and can therefore allocate more resources to repairing physical damage since they will be able to 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 lifespans, whereas safer environments favor the opposite. Studying Virginia opossums in South Carolina and Georgia, 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.

THE GENOME MAINTENANCE HYPOTHESIS OF AGING

Damage to our DNA happens thousands of times every day in every cell in our body throughout our lives. This damage can be caused by oxidative free radicals, 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 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. Mitochondria create damaging free radicals as a by-product of normal energy production. Somatic mutations in the DNA of the mitochondria accumulate with age, increasing free radical production, 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.

Luckily, our bodies have repair mechanisms to take care of much of that damage. In fact, many scientists believe that humans have long lifespans because we are much better at repairing our genome than short-lived animals like mice. This is related to an evolutionary theory of aging called the "disposable soma" theory. Defects in DNA repair seem to be directly related to aging. Evidence exists for the decline in DNA repair and the accumulation of DNA damage in several different types of cells taken from elderly subjects. Elderly patients' blood and skin cells have less capacity to repair themselves than those from young adults. Indeed, one study that looked

in white blood cells found DNA damage in two to four percent of the cells from young adults, but six times more often in cells from the elderly. These aging white blood cells with their higher level of DNA damage may explain some of the decline in immune function associated with aging.

In addition, scientists have linked Werner's syndrome, a rare disease of premature aging, to mutations in the WRN gene. These mutations lead to abnormalities in DNA replication and repair of DNA damage. Poor capacity for DNA repair is also linked to the most prevalent disease of aging, cancer.

Exploring the role of DNA damage and repair remains a critical area of aging research.

THE NEUROENDOCRINE HYPOTHESIS OF AGING

The neuroendocrine system refers to the complex connections between the brain and nervous system and our endocrine glands, which produce hormones. The hypothalamus, a structure at the base of the brain, stimulates and inhibits the pituitary gland, often called the "master gland," which in turn regulates the glands of the body (ovaries, testes, adrenal glands, thyroid) and how and when they release their hormones into our circulation. As we age, this system becomes less functional, and this can lead to high blood pressure, impaired sugar metabolism, and sleep abnormalities. The effects that the various hormones our different glands produce have on different facets of aging have been studied extensively.

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.

A flood of recent evidence has pinpointed this effect to one area: the insulin/IGF-1 hormonal pathway. IGF stands for insulin-like growth factor, a substance activated by growth hormone. Single-gene mutations in fruit flies and the roundworm *C. elegans*, widely studied by aging researchers, have recently been tied to the insulin/IGF-1 pathway. In 2002, a study by French researchers published electronically in *Nature* showed a similar effect in mice. In all the laboratory

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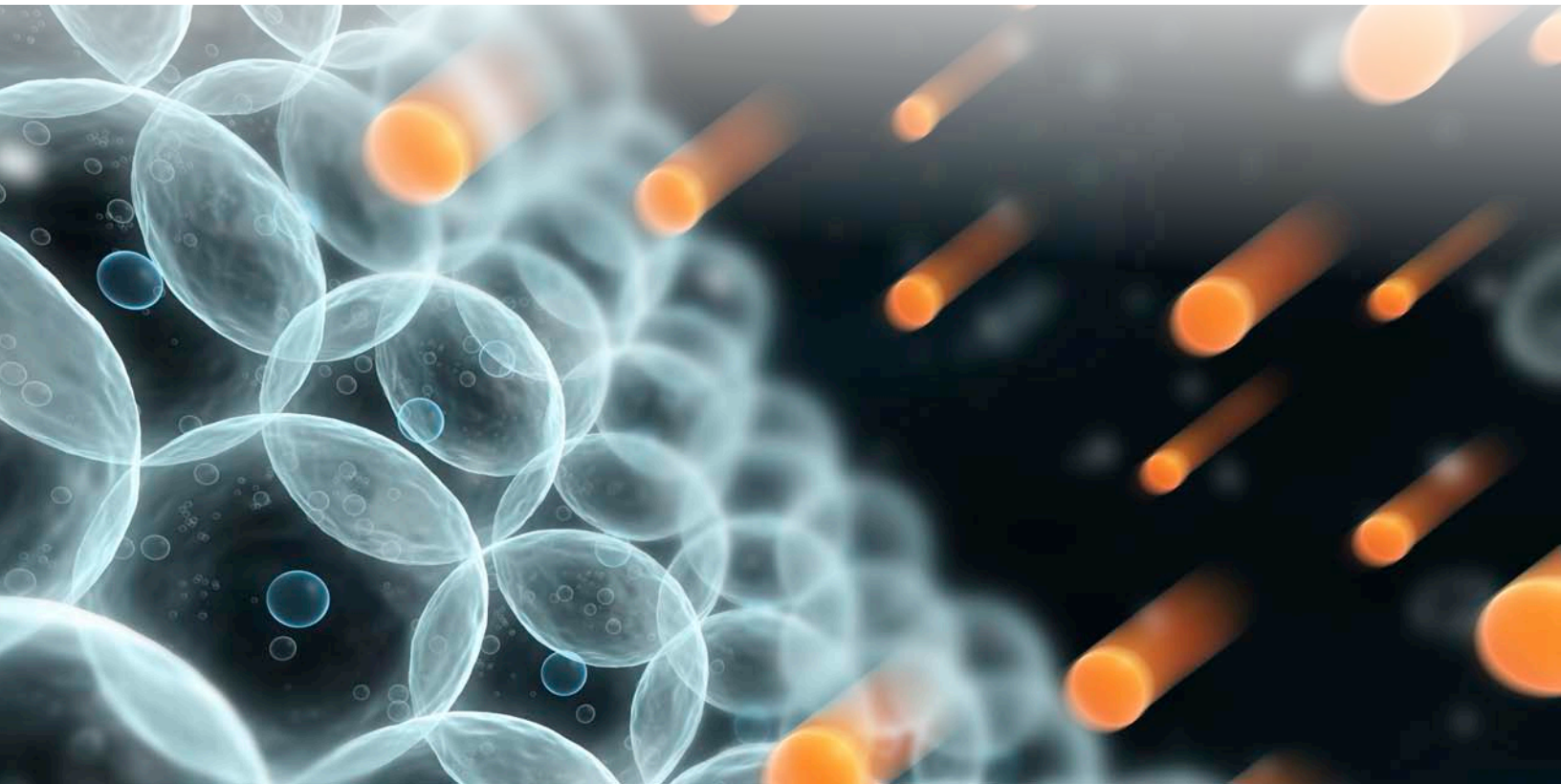

