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Chapter 4 Understanding Why We Age

We now are prepared to examine in greater detail the new knowledge in biology that has raised the likelihood of a breakthrough on aging. The knowledge can be separated into two large areas that deal with two different questions: Why do we age and how do we age? "Why" we age refers to the underlying reasons for the existence of aging—why have aging bodies evolved in nature? Is there a reason why natural selection has not or cannot design our bodies to last forever? These are the kinds of issues that will be dealt with in this chapter. In contrast, "how" we age refers to the many things that go wrong with us as senescence occurs—from wrinkled skin to loss of muscle mass. The "how" question deals with the specific mechanisms and events that occur within us as we age. I will consider how our bodies age in Chapter 8, and will indicate in Chapter 9 that there likely is a smaller number of causes of aging at the molecular level that underlies the many manifestations of aging that our bodies exhibit as we grow older.

We need to understand why we age if we are to grasp how close we may be to a partial solution to the problem of aging. In this chapter, after discarding some popular, but incorrect, ideas about why we age, I will present an overview of current theories in the evolutionary biology of aging. These theories build from earlier views of deleterious genes to a more sophisticated perspective emphasizing senescence as resulting from evolutionary tradeoffs between reproduction (numbers and vitality of offspring), on the one hand, and body repair and maintenance processes, on the other. Both reproduction and repair and maintenance require considerable energy expenditure by individuals, and most animals, including humans during most of our evolution, have had limited sources of energy. While these evolutionary perspectives are likely not in final form (and few views in science are), they represent a significant advance in our understanding of why we age that developed over the last century.

During the 20th century, theorists grappling with the problem of aging from the perspective of evolution have predicted the existence of deleterious genes that contribute to aging. Other biologists have advanced our knowledge of organisms, their life histories and life spans, as part of the science of ecology. Gerontologists working with the ideas from these fields have contributed to a more sophisticated view of why we age, culminating in Tom Kirkwood's disposable soma hypothesis, which I'll present below. It is Kirkwood's modern view of why we age that leads to an obvious direction in which to look for ways to delay senescence.

Making Way for Baby?

Some of the more traditional views of the reasons why organisms, including humans, undergo senescence came from an incorrect understanding about evolution and the way that natural selection works. For instance, it was once believed by some that aging existed as an aid to the next generation--parents and grandparents were viewed as consuming the limited resources that the next generation needed to survive. Since the parents and grandparents already had offspring, it was thought that the species would be better off if they died to make way for the new generation. While this might sound attractive to some who are impatient for their inheritance, this is not the way that natural selection works. George Williams pointed this out in his classic work (Williams, 1966).

In brief, we don't know of a mechanism within natural selection that would promote parental death just to allow more resources for others. The food or resources saved by early death of a parent might as likely go to another, unrelated individual as to its own offspring, and all else being equal, there is no reason for natural selection to prefer a child over a parent. Premature termination of a parent would cause there to be a reduced numbers of offspring from the parent, the opposite of what natural selection would favor.

Instead, natural selection favors those individuals who produce the most viable offspring--the genes of such individuals will be in greater abundance in the next generation. To the extent that those genes contributed in positive ways to fitness, they will become more abundant in the population, as they contribute to individuals having more offspring than others do from generation to generation.

It is not that parents don't make sacrifices. For an extreme example consider the male praying mantis who risks being eaten by the female just after mating, assuring the mother of nutrition for the development of the newly fertilized eggs. This sacrifice of the male contributes to the female having more, or stronger, offspring of his.

Another case of extreme parental sacrifice comes from certain kinds of hermaphrodite nematodes that carry self-fertilized eggs. Each of these worms normally lays several hundred eggs and leaves them to survive on their own. However, if environmental conditions are unfavorable because of lack of food or dryness, the eggs can remain in the individual parent, hatching and beginning development there. The parent is then called a "bag-of-worms" because that is what it becomes—its insides are replaced by dozens of young offspring, protected for a while by the outer "skin," or cuticle, of the parent. When that outer shell finally breaks apart, it releases the developing offspring into an environment that has had some time to improve, and, thereby, increase the chances of the offspring (and the parent's genes in them) surviving the bad times.

