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Chapter 10 Learning from the Birds and Bees (and Worms): Aging Can Be Slowed

Adding Life

What evidence is there that aging can be delayed significantly? Biologists have found several different ways to increase life spans in a variety of animals, from small increases to five-fold extensions of life expectancy. Longevity has been increased by both genetic and environmental changes. In many of the more extensively studied cases, the life span extension seems to involve an increase in the expression of repair and maintenance proteins, as might have been predicted by our understanding of why we age, and this observation further strengthens the main thesis of the book—that we are close to knowing how to increase human life expectancy significantly.

Simple genetic changes have produced longer life expectancy in more than one kind of organism. Even changes in just one gene have resulted in doubling the life span of one organism. These studies extend those described in Chapters 5 and 6, where we examined organisms and cells with naturally long life spans as well as special states that some animals can use to extend their life expectancies. I will examine three animals in which genetic mutations have been shown to increase life span: nematode, fruit fly, and mouse. We will see a common theme in a number of the cases of life span increase—a rise in levels of repair and maintenance proteins. While there are other kinds of mutations that increase life span in other ways, it appears to be common among these animals that increasing repair and maintenance is one way to do it.

We also will see a common theme in a particular biochemical pathway in the cells of these organisms—the insulin and insulin-like growth factor (IGF)-1 pathway. As you probably know, insulin is a hormone involved in glucose uptake into the cells of the body. The insulin hormone itself actually is a small protein, and there are other proteins similar to insulin, called insulin-like growth factors, that play roles in the growth and survival of cells. We will see that involvement of the insulin/IGF-1 pathway, which appears linked to the expression of repair and maintenance genes as well as to important aspects of metabolism in cells, is a common feature of many longevity enhancement interventions in animals. However, I don't want to suggest that activating this particular pathway will extend life in humans. Such a pathway influences a variety of processes in humans, and not all of them may be beneficial for life extension (Jazwinski, 2005). We will need to find ways to selectively enhance expression of repair and maintenance genes in humans, and that might well involve parts of this pathway, and perhaps parts of one or two other pathways. That is a big piece of the remaining puzzle for those interested in lengthening human life. Nevertheless, these studies demonstrate the possibility of such life extension in other animals and suggest pathways to begin to examine and explore in humans.

I will not say much about another model organism—yeast. The story there has been complex and not always directly relevant to aging in other organisms. A recent review by Rine (2005; see also Sinclair and Guarente, 1997, and Sinclair, 2002) points to some of the complexities and twists-and-turns in this ongoing work. Some useful results may come from it, but it is too early to tell. It has produced an interest in Resveratrol, a compound found in small amounts in red wine, and in Sir2 and other sirtuin genes which may play a role in life extension from caloric restriction. There also are indications of a

correlation between longevity and stress resistance, as found in other model organisms. Thus, these studies have been useful and have related, and even extended, some of the work in other "model" organisms that I will discuss, but the details are still unfolding.

We will examine studies of human centenarians (those 100-years-of-age and older) that indicate that special variants of some genes, combined with the right lifestyles, predisposes us to longer lives. The examination of centenarians by scientists such as Tom Perls is contributing to our understanding of what versions of human genes might be involved in reaching extreme old age. From what is understood at this time, there appear to be particular types, or alleles, of some genes that help carry humans to today's centenarian extremes (Perls and Terry, 2003). Some of these may be involved in reducing the chances of getting particular age-related disorders.

Environmental influences also can trigger dramatic changes in longevity. I will look at the social insects—ants and bees, where simple diet changes can induce a 50-fold longevity increase. Getting closer to humans in an evolutionary sense, we also will examine the role that calorie restriction plays in increasing life expectancy in mammals. Under the right circumstances, diet or calorie restriction has been confirmed to increase life expectancy by 30% or more in rodents, and current studies in primates show high promise as well. This is the one environmental influence that has been shown to significantly increase life expectancy in mammals by what appears to be a slowing of the rate of aging. Another recent study in mice indicates that there is a hormone-producing gene that can contribute 20-30% increases in life span when it is overactive (Kurosu, 2005). The gene is called Klotho, after a Greek goddess. I'll discuss Klotho in more detail later in the chapter. In both cases, there may be involvement of the insulin/IGF pathway, as with many of the mutants that extend life expectancy.