organisms studied, mutations that reduce the amount of circulating IGF extend life. In many cases, however, the long-lived mutants have defects that could potentially affect their ability to survive in the wild, possibly making the IGF-1 pathway's relationship to aging an example of antagonistic pleiotropy.

This consistency among species makes scientists optimistic that the insulin/IGF-1 pathway may work in a similar fashion in humans, and may be an excellent target for interventions that could affect aging. Interestingly, this evidence flies in the face of popular support for anti-aging treatments involving injections of growth hormone, which increases circulating IGF-1. Rather than prolonging life as some companies claim, such treatment may instead do the opposite. A recent study of humans who genetically lack an ability to use growth hormone found that these people were protected against cancer and the development of adult-onset diabetes.

THE OXIDATIVE DAMAGE/ FREE RADICAL HYPOTHESIS OF AGING

Oxidative 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. This 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 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.

Many scientists focus on the specific effects of free radicals on mitochondria, the tiny powerhouses of our cells that transform energy into useful forms. More than 90 percent of the cell's free radicals are produced in the mitochondria, so they are at particular risk of damage. Oxidative free radicals, unless quickly neutralized by antioxidants, can cause considerable damage to the membranes of mitochondria and to mitochondrial DNA. Scientists studied the connection among mitochondria, oxidative stress, and aging in fruit flies by housing the flies in an environment of 100 percent oxygen. The elevated oxygen levels cause the mitochondrial membranes to crimp in swirled patterns, which in turn decreases the lifespan of the insects from two months to about a week.

The injury caused by free radicals initiates a self-perpetuating cycle in which oxidative damage impairs mitochondrial function, which results in the generation of even greater amounts of free radicals. Although mitochondria have some capacity to repair their DNA, these repair mechanisms may not be as effective as those used to repair damage to DNA in the nucleus. In addition, evidence shows that the ability of mitochondria to repair DNA damage declines with age. Why this occurs is not known.

Over time, the affected mitochondria become so inefficient they are unable to generate sufficient energy to meet cellular demands. Mitochondria from the cells of older individuals tend to be less efficient than those from the cells of younger people. In addition, too much mitochondrial damage can cause apoptosis, a form of cell suicide.

Experiments attempting to reverse the effects of oxidative damage by feeding experimental animals dietary antioxidants, and other experiments that genetically increase oxidative damage, have not yielded conclusive results. But because oxidative damage is associated with so many of the problems associated with aging—less efficiency of cellular systems, deterioration of certain tissues, and increased susceptibility to age-associated diseases—investigating oxidative damage remains one of the hottest areas of aging research.

THE RATE OF LIVING THEORY OF AGING

The rate of living theory of aging is perhaps the oldest explanation of aging. Ancient philosophers believed that we possess a finite amount of some "vital substance." When that substance is consumed, we die. Philosophers even argued that each person had only a finite, predetermined number of breaths or heartbeats, and that once they were used, death ensued.