But in these special cases, it is the very offspring of the parents that gain a selective advantage by the death of a parent. Beyond such special cases, there would seem to be no selective advantage in the death of a healthy individual, still capable of having more offspring. In fact, natural selection would promote the continued life of any such individual, so as to maximize the number of offspring that it has.

No "Death" Genes

Consider the opposite situation, with a gene in an individual that causes it to die at a young age to make way for its offspring to have more in the way of food or territory. There is good reason to think that natural selection would act against any such death gene, as can be shown with a simple "thought" experiment. Consider a population, each member of which has a death gene, a ticking time bomb, speeding aging or ending life early. By its nature such a death gene would cause these individuals to die at a younger age than they otherwise would, and at a time when they would still be capable of living and having more offspring were the gene not to be present.

Now imagine a mutation in the death gene that caused it to be inactive. Any members of the population with such a mutation would tend to live longer and have more offspring than those with an active death gene. So, they would tend to increase in numbers over succeeding generations, compared to those with an active death gene. As a consequence, the mutated, inactive death gene would be selected, and fewer animals

would carry an active one as the generations pass. Thus, natural selection favors those without a death gene. Since natural selection would assure that the death gene became inactive in more and more of the population, the idea of a death gene, and the view that aging arises to make room for the next generation doesn't seem to work.

Instead, natural selection would appear to drive populations of organisms toward aging rates that are low enough that individuals have life expectancies allowing them to fulfill their reproductive potential. For different organisms, that length of time will differ. Members of our species, *Homo sapiens*, during most of its 200,000 or so years of existence, are believed to have lived, on average, only 15 to 25 years (see Chapter 1, Figure 3). It is only in the last 100 years or so that we have begun, in some nations, to have average life expectancies of more than fifty years. Considering such an evolutionary history, natural selection has done pretty well by us, allowing most of us in developed countries to live over 70 years, with a little help from our lifestyles, modern technology, and medicine. One reason we have as many years as we do may relate to our extended period of care for offspring—young children who lost their parents in centuries past would be at higher risk for not surviving themselves. It paid to have parents who would survive long enough not only to have children but also to provide their children a protected learning environment until adulthood.

On the other hand, there would appear to be no reason for over-design of body survival well beyond that normally experienced by a population of organisms, especially if the energy expended on such an over-design could be re-oriented to promote reproduction and/or offspring survival. That may explain the timing of our senescence, and the varying senescence rates seen for other organisms in zoos or protected environments.

We will see that, as environments change, the length of life for populations can evolve in succeeding generations by natural selection, as I give a specific example for opossums in a later chapter. Many studies of fruit flies, where, generation after generation, those that are selected to have offspring later in life (artificially, by allowing only late offspring to produce the next generation), show increasing life spans. Humans could experience the same thing, through generations, if we keep having babies later and later in life. That will select against the genes currently in our population that predispose death at younger ages today. But the change would be very gradual, through many generations, and result from the selective reduction of genes from those who die before having as many offspring as the average. This is not the solution that I am proposing will give us a dramatic increase in life expectancy in just a couple of generations, but we will see that animals studies do give some insight into the gains that might be possible by more general manipulations, and how these gains are achieved.

Has Evolution Been Unable to Figure Out How to Avoid Aging?

Another, once-common misconception about why we age is that evolution through natural selection has not been able to "figure it out" and prevent aging from occurring. This view would suggest that most populations of animals would live longer and longer with passing generations as evolution and natural selection got rid of the errors and mistakes that cause aging.

Some with this mindset might even think that mice don't live as long as humans because humans evolved later, so more of the mistakes were "fixed" by the time we came

along. Actually, this turns reality on its head. Mice, having evolved earlier, have had a longer time, as a species, to fix any such errors. By this simplistic analysis, one might conclude mice should live longer than we do! In reality, today's mice and today's humans both evolved from a common ancestor, tens of millions of years ago, and our rates of aging have evolved to match other life history characteristics for each of our species.

Natural selection is not directly concerned with life spans. Reducing aging is not a direct goal of natural selection. In fact, through natural selection, a population could evolve to show a reduced average life expectancy (over a number of generations), if there is some way that the average individual, over that shorter lifetime, could be made to produce more viable offspring. For instance, there is little reason for an insect to expend extra energy to gain the potential to live many years if it cannot avoid freezing to death during its first winter. Instead, for such an insect, natural selection during evolution will press for its energy to be spent producing a few more offspring during the summer, leaving more larvae in the ground to over-winter.