Humans already possess a decent life span—we among the longest living mammals, along with such large animals as elephants and whales. The human record currently is 122 years. Even if some shorter-lived animals can show life span increases, in part by increasing repair and maintenance gene expression, are humans already at or near a limit in terms of avoidance of aging? Are our repair and maintenance gene products and our environments already at or near limits that prevent any further increase in life expectancy beyond an average of, say, 80 or 85 years? We began to address this question in Chapter 6 when we examined organisms that live much longer than we do. Clearly, other organisms have found ways of surviving for many more years than we do. In Chapter 9 we learned of the important role that free radicals and oxidative damage play in causing senescence. Here that knowledge will be used to help us appreciate the positive news for potential human life extension that comes from birds and bats.

Genetics--Aging Mutants

Nematodes

Some may be puzzled about why scientists seem to choose such strange organisms for their studies. Why, for instance, do we choose to work on nematode worms when we want to know about aging? One reason involves the rate at which progress can be made in solving a particular scientific problem. Selecting the right organism can save many years of work.

In the 1960s, Sidney Brenner searched for an animal that would serve as a good model system for studying animal development. He selected the nematode,

Caenorhabditis elegans, which contains fewer than 1,000 cells (compared to trillions in a human), can be grown easily by the thousands in a single petri dish, and develops from egg to adult in only three days. For those of us interested in the biology of aging, the nematode has the additional advantage of reaching old age in only two to three weeks.

Most of the nematodes growing on a petri dish are hermaphrodites, meaning that they produce both eggs and sperm, and, in the case of nematodes, these hermaphrodites also can self-fertilize. This may make for a dull sex life, but it certainly helps genetic studies and makes the isolation of mutant strains easier.

Some years ago, I studied a hermaphrodite that was not self-fertilizing--the sea hare, or sea slug. Since they still each make both eggs and sperm, groups of sea slugs can form mating strings, and even circles, with each member serving simultaneously as both male and female. Now that's group sex! The sea slug would not have been a good choice for mutant studies related to aging because of its longer reproductive cycle and the difficulty in maintaining large numbers, but it served me well for some studies on single neurons because these slugs had very large nerve cells. Different scientific questions can best be advanced by different model systems. Brenner's nematodes would not have been a good choice for my studies of proteins in single neurons, but I was quite happy that he and his colleagues had done their pioneering work when I chose his model animal for some genetic studies of aging in my own lab. Brenner and a couple of his co-workers were properly recognized for their efforts with the little worms when they were awarded a Nobel Prize in 2002.

By the time I began aging studies in the nematode, Michael Klass (1983) already had isolated a mutant worm with extended life span, and Tom Johnson (1990) had explored the nature of the mutant and named the gene in which it was found, *age 1*. The mutant lived almost twice as long as the normal, wild-type nematode. It had a greater MRDT, suggesting that it had a reduced rate of aging.

Serendipity in my lab actually played a small part in determining the way that the mutation in the *age*-1 gene extended life span. It was in late August, 1992, a time that is impressed deeply on all of us who then lived in south Florida. Hurricane Andrew hit just as I was in the middle of a study of the *age-1* mutant strain, comparing its life span with the wild-type (non-mutant) strain of nematode. In an earlier comparison of the pairs of strains, the wild type had lived for a maximum of three weeks, while a few of the mutants managed to live for more than five weeks. In the study I now call my Hurricane Andrew serendipity study, the power went off in my laboratory for about three days due to the hurricane. Without air conditioning, the temperature got much higher than these nematodes, which were originally isolated in England, seemed to like. As a break from hauling downed trees out of my back yard, I came over to my lab daily to update the experiment. Most of the wild type organisms were dead by ten days of age, much earlier than usual. However, the mutant strain hardly seemed to notice the temperature change! Its life expectancy did not seem to be significantly altered by the heat, which was a most unusual situation, especially for an invertebrate. I shared my serendipitous observation with Tom Johnson, and he and his colleagues quickly confirmed and extended the finding that the mutant organisms resist high temperatures.

It was easy to guess that the most likely explanation for the increased temperature-stress resistance was that these animals had higher levels of a class of repair proteins to protect them against the effects of heat. This class of proteins had already

been well studied by others. They were originally called heat-shock proteins since high temperatures induced their production. These heat-shock proteins now are also called chaperones, because of their role in keeping other proteins properly folded. They are very useful under heat shocks because proteins tend to unfold at higher temperatures, and the chaperones refold the proteins, allowing them to continue to function. The mutant nematodes seemed to have higher levels of these protective molecules already present. Combining this result with that of others, who had already shown that *age-1* mutant animals were resistant to oxidative damage, suggested that these mutants had increased levels of a variety of repair and maintenance proteins, allowing them to resist a variety of stress conditions.