In the 20th century, scientists proposed a new twist on this old theory: energy consumption limits longevity. In other words, an organism's metabolic rate determines its lifespan. This idea was consistent with the discovery that reactive oxygen species (free radicals), a byproduct of normal metabolism, can damage cells and contribute to aging. Experiments in cold-blooded organisms showed that their lifespan was inversely related to the temperature they

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lived in or how active they were. More recent work with *C. elegans*, a roundworm, showed that changing just one gene related to metabolism could significantly extend the worm's lifespan.

On the other hand, some experimental evidence has shown no clear relationship between temperature and longevity. Experiments in fruit flies have shown that temperature either has no effect, or the opposite effect. For example, a 1997 experiment showed that briefly exposing fruit flies to elevated temperature could actually slow aging for several weeks. Scientists now believe that although metabolic rate can affect aging, that doesn't mean that it always does so. Caloric restriction, the only intervention known to extend life in mammals, does so without reducing the animal's metabolic rate. In addition, experimentally boosting an animal's metabolic rate does not always reduce longevity. And even though there is a rough correlation among species between body size, metabolic rate, and longevity, there are many exceptions to this rule. For example, small short-lived mammals expend more energy per cell over their lives than larger long-lived animals. Also, birds typically have a metabolic rate 1.5 to 2.0 times as high as similar-sized mammals, yet they live on average about three times as long. These broad patterns are clearly inconsistent with the rate of living theory.

Modern scientists have now rejected the rate of living theory as being a valid overall explanation for why we and most other species age. However, oxidative damage is still considered one of several mechanisms contributing to the aging process, and numerous aging researchers are pursuing research in this area.

THE REPLICATIVE SENESCENCE HYPOTHESIS OF AGING

Fifty years ago, Dr. Leonard Hayflick and his colleague, Dr. Paul Moorhead, discovered that many human cells have a limited capacity to reproduce themselves in culture by dividing. They found that these and many other normal human cells derived from fetal, embryonic, or newborn tissue can undergo between 40 and 60 cell divisions, but then can divide no more. This number is often referred to as the Hayflick Limit.

Most scientists today believe that what determines the Hayflick Limit for dividing human cells is the length of a cell's telomeres. Telomeres can be pictured as protective 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 chromosome reproduces itself, it loses a small bit of its telomeres. Oxidative damage can also shorten 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 become "senescent" in the sense that although they do not die, they can no longer divide.

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. However, there are some problems with this idea. In humans, not all types of tissue contains actively replicating cells. Brain cells are one example. Muscles cells of the heart are another example. Telomere shortening is also not universal among species. The cells of flies and roundworms, for example, do not replicate very much. And in mice, telomeres are routinely lengthened by an enzyme called telomerase, which is rare in humans in non-cancerous cells. Scientists have concluded that while telomeres and senescence may contribute to human aging, they do not govern it. Very interesting recent experiments find that mice genetically engineered to accelerate telomere shortening show signs of accelerated aging and mice engineered to maintain telomere length show signs of slowed aging. The role of telomere biology in aging is clearly complex and as a consequence remain a key focus of aging research. As normal cells approach the end of their ability to divide, they incur hundreds of biological changes that affect virtually all of their activities. Many of these changes are similar, if not identical, to the kinds of changes that we see occurring in aging humans themselves. Thus, the study of cellular senescence continues to provide important clues to the aging process at the most fundamental level—the cell.

For example, certain skin cells produce collagen during their younger, reproductive years. When they reach senescence and can no longer divide, they produce collagenase, an enzyme that breaks down collagen. Some researchers suggest that this process may be responsible for the thinning and wrinkling of skin as we age.

Some scientists also speculate that the growth arrest associated with replicative or reproductive senescence may retard the regeneration or repair of damaged tissue, which could play a role in the aging of the body. Cellular senescence is also related to cancer, one of the most common age-related diseases, in two ways. In young adulthood, the major role of cellular senescence may be stopping the replication of damaged cells which could turn into cancer. Yet more recent research, led by Dr. Judith Campisi of the Lawrence Berkeley National Laboratory, implies that cellular senescence, while it may be protective against cancer in early life, may actually contribute to the development of cancer later in life. She studied senescent human fibroblasts, a variety of skin cell. She found that these senescent fibroblasts have the effect of stimulating other skin cells that are precancerous or already cancerous to proliferate. They do not stimulate normal cells to proliferate. This relationship is another example of antagonistic pleiotropy, or early life benefits trading off against unhealthy effects later in life, an important component of the evolutionary senescence theory of aging.

Short telomeres themselves are also associated with aging. Some research has found shorter telomeres in patients suffering from cancer, or found a correlation between telomere length and lifespan. Research has found that when telomeres become short, they can break, occasionally prompting inappropriate responses from DNA repair mechanisms. This can cause chromosomal damage or cell death, both of which may contribute to age-related diseases and conditions.

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