

# WHAT IS AGING?

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**C**onfronting the problem of aging. I have a daughter, a fiery blonde bundle of energy, and a couple of years ago she went through a phase of not being able to sleep at night – she was nine then, I think. The problem was that the full implications of aging had dawned upon her. Night after night she shed tears over the fact that aging would take her mother and father away from her, and the prospect of her own death filled her with terror. To try to assuage her anguish I told her that I would try to save her. I am a biogerontologist – a scientist studying one of the greatest unsolved mysteries, namely: what is aging? By helping to understand nature, science has made so many great things possible – including cures for diseases that have blighted humanity throughout history. If we can understand aging, I told her, who knows what might be possible? There is at least hope. This seemed to help her to sleep. But could we really ever do something about aging, the greatest disease of all? The word from the frontiers of science where researchers labor over the question of aging is that we probably can – and perhaps even are already.

## Is aging a disease?

A moment ago I described aging as ‘the greatest disease of all.’ But is it really right to say that? In fact, this is controversial: there are different views. For example, one view is that aging is punishment meted out to us by God for original sin. Adam and Eve in the Garden of Eden were at first immortal, until Eve ate the fruit of the tree of knowledge of good and evil. Yet there is much to be said for trying to understand the world based on what can be demonstrated or logically proven (rather than on tradition and untested belief), and, as a scientist, of course that is my way. Although some aspects of reality revealed by science and reason can initially be shocking and hard to accept, in the end facing uncomfortable truths is usually for the best since it allows us to adapt to the world as it actually is. But aging is in some ways a difficult reality to face without illusions. So let us take a bleak but scientific look at aging.

To start with, the word aging can mean different things in a way that can create confusion. Aging can mean getting older simply in terms of calendar time, or it can refer to the changes that one undergoes as one gets older. Such age changes can be positive and involve maturation, such as when older people become wiser thanks to their accumulated experience. Or they can be negative, and involve becoming old and decrepit – and diseased. For clarity’s

sake, biologists refer to this latter kind of aging as senescence. Senescence is the bad part of aging.

Many doctors will tell you that aging is not a disease, but this largely reflects tradition and our lack of understanding of aging. Yes, they will say, as we get older we do get many illnesses, including some that are really awful, such as heart disease, dementia and cancer (and so many others that it is depressing to list). However aging itself is not a disease, they will say, but rather a natural process, like birth and development. Thus, it is often said, what medicine should try to achieve is to allow people to age naturally but without disease. Yet many scientists who study the biology of aging would argue that this does not make sense, since the entire process of senescence is one of deterioration and malfunction. It is true that some old people are horribly ill for months before they die, while others appear quite well until just prior to their death – and that the latter outcome is surely something to aspire to. But to suggest that people who die suddenly had nothing wrong with them does not make sense. If they died, then there must have been something very wrong with them.

## What is aging for?

To fully understand aging one needs to explain what it is there for. We are clearly programmed to age since aging (senescence) affects everyone who lives to a ripe old age. Does this mean that aging has an evolved biological function that promotes the survival of the fittest? Is aging an adaptation, like the tiger's sharp claws or the anteater's long, sticky tongue? Originally it was thought so. Contemporaries of Charles Darwin proposed that by removing worn-out elderly people, aging frees up precious resources thus making the younger generation better able to survive and reproduce. In this way, they argued, aging promotes the survival of the species. But evolutionary biologists have been unable to detect any advantage of this type conferred by senescence.

The key to understanding aging is in this old photograph, taken in 1924 in Okemah, Oklahoma. It shows the family of Woody Guthrie, the great American folk singer and champion of working people. Woody is on the left, with his father Charlie beside him and his brother George in front. The slightly eerie figure behind them is his mother Nora, by this time already experiencing symptoms of the Huntington's disease that would eventually take her life. Huntington's causes severe neurodegeneration and loss of motor control in mid-life, and is caused by an inherited mutation – a bad gene. Most genetic



The Guthrie family at their home in Okemah, Oklahoma (1924). Woody - here on the left - and his mother died of Huntington's.

diseases require inheritance of bad copies of a gene from both parents, but in the case of Huntington's a single bad copy is sufficient; to use the language of genetics, the mutation is dominant. George did not inherit the disease from Nora but Woody was not so lucky, and died at age 55.

For a disease caused by a dominant mutation, Huntington's is unusually common. In the 1930s the British geneticist J.B.S. Haldane reasoned that because Huntington's only appears in middle age, the bad gene has the chance to be passed to the next generation. He realized that this demonstrates a principle: that the later in life a mutation has a harmful effect, the more likely it is to be passed on to the next generation. This predicts that genes with bad effects in late life will naturally accumulate in populations; perhaps, suggested Haldane, this is what aging is? The American evolutionary biologist

George C. Williams then thought about this some more. He noted that a given gene can have different effects at different phases of life, so that a gene might change in a way that boosts fitness in early life, but causes worse health later in life (Williams, 1957). Critically, he argued, such changes could enhance fitness overall, because early benefits can outweigh later detriment. In this way, natural selection can favor a gene variant that promotes senescence – hence aging evolves. This idea of trade-offs between early life benefits and late life costs as an explanation for aging has been supported by subsequent research.

So although aging evolves it is not an adaptation of any sort. Instead, it is a kind of complex genetic disease syndrome inherited by everyone. It is the most formidable disease of them all – and in fact is now the number one cause of serious illness and death in the world. This stark truth about aging is a tough pill to swallow. It is sometimes suggested that scientists are nasty to say things like this, and that it is offensive to old people – as if they did not have enough to suffer already! Brutal honesty is less the traditional way with geriatricians than among scientists. But scientists certainly do not mean to be callous or disrespectful; they simply believe that knowing the truth can help to make things better. There are times when it is better not to reveal a painful truth, particularly when there is nothing that can be done about it. Perhaps that was once applicable to aging, but given our progress in understanding aging, it is not any longer.

## What goes wrong to cause aging?

If aging really is a disease, then what is the cure? Key to treating disease is understanding its origins, its etiology; so to tackle malaria, identification of the protozoan parasite that causes it was critical. But what causes aging? Unfortunately, the answer to this big question is not yet known. Some even say that aging cannot have a cause like other diseases, since aging is not a disease; one simply grows frail and vulnerable to diseases which are not caused by aging itself. Perhaps some people want to hold this view so as to maintain the traditional and comforting view of aging as natural and not a disease. Many theories about the cause of aging have been put forward; scientists like to dream up these theories, particularly when they start growing old and find it difficult to forget about aging – as the young often do. Many of these theories have now been disproven, but there are some that might be true. Almost certainly there is no single cause of aging, but rather many different causes, big and small.

The evolutionary theory implies that aging is the result of the harmful action of genes in later life, but it cannot tell us what these harmful actions might actually be. One theory that has received a lot of attention from biogerontologists is that aging is a process of wear and tear, akin to that which causes old cars to break down or old buildings to crumble. The idea that bodies just wear out after a while certainly sounds common-sensical. The ultimate constituent parts of living organisms are the molecules of life, such as DNA, protein and lipids. It has been suggested that such molecules accumulate damage, particularly because of oxidation: much as metals rust due to oxidation, so molecular oxidative damage causes aging. Thus, over time damage accumulates, leading to diseases of aging. For example, damage to DNA is a major cause of cancer, which is largely a disease of aging, occurring most frequently in the elderly.

Living cells possess many maintenance mechanisms to protect themselves against damage, such as antioxidant defense, repair and replacement of damaged molecules. The molecular damage theory predicts that protection against molecular damage will protect against aging. Thus, in theory one ought to be able to slow aging by boosting maintenance. By the same principle, in the streets of Havana one sees many 1950s vintage Chevrolets, Fords and Plymouths (which are far more beautiful than the dull looking cars of today), their increased lifespan resulting from extensive repair and replacement of their constituent parts.

There is no doubt that molecular damage contributes to aging to some extent. What is far less certain is whether it is the primary cause of the main pathologies of aging that limit lifespan. One prediction of the oxidative damage theory of aging is that boosting antioxidant defenses should slow aging. For this reason one sees antioxidant pills on sale with the claim that they can protect against aging. But thorough tests by scientists have not been able to show that levels of oxidative damage control the rate of aging. Enhancing antioxidant defense in laboratory animals that are naturally short lived such as nematode worms, fruit flies and mice generally does not increase their lifespan. Thus, many biogerontologists now doubt that oxidative damage is the main cause of aging, though the theory has not been entirely disproven.

## Beating aging

Because the causes of human aging have been so difficult to discover, scientists have taken the approach of trying to understand aging first in simpler,

shorter-lived animals. These include the nematode worm *C. elegans*, the fruit fly *Drosophila* and that old favorite, the laboratory mouse. Such knowledge could at least get a foot in the door of an understanding of human aging. Studies of aging in short-lived animals have yielded some startling results that have created a new optimism about the prospects of tackling aging. It turns out that there are many ways to slow aging down and extend lifespan in such animal models. For example, as long ago as the 1930s it was found that dietary restriction, a controlled reduction of food intake, could markedly increase lifespan in rats. Remarkably, in later life these rodents not only showed reduced levels of age-related diseases, but also appeared more youthful, with glossier fur, eyes unclouded by cataracts and generally showing more signs of ratty joie de vivre.

More recently, scientists have searched for genes that control aging in short-lived animals. An expectation from the evolutionary theory is that some genes will increase early life fitness but promote senescence, so that reducing the activity of such genes will extend lifespan. Some such genes have now been found, and these give insight into the nature of the mechanisms at the heart of aging. For example, a number of gene products essential to growth (with names like target of rapamycin [Tor], insulin-like growth factor 1 [IGF-1], and growth hormone) promote aging. In *C. elegans* worms, which normally live only two to three weeks, inhibiting growth control pathways can increase lifespan up to 10-fold and produce lifespans that are the human equivalent of more than 800 years. Thus, it appears that evolution has led to overactivity of pathways that promote growth and development, which enhance early fitness but promote the development of life-limiting pathologies. Consistent with this, overactivity of Tor, for example, has been linked to numerous late-life diseases. Moreover, pharmacological inhibition of Tor can increase lifespan, at least in mice – even when initiated at mid-life (Harrison et al., 2009).

These findings provide several fundamental insights about aging that are of value to anyone wondering about trying to take control of their own aging process. Firstly, they show that the rate of senescence is not fixed, but rather is malleable. That this is the case in short-lived animals suggests that the same is likely to be true of human beings; consistent with this, mortality rates among the elderly have been dropping markedly over the last century in many parts of the world for reasons that are not entirely clear. Secondly, they show that intervening in aging has a specific effect: not to halt or reverse aging, but to decelerate it (i.e. to slow it down). The result of decelerated aging is a slowing of the development of late-life pathologies, leading

to improved late-life health and extended lifespan. Thirdly, it implies that the most effective way to improve late-life health involves prevention rather than cure.

How to beat aging, then? The key, I believe, is the active decision to do so, the earlier in adulthood the better – but it is never too late to take it. Then there is an obvious next step, easier for some than others, which is to follow basic health advice that your family doctor would give you: do not overeat, or drink too much alcohol or smoke, and get a reasonable amount of exercise. Without following these basic rules of self-preservation, more sophisticated approaches to beat aging are relatively futile.

What about actual therapies to slow aging? Here, unfortunately, things are complicated by the existence of a multi-billion dollar industry dedicated to swindling older people by marketing bogus ‘anti-aging’ therapies. Such phony products are advertised and sold widely, and current regulatory arrangements allow vendors to lie to you about them with impunity. These conmen can be highly convincing, even using bona fide scientific papers to claim support for the validity of their fraudulent products. Thus, caution and scepticism is needed; one way to avoid being ripped off is to ask your family doctor for advice about such products.

Work in the laboratory suggests that preventative treatments for human aging (sometimes referred to as geroprotectants) could work in principle. Such geroprotectants could, like some of the treatments shown to be effective in short-lived animals, protect against a broad range of age-related pathologies. Alternatively, they could slow only parts of the aging process, i.e. one or a few individual senescent pathologies. As yet, there are no broad spectrum geroprotectants for which efficacy has been clearly shown in humans. But there do exist narrow spectrum geroprotectants. One example is sunscreen, which has the potential to slow skin aging by reducing damage caused by ultraviolet radiation from the sun.

Sometimes people ask me whether, with my knowledge of the biology of aging, I take anything to stave off aging. In fact I do not, though I have been keeping an eye on the recent scientific literature on the possible preventative benefits of drugs that promote cardiovascular health (such as those that reduce blood cholesterol and high blood pressure). And my daughter is now interested in the idea of life-long use of facial sunscreen, so that she can enter her 70s with relatively youthful skin.

## Aging: to treat, or not to treat?

So, can anything really be done about aging (i.e. senescence)? The good news is that beating aging is almost certainly possible. The bad news is that victories over aging will only ever be temporary: aging will always win in the end. Here one might wonder: if that is so, is it not ultimately futile to challenge aging? I think not. After all, in the end medicine can only ever offer beautiful reprieves, since curing one life-threatening illness only exposes us to illnesses of later life, and the greatest disease of all: aging (Gems, 2011). Life is a precious thing, and in a way every human being is a miracle, to be treasured and protected. Should one fight aging? This is like asking: Should one love life? Or, should one live? Some people cherish life more than others, and if you are reading this and wondering about tackling aging, then you are probably one of those who love life more.

### References

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