It was not long before Cynthia Kenyon lab, and others, were able to show that several genes in the daf (dauer forming) pathway also were able to increase life span in the nematode (Dorman et al, 1995). *Daf* mutants are in the dauer pathway that was described in Chapter 6. Nematodes in the dauer state are developmentally stalled larva that are able to extend their life expectancy while waiting for more favorable environmental conditions. In fact, it has now been shown that the *age-1* gene is identical to a gene that had already been identified as a *daf* gene. That gave us deep insight into how life span was being increased. These age-extending mutations were allowing nematodes to live much longer because, it appeared, they had induced part of the dauer state, enhancing the production of repair and maintenance systems. However, the entire dauer state was not being induced, because the mutant worms became adults.

In these nematode mutants, we have a confirmation of the idea that increasing repair and maintenance can produce a longer life span. Further studies have shown that, in this particular mutant nematode, longevity increase involves the regulation of gene expression through a signal pathway containing insulin-like growth factors, similar to a pathway that humans possess. In nematodes the pathway begins with DAF-2 (the capital letters indicate the protein product of the gene *daf-2*), which adds phosphate groups to DAF-23 (AGE-1), which in turn adds phosphate groups to another molecule. They team up in a cascade of phosphate group additions until DAF-16 is reached. This sequence of phosphorylations is not an unusual way for a signal to be transduced in a living cell. DAF-16 is a transcription factor (a direct regulator of gene expression) that is inactivated by the addition of a phosphate group. If the pathway is disrupted, such as by a mutation in the *age*-1 gene, DAF-16 remains active, enters the nucleus, and, increases expression of genes that specify a variety of repair and maintenance proteins, including anti-oxidants, proteins that protect against heat damage, and DNA repair proteins. These *daf* genes are part of the insulin/IGF-1 pathway that I mentioned above. We are tapping into this regulatory system with the mutants that extend longevity in the nematode.

In humans, there are three genes that are evolutionarily related to DAF-16—FOXO-1, FOXO-3, and FOXO-4. These genes in humans are known to regulate expression of genes involved in oxidative stress, DNA repair, apoptosis, and growth control. However, the story in humans probably is more complex, and I don't want to indicate that the solution is just around the corner (Jazwinski, 2005). The FOXO genes in humans may do much more, and one probably would want to activate just the subset of processes that relate to repair and maintenance if one wished to try to increase life expectancy.

You might wonder about humans and nematodes sharing the same kinds of genes, especially since our last common ancestor with a nematode existed several hundred million years ago. But, from other perspectives, perhaps it should be no surprise that there are similar genes and genetic regulatory pathways between worms and humans. If we examine the 19,000 genes that have been sequenced in this nematode, a good number are similar to those that are found among the 25,000 (more or less) genes that humans possess. Although we look very different from nematodes, and several hundred million years have passed since we had a common ancestor, we still share a surprising number of genetic and physiological features—muscles, nerve cells, and digestive track, to name a few. At the same time, we cannot expect complex control pathways to have remained exactly the same, and it will take more studies before we know what pathway, or part of a pathway, would be the best one to activate or suppress in order to up-regulate the human genes needed for repair and maintenance. It also will take more studies to determine how, exactly, to stimulate this particular pathway or sub-pathway.

My former student, Yulong Yang, and I managed to find a mutation in another aging gene, *age-2,* which increased average life expectancy and maximum life span by about 20%.[5] When we combined it with the life-extending *age*-1 mutation, more than a doubling of life span resulted. In contrast to the age-1 mutant, the life span increase seen in *age-2* mutants seemed to be the result of a lower initial mortality rate. In *age-2*, the increase was largely due to an actual slowing of the increase in mortality rate that reflects senescence. The combined mutants showed decreased initial mortality as well as a reduced rate of senescence with age. Kenyon and others have also combined some of their age-extending mutations, and such combinations can produce more than five-fold increases in life expectancy for the *C.* elegans nematode.