The main point is that the rate of senescence is indirectly selected, as a consequence of other environmental influences and life history traits. Natural selection adjusts longevity and other life history traits as it attempts to maximize the number of viable offspring that an individual has, given the environment.

Different Strokes for Different Species

We can see the consequences of life history "decisions" made through natural selection by examining the varieties of life histories and life spans among different species. Life spans show a tremendous range, from some trees that live thousands of years to some insects whose adult life span is measured in hours, and the life span differences seem to be linked to other life history traits, as would be expected. Because of such links, scientists have observed a number of correlations when traits such as body size or number of offspring from a bout of mating are compared to life span. Some organisms live life in the fast lane, developing to adulthood quickly, having offspring early, not investing much in repair and maintenance, and aging rapidly. Others develop more slowly, often with parental support, usually have multiple bouts of reproduction, invest more in repair and maintenance, and age more slowly.

Of course, one primary factor that drives selection for these various life history traits is initial mortality rate. The life history traits set the level of investment made in longer life spans for a species. If animals are subject to predation at high rates, they need to mature fast to leave offspring before they are dead and won't need as high a level of repair and maintenance because they are going to die soon anyway. Organisms that are dying at high rates from predation, infections, or injuries, need to mature fast to leave as many offspring as possible before death from causes unrelated to aging.

Animals that show reduced initial mortality rates from predators, infections, and accidents tend to evolve a lower rate of aging—an added investment in repair and maintenance pays off for these organisms because they are more likely to remain alive longer. By investing in greater maintenance, they help assure that they will still be healthy for reproduction later in life. With lower initial mortality rates, natural selection may also find reproductive advantage in allowing a more extended development time,

and a larger investment in a smaller number of offspring, allowing offspring to be more robust and to increase their survival probability.

These life history differences drive the level of investment in repair and maintenance processes in the individual. Organisms need to stay vigorous and healthy long enough, but only long enough.

The Declining Force of Natural Selection With Age

An earlier generation of researchers, including Haldane (1941), Medawar (1952), and Williams (1966), paved the way to our current understanding of why we age by suggesting the existence of certain genes that, while not "death" genes, could be involved in aging. These were of two kinds-- deleterious, late-acting genes, that have negative effects only late in an organism's life and antagonistic pleiotropic genes (which I'll define shortly).

The reason these two kinds of genes come to exist is crucial to understanding the current view of why aging exists. These two "bad" versions of some genes are thought to be present in populations because of the declining force of natural selection with age. The force of natural selection declines because, as organisms within a population grow older, there are fewer and fewer of them still alive, and those remaining have already had most, or all, of the offspring they will ever have. Inevitably, with age, even without senescence, fewer individuals are left alive because of deaths due to illness, accidents, and predators. Only those left alive can still contribute offspring, and as their numbers decline, they are contributing fewer and fewer offspring to the next generation. As a consequence, the ability of natural selection to act on problems that arise late in the natural life of organisms is reduced, or, in other words, the force of natural selection declines.

There are fewer survivors at older ages because they die of other causes—injury, infection, predation, etc. This is without even considering the effects of aging--even without aging, we all eventually die, as we saw in Chapter 3. Because fewer are still around at older ages, they can contribute fewer total offspring to the population, compared with younger individuals—if only 10% of a population lives to age 40, then, all else being equal, they will contribute only 10% of offspring. Older individuals contribute less and less to the next generation because there are fewer and fewer of them to make the contribution. This explains the declining force of natural selection with age. It makes it harder for natural selection to "fix" problems that pop up late in life because the extra contribution of offspring by individuals who avoid such problems becomes smaller and smaller as their numbers do.

As a result of this decline in the force of natural selection, there are two kinds of genes, or versions of genes called alleles, that are postulated to be present in populations, including humans. One of these consists of deleterious, late acting gene alleles. Simply put, if a gene, or a version of a gene, has bad effects that only show up late in life, this is a deleterious, late acting allele. These will be hard for natural selection to eliminate from the population, and the later they act during life, the harder it is to eliminate them. Consider a gene that has a breakdown product that does not get digested all the way. The partial breakdown product might not cause any harm in our youth, but could build in concentration in our cells with age. If it only causes a problem at an age when most of the members of a population have already died of other causes, or have become post-

reproductive (have ceased having offspring), then natural selection might have a very hard time "fixing" this deleterious, late-acting aspect of the gene's function. In fact, it is possible that a number of genes of this sort might exist in a population, all having detrimental effects only late in life. We will later see that such a partial breakdown product that is not properly removed from the brain might cause Alzheimer's disease.

Another kind of gene might actually have good effects early in life, benefiting the organism or its offspring, but its action can causes problems later in life. These are called antagonistic pleiotropic genes or alleles. Genes that are pleiotropic have more than one effect, and those that have opposing effects, early and late, are called antagonistic. An example of an antagonistic pleiotropic gene might be one that causes release of higher levels of stress hormones in response to a threatening situation. The individual who produces such responses might be more likely to survive an early threat, but might undergo irreversible body damage that would mount with repeated stresses as one goes through life. We think that something of this sort actually occurs with the glucocorticoids and mineralcorticoids, which are hormones we release in response to long-term stress situations. These hormones, and the genes whose products produce them, cause increased salt retention and fluid retention, leading to higher levels of blood pressure. This state might indeed help us in certain kinds of stressful situations in the short run, but is known to increase the risk of heart disease and stroke in the long run.

These ideas about antagonistic pleiotropic genes and deleterious, late-acting genes or alleles contributed to our understanding but, alone, they leave us with only a partial explanation of why we age. They suggest that damaging effects of genes tend to cluster late in life. In future chapters I will refer to these views by writing about deleterious, late acting genes, but realize that I am speaking also of antagonistic, pleiotropic genes as well, when I do.

Here I will add an idea of my own that may not be shared (yet!) by most gerontologists. I suspect that deleterious, late acting alleles of genes primarily play a role in aging as contributors to age-related diseases, rather than being responsible for the underlying causes of aging. We are beginning to find deleterious versions of genes related to a variety of age-related disorders—genes versions that predispose us to particular cancers, others that contribute to higher risks of heart disease, etc. For example, there are three variants of apolipoprotein E in the human population, E2, E3, and E4. Having one copy of E4 increases our risk of both heart problems and Alzheimers, compared to version E2 or E3. That risk is further increased if one is unfortunate enough to have two copies of the E4 variant. My suspicion is that these late-acting, deleterious versions of genes have age-related diseases as their primary consequence, and that the underlying causes of aging are distinct from most of these deleterious alleles.

Kirkwood's Disposable Soma Hypothesis

Genes that are detrimental over the long haul appear to be part of the story, but Kirkwood (1977, 1999) has produced a view of why we age, and has packaged that view in a form that allows one to combine evolutionary insights with knowledge from ecology and population studies.

More and more, we are realizing that life span differences between different species may be due not only to the specific genes, found in an individual but also to the

levels of expression of some of the genes, especially those genes involved in repair and maintenance. Variations, or alleles, for particular genes can make a difference in longevity, as we are now seeing by examining the genes present in human centenarians (those who have lived 100 years or more), but, while these gene variants may allow us to avoid early deaths due to heart attacks or particular cancers, the genes and other DNA sequences that we probably need to focus on for reducing aging are those which more generally set the rate of ticking of our biological aging clock. I will describe some of these important genes and the functions of their products in more detail in a later chapter, but they protect the integrity of our molecules of life—DNA, protein, lipids, etc. The level of expression of these repair and maintenance genes appears to be a key factor in determining the rate at which we age.

If we look at different kinds of animals, we see a wide range of life spans. On average, mice live a couple of years in the protective environment of a laboratory; some dogs can live more than fifteen years in a good home; and humans typically manage seventy-five to eighty years in the protected environments offered by most developed countries. All three are mammals, and we can compare their mortality-rate doubling times. Mice have MRDTs of about one-quarter of a year; dogs have about 3-year MRDTs, and human populations take about 8 years to double mortality rates. MRDTs typically increase with species lifespan. Shorter-lived animals tend to have quicker development to maturity, multiple offspring at a time, and increased chances of an early death due to such non-aging causes as predation, injury, or infection, as we have discussed.

Natural selection has driven those with shorter lives to rapid development and reproduction, as this is necessary to preserve the species. If it took mice as long as it takes humans to mature, all would die before reaching maturity, and the species would go extinct in a single generation. Since mice have short live spans whether they age or not, natural selection will not favor the investment of resources and effort to preserving their bodies much beyond the time they normally live. Consider a mouse with DNA and protein repair mechanisms that would allow it to live for, say, 20 years. If some of the energy that such a mouse devotes to keeping its DNA repaired and its proteins fresh could instead be redirected to allow for the production of an additional offspring, or to its offspring having a bit more weight at birth, that trade-off would make the mouse more fit, in a Darwinian sense, even if potentially shorter lived. Making such a trade-off would cause its body to age at a bit higher rate because of the mounting DNA and protein damage, but it was not going to live to be 20 years old anyway. The change in DNA and proteins might hardly be noticeable in a mouse that will die before reaching two years of age, and it would have another offspring to show for it—a no-brainer for natural selection.

Humans have experienced similar evolutionary pressures. This is the crux of Kirkwood's disposable-soma theory. "Soma" means "body," and our bodies are, literally, disposable according to Kirkwood. What is more important for natural selection is that we maximize the potential number of healthy offspring that we leave behind, given the environmental stressors and risks with which we have evolved. Thus, the current view of why we age is that evolutionary trade-offs between reproduction and maintenance are responsible for the observed aging rates in humans and other organisms. Some of these repair and maintenance processes also can delay the effects of deleterious,

late acting alleles and antagonistic pleiotropic genes by helping to repair or renew damaged molecules or cells that cause the deleterious effects, or by more rapidly repairing damage before it becomes irreversible.

But notice that the underlying, evolutionary justifications for these trade-offs between reproduction and maintenance in humans are largely irrelevant to our culture today because the enhanced, early reproductive abilities of humans go largely unused today (at least among most of us in developed countries). Not too many 11-13 year olds are having babies, and most men and women only have a few offspring, at most, over the course of their lifetime, by using various forms of birth control. With education, women decide to have fewer offspring, and we need only look across the last several generations to witness the smaller average family sizes and later time of first offspring.

We now are living much longer than average humans did prior to the development of civilization. Consider the set of survival curves shown in Figure 3 (in Chapter 1). For most of human evolution, as depicted by the "Stone Age" curve (filled circles in Figure 3), our ancestors were lucky to be alive at age 20, and only a small fraction lived to see 50 years. During most of human evolution, with our shorter life expectancy, with females going through menopause at age 45-55, and with males experiencing declines in fertility with age, there was no reason for natural selection to influence our genetic make-up so as to favor average longevity beyond 75 or 80. Given our history, it is remarkable that we are able to live as long as we do.

Of course, natural selection can drive repair and maintenance levels both higher and lower. If a population of organisms experiences an increased level of predation, perhaps because a new predator has recently been introduced into the environment, natural selection might well press for low investment in repair and maintenance as the energy is invested in faster development and earlier sexual maturity instead.

What is Meant by Repair and Maintenance?

I use "repair and maintenance" to refer to a variety of mechanisms that have evolved to allow cells and organisms to maintain function. Living things are not unlike inanimate, mechanical objects in their tendency to incur damage. While we have to bring our cars in for repair and service, our bodies are designed to undergo repair and maintenance even without visits to the doctor.

In molecules like proteins, damage can consist of chemical changes—additions, deletions, or modifications in the molecular structures that compose the protein—or can simply be the unfolding of the shape of the protein, which destroys proper functioning of most proteins. The repair and maintenance processes for our proteins include a set of chaperones, also called heat-shock proteins, which are able to help other proteins to refold after they have lost their active shape, or conformation. There also is a marker system that signals destruction for unfolded or otherwise modified proteins that cannot get properly refolded. A small molecule called ubiquitin is linked to such proteins, and several such ubiquitins on a protein allow it to be recognized and destroyed by a special protein complex called a proteosome. We are constantly making new proteins to replace the destroyed ones. The average protein in a human lasts only about two weeks (but some have much longer lifetimes, as we will see later).

This repair and replacement of proteins comes with a cost—constantly building new proteins takes energy, which we gain from the food we eat. The repair and turnover

systems for proteins are very good, but not perfect. As we age, a small, but growing, proportion of the proteins within us are damaged in some way, and the damaged, sometimes partially degraded proteins can build-up in cells, causing or contributing to such disorders such as Alzheimer's disease.

In the case of DNA, our genetic material, any chemical modification or change in proper base sequence can lead to mutation or malfunction. There are numerous repair mechanisms for our DNA, each selective for a particular kind of damage to DNA. For instance, the DNA in skin cells can be damaged by ultra-violet radiation from the sun—the same U.V. rays that can cause skin cancers. There are special repair proteins that search along DNA molecules for the kind of damage that the U.V. light is most likely to cause--thymine dimers, where two, adjacent thymine-containing nucleotides in the DNA are chemically linked together. The repair enzymes recognize the thymine dimer, excise it, and replace those nucleotides and nearby ones on the same strand, using information from the other strand of DNA to determine the proper sequence of replacement nucleotides. This is but one example of a DNA repair system among many. DNA is too important a molecule not to have a variety of protectors readily available. Of course all of this repair machinery has a cost, and the more one makes of each kind, the more likely that a repair will be made, but also the more the energy cost, as with the protein replacement machinery. In dividing cells, the challenge is to repair the DNA before it is replicated (copied). If copied when damaged, a mutation is a likely result in one or both daughter cells. High levels of DNA repair systems might repair 99.9% of the damage in time, and even higher levels might protect against 99.99% of such damage, with ever greater energy costs for the higher levels. It is the remaining, unrepaired 0.1%, or 0.01% of damage that contributes to senescence and can contribute to such age-related diseases as cancer.

A very different kind of maintenance system, quite beyond that for such important macromolecules as proteins and DNA, arises from the need to maintain differences in concentrations of materials in different compartments within and between cells. One of the most significant of these is critically important for the proper functioning of our brains. The electrical signals critical to neurons and neuronal activity depend upon ion gradients between inside and outside of each neuron. Sodium ions are much more abundant outside of our cells than inside, while the opposite is true for potassium. There is a special protein pump in the membrane of neurons that maintains high sodium outside and high potassium inside by pumping sodium from inside to out and potassium from outside to in. That pump uses ATP as an energy source. Indeed, this sodium-potassium pump is responsible for much of the energy consumption in the brain. Its role is critical in that the brain cannot function without the proper ion gradients, and the constant energy investment that the brain makes to maintain this gradient is unavoidable. There are similar maintenance tasks involving a variety of pumps that distribute molecules and ions between inside and outside of cells, as well as among compartments within cells.

Thus, there are a variety of mechanisms that maintain healthy cells, and these carry with them a considerable energy cost. We will examine these in more detail in Chapter 9. Kirkwood's suggestion that the balance in energy expenditure between reproduction and repair and maintenance should now be a bit more understandable—keeping us from falling apart is costly, energy wise, and the investment that is made can limit the energy that is left for reproduction. Obviously, natural selection would seek a

balance, allowing enough investment in repair and maintenance to allow an organism to live long enough to reproduce, but not investing so much as to detract from the number and quality of offspring produced during a normal length of life.

Stress Tolerance, Repair Mechanisms, and Longevity

Repair and maintenance, stress tolerance, and longevity are interrelated. It would appear that, during development, animals can be "built" with enhanced levels of tolerance to a variety of environmental stressors. For simpler organisms, in the laboratory, stress tolerance can be examined by desiccation, starvation, exposure to oxidative molecules, and temperature extremes. Those less able to tolerate such stressors are frailer, and also are more likely to die at younger ages due to environmental stresses. Repair and maintenance processes keep cells and tissues organized and fix or replace the molecules, cell parts, or whole cells that exhibit damage. Some of the mechanisms underlying stress tolerance are related to repair and maintenance. For example, because high temperatures denature (unfold) proteins, one aspect of tolerance to temperature is the repair process for refolding or replacing denatured proteins. That process is linked to normal repair and maintenance for proteins—the same chaperone system of folding new proteins or refolding those that unfold operates in both cases. Enhancing tolerance to heat involves an increased production of these heat-shock proteins, or chaperones, which help refold heat-damaged proteins. But some stress tolerance goes beyond simple repair. For instance, in the case of starvation, insects that generate greater stores of fat during larval development show higher resistance to starvation. Most generally, individuals that combine high tolerance to stress with high levels of repair and maintenance tend to have longer life spans.

With our evolutionary explanation for why we age, we are in a position to appreciate why some organisms and cells age more slowly than we do, if they age at all. That is the subject of the next chapter.