The life-span increase does come with a fitness cost, which can be seen if the *age*-1 mutant animals are grown alongside the wild-type animals. It has been shown that, while the mutant nematodes with longer life spans compete well with wild-type animals when food is abundant, under conditions where food abundance varies, the wild-type animals out-competes the mutants, and the mutants become less abundant each generation (Walker et al, 2000). That such environmental conditions detrimental to the long-lived mutants exist should not be surprising. Were there to be a selective advantage for the mutant in the wild, where food abundance can vary, selection for the mutant would already have taken place. However, this study suggests that the cost for longer life spans is quite manageable in this case--just keep the food abundant.

So, what do these animals exhibiting extended life look like as they get older? Do they begin to decline and then show extended periods with high levels of morbidity before they die? There is something unavoidably enticing about seeing 20-day-old wild type and *age*-1 mutant animals on the same petri dish. Most of the surviving wild-type animals at that age are barely able to move their heads around, and some animals, near death, only move when prodded. In contrast, most of the *age-1* mutant animals are still scurrying around the dish like younger wild types, and continue to do so for many days. It would appear that their extended lives are vigorous. They do exhibit declines, but these occur later. This is especially true of their muscles, which deteriorate towards the end of life, but later in the mutant. There may be some aspects of aging in the nematode, related to reproduction, that are not delayed by the mutation (Herndon, 2002).

Fruit Flies

Several different research labs, including those of Leo Luckinbill, Michael Rose, Robert Arking, Linda Partridge, and Philip Service, have bred the fruit fly, *Drosophila melanogaster*, over a number of generations, selecting either for stress resistance or late offspring. In this way, they were able to observe the evolution of strains that have higher levels of stress resistance or have offspring later and later in life. In all cases, the animals also were found to have longer overall life spans. After 25 generations, life spans can increase by 25% or more. In one strain that was studied in more detail, the females actually were more active than the normally selected animals, ruling out the possibility that the longer-lived animals had just slowed their metabolism. Such artificial-selection approaches show that the potential exists in these animals to evolve increased life expectancy, given the right conditions. In some of these longer-lived strains, the larvae take more time to develop and grow to a larger size before becoming adults. They also exhibit increased resistance to such environmental stressors as starvation and desiccation (drying).

More recently, several mutations in fruit flies have been found that show increased life expectancy, extending to another organism what had already been shown in nematodes. One example of a fruit fly with extended life is the so-called *Indy* mutant ("I'm Not Dead Yet") that nearly doubles life expectancy in the fruit fly. The *Indy* mutant was identified by Blanka Rogina and colleagues in Stephen Helfand's laboratory (Rogina, 2000). It flies just as fast as the wild type and has the same resting metabolic rate, but manages to about double its days on earth. The mutated gene is related to metabolism in the fly. The view that alterations in energy metabolism are involved in the *Indy* mutant points to the possibility of reduced production of free radicals and free radical damage contributing to life expectancy in the fly.

A relationship between life expectancy and ability to resist oxidative or heat stress was found in another mutant that extends life expectancy in fruit flies by 35%. This is the *methuselah* gene mutant isolated by Yi-Jyun Lin and coworkers in Seymour Benzer's laboratory (Lin et al, 1998). Of course, the mutant is named after the biblical character purported to have lived a long life. Here we see a similar increase in stress resistance occurring in this long-lived mutant to that we saw in the nematode *age-1* mutant, pointing again to the contribution of repair and maintenance processes to life expectancy.

Mice

For those who think that examples from invertebrates are not enough, there are mutations in mice that significantly extend life expectancy (Flurkey et al, 2001). Two of these are the Snell and Ames dwarf mutants that live 50-75% longer. These mutants impact on the pituitary gland's release of hormones that govern metabolism in the mice, as well as their size. Among the specific findings is that a reduced production of Growth Hormone appears to lengthen life in mice. The mice show reduced aging in their immune system and connective tissues. It is possible that that changes in general metabolism underlie the increased life expectancy of these mutant animals, suggesting at least the possibility of a contribution to life expectancy from a reduction in the rate of accumulation of free radical damage in the mutants.

Of course, such a result also suggests great risks of reduced life expectancy for those who decide to take growth hormone injections. Such injections are regularly being offered by some physicians, but are not approved by the U.S. Food and Drug Administration as safe or effective as an attempt to combat normal aging in humans.

Recently there has been a report of a gene product in mice that acts like a hormone and may enhance life expectancy. If one disrupts the gene, animals show many early signs of aging and die younger than normal animals. Most recently, scientists have over-expressed the gene in mice, producing more protein product, and found 20-30% increases in life span as a result (Kurosu, 2005). This gene is called Klotho, and it is found in humans as well as mice. It is expressed in kidney and brain, and a fragment of the protein specified by the gene is found in blood, where it may be acting as a hormone. Klotho appears to modulate the insulin/insulin-like growth factor pathway. Remember that this is the same pathway that is modulated by long-lived mutants in nematodes and flies. Only further experiments will tell us whether something like Klotho would work and be safe in humans, but the discovery of this aging-supressor hormone certainly points to the speed with which a breakthrough could be upon us. A more recent paper suggests that Klotho may play a role in calcium homeostasis in cells (Imura et al, 2007).

Another potentially interesting preliminary study concerns a chemical found in red wine, called resveratrol. In a recent study in rodents, resveratrol appeared able to reverse at least some of the usually negative effects of obesity. Before you go drinking red wine to gain the resveratrol, realize that, to get the amound of resveratrol that the rodents were being fed, you would have to drink many gallons of wine a day! I can assure you that your liver won't last. If resveratrol, or something like it, were to be shown to aid humans, it will be given in a concentrated form, not by drinking wine. But, were I obese, I'd certainly wait until there was some evidence to support its use in humans. Taking it now would be little different from taking a snake oil, and there are plently of those around, as we'll see in the next chapter. Resveratrol does serve as another example, along with Klotho, of the kinds of agents we are beginning to discover that might play a role in aging. Sooner or later, the right agent will be shown to have high potential as an age-delaying treatment, but it will take some studies before it would be ready for testing on humans.

Environmental Influences

In humans, it is well known that we can add a few years to our lives, on average, through lifestyle adjustments. For instance, regular exercise seems to add, on average, a couple of years of life (Paffenbarger, 1986), but this may be as much a matter of avoiding early death from age-related diseases as an actual slowing of senescence. Life-long exercise also appears to reduce or delay late-life morbidity.

In terms of environmental manipulations that might actually slow the rate of aging, there are a couple of well-studied examples that depend upon environmental influences rather than genetic alterations. One example comes from the social insects, and their long-lived queens. A second involves the only known environmental change that can substantially increase life span in mammals—calorie restricted diets.

Diet Enrichment

Ants and bees consist of workers, drones, and queens. The drones are there to fertilize the queen, and in some bees they do so on mating flights, where multiple males deposit enough sperm to last the queen a lifetime, literally, since the workers kill the queen once her sperm stores run out. All of the workers are females, and they are no different, genetically, from the queen in the sense that any one of them might have become a queen had they had the right diet. What makes the queen so different is not her genes but the royal jelly that she is fed during development. As a consequence of the special diet, the queen is much longer lived than her workers. Worker ants or bees might live for a month or two, unless over-wintering when foraging activity can diminish and life expectancy increase to several months. But, at the height of the summer, life is short--perhaps 30 to 60 days long. A typical bee starts life in the hive and later takes up roles outside the nest, gathering nectar and pollen. In contrast, a queen, as the sole supplier fertilized eggs for producing new bees, can continue to live and produce for years! The life span difference is extraordinary, as is the overall life span for such a small creature. Queen bees can live for more than five years. Queen ants and termites have similar life extensions--thirty to fifty times as long as the average worker, an amazingly long time for an active, egg-laying animal of such small size. This shows that developmental control and gene expression can be greatly influenced by nutritional factors, in these animals at least, and that such regulation of gene expression can lead to dramatic increases in life expectancy. It again reflects the importance of regulation of gene expression, rather than the genes themselves, which are the same in workers and queens.

Diet Restriction

For over seventy years, there has been one known way to substantially extend the life span of mammals—by feeding them only 60-70% of what they eat on their own when given unlimited access to food (McCay et al, 1935). Such calorie restriction remains the only known environmental manipulation that substantially increases mammalian life expectancies.

Most of us living in developed countries today are able to consume as many calories as we want. The studies in rodents suggest that we, along with other mammals, tend to overdo it, and I am not just talking about the current excesses that are increasing obesity in some of us, as was described in Chapter 2.

A reaction by some on hearing about caloric restriction is to think about the malnourished people of the world, and their lack of health and early death. How can diet restrictions be good for longevity? Such individuals are suffering from malnutrition as well as under-nutrition—that is, they are missing essential nutrients as well as having insufficient calories for sustaining life. In such cases the body will first consume its carbohydrates, especially the stores of glycogen in muscles and liver, then move on to fat in adipose tissue, which serves to insulate and supply high-density energy (about twice the calories of sugars or proteins per gram). Finally, when most stored carbohydrates and fats are consumed, the body begins to break down protein—muscle protein, and, ultimately, brain protein, which can bring irreversible brain damage. Clearly this is not what is being spoken of with the kind of dietary restriction being used in the experiments. Instead, these calorie-restricted animals are given the full range of needed nutrients, but are restricted to a limited number of total calories. They remain slim, but quite healthy under laboratory conditions.

The first evidence of life span enhancement by reduction of caloric intake in mammals came from laboratory studies in mice and rats. If rodent caloric intake is restricted to about 60-70% of normal "ad lib" (as much as they want) intake, while their essential nutrients are supplemented to assure adequate levels of vitamins, minerals, and essential amino acids, life expectancy can increase 30%-40%. Even beginning late in life, a calorie restricted but nutrient rich diet leads to a greater life expectancy, although not as great as when the dietary restriction is begun earlier in life. Most recently, there has even been some support from studies on wild rodents, which may not normally have the luxury of unlimited food supplies. There is a small effect on further restriction even in these wild animals, it appears.

In the last few years, these studies in rodents have been extended to many other organisms. Even yeast show increased life expectancy when fed diets with a lower concentration of sugar present. Nematodes and fruit flies also show enhancements. Most recently, studies have been extended to primates, with preliminary results indicating delays in the signs of aging. Since primates live much longer lives, the actual data on life expectancy is just beginning to come in, but the biomarkers of aging that are being followed are consistent with a delayed rate of aging in the biomarkers of the monkeys being studied. This suggests that the benefit of a restricted diet may extend to longer-lived mammals, and primates, as well, but some researchers have urged caution until more data are in (Lane et al, 2004).

How does dietary restriction bring about an increased life span? Interestingly, we still are not sure. In part this is because of the very complex impact that such restriction has on the animal. Many changes occur in organisms with reduced food intake. Dietary restricted animals are considerably lighter than their "ad lib" controls. Total metabolic activity is reduced, and this initially led some to suggest that it was the reduced metabolic rate that was causing the increased life expectancy. However, once an adjustment is made for the lighter weight of the calorie-restricted animals, their metabolic activity, per weight, actually was the same or higher than the heavier control littermates. In fact, the reduced weight of the dietary restricted animals is one of their most obvious outward characteristics. If a group of rodents is raised ad lib and then started on a restricted diet after reaching adult weight, the restricted animals quickly lose weight, and then stabilize at perhaps 70-75% of their former weight. The restricted animals are lean and long-lived, with reduced body temperature, but they remain quite active.

Many animals, rodents included, appear to have evolved protective measures that are activated during periods of food shortage, including reduced reproductive efforts coupled with higher levels of body maintenance. The body becomes more efficient in its use of energy from food. Calorie restricted animals show lower levels of damaging oxidative compounds, such as free radicals, and appear to have higher levels of protection against oxidative damage. Once again, we see the repair and maintenance story popping up. Notice, too, that the life preserving strategy developed by evolution for food shortages could also select for a coordinated expression of many different genes involved in repair and maintenance, and if such a system of coordinated control exists in humans, it will make intervention in humans to extend life expectancy easier to achieve. There is evidence that the pathways involved in the gain in life expectancy with caloric restriction are the same, or similar, to the insulin/insulin-dependent growth factor pathways that have produced extensions of life expectancy in mutant nematodes and flies. Even in such

a distant organism as yeast, calorie restriction induces gene regulators, such as Sir2, one of a class of sirtuins, that have links to the insulin/IGF-1 pathway in the yeast. A useful summary of genetic studies in both yeast and nematodes was written by Guarente and Kenyon (2000).

However, recent evidence in nematodes suggest that insulin/IGF-1 is not the pathway that controls the enhanced expression of repair and maintenance genes with dietary restriction in these animals (Houthoofd et al, 2005). There also has been growing interest in another pathway called TOR (Target-Of-Rampamycin; see Guarente and Kenyon, 2000) for a good review). I do not wish to identify a particular signal transduction pathway as being the one that we will use to reduce the rate of aging, but want to suggest that such a pathway, or branch from such pathways, will likely be useful in giving us the ability to reduce aging rates in humans. Irregardless of the pathway involved, it does seem that repair and maintenance enhancement plays a role in the lifespan extension seen with calorie restriction. It also appears that there may be several signal transduction pathways that can be influenced to increase the expression of these repair and maintenance genes, and caloric restriction may be acting in more than one way to extend life expectancy.

A lifetime of diet restriction to 60-70% of normal caloric intake is not something I would recommend for adult humans to try. It apparently is not much fun—one begins to think a lot about food, as those who have tried temporary diets of this sort might know. However, there are some people who are trying it, even in the absence of good data on whether it will help humans as it does other animals. Check out the web site: http://www.calorierestriction.org for more information. In addition to other difficulties, one would need to be very careful about maintaining proper nutrition with the lower number of calories. Instead of reducing calories, what some scientists now are searching for is another way of inducing the changes in gene expression with normal caloric intake. The Klotho hormone mentioned earlier indicates at least one possibility for such a treatment, but it is much too early to tell whether it will work, without significant negative side-effects, or whether we will need to keep looking for other, similar molecules that might influence the same pathways. In rodents, Resveratrol, as mentioned above, seems to help avoid the usual age-related diseases associated with obesity, and serves as an example of the general direction that the search is leading us.

A final footnote on animal mutants and calorie restriction. One of the aging mutants in the nematode, when reared in special (axenic) culture conditions, showed a 7.5-fold increase in life span (Houthoofd et al, 2004), an amazingly long extension, perhaps, as a percent of normal life span, the record for any organism. It can be viewed as being produced by a combination of genetic and environmental manipulation.

Centenarians and Their Genes

Long-lived humans have always been a fascination for most of us. Jeanne Calment, who lived to be a well-documented 122 years of age (Allard et al, 1999), used to joke that she had only one wrinkle, and she sat on it! Her long life gave her something to laugh about—when she was already a senior, she sold her apartment to a younger individual in return for monthly payments from the buyer for the rest of her life, a not uncommon practice in her native France. The buyer, who, in a sense, was making a “bet” that Calment would not live for much longer, actually died long before she did, and his

children needed to keep making the monthly payments, which eventually exceeded the value of the apartment several fold. While there have been many claims to longer lives, from the biblical Methuselah to some living in remote populations, none has been confirmed to have lived longer than Madame Calment.

Now scientists, including Tom Perls and coworkers (Perls and Terry, 2003), are trying to determine if there is anything special about those who manage to live to extreme ages. They are studying centenarians, those at least 100 years of age, and the few supercentenarians (110+ years) among us. Some are identifying versions of genes that might be more abundant in centenarians. One example is the apolipoprotein E (apo E) gene, which is involved in movement of lipid (fat-like) materials, such as cholesterol, in us. We have known for a while that one variant of the gene, apo E4, is not good for us late in life. We all carry two copies of the apo E gene—one came from our father and the other from our mother. If one of the copies is apo E4, our chances of getting Alzheimer's disease is increased. It is further increased if both of our copies are the apo E4 version. In contrast, another allele, apo E2, appears to be beneficial, and reduces the incidence of Alzheimer's disease, among other things. Centenarians are more likely to carry one or two copies of apo E2, and very few of them carry a copy of the apo E4 allele. Further studies of centenarians should bring us more insights about the genetics of aging and age-related diseases.

Are We Already Living As Long As We Can?

We already live long lives for an animal. Does 85-or-so years set a limit for average human longevity? Are the above mutant and environmental studies not much use to us because these animals are just working toward our limit? There are several lines of evidence that suggest otherwise.

Starting at about 85 years of age, there is a "break" in the exponential climb in the mortality rates of humans with age (Chapter 1). It is not that mortality rates start to fall for humans, although they have been shown to do so for some animals, such as medflies. Instead, for us, mortality rates continue to climb with age, but at a somewhat slower rate. One possible explanation for this is that the oldest old actually age at a slightly slower rate than the rest of us throughout their lives, because of the favorable combinations of genes and environments that they have. According to this view, the lower rate of aging of the oldest old and centenarians is unmasked when most of the rest of the population, who age at a faster rate, have died. This observation of a reduced rate of increase in mortality at old ages, which is repeated in most nations today, lends indirect support to the notion that most of us are not aging at the slowest rate possible. However, other explanations are also possible--the reduced mortality of centenarians may not be related to basic aging processes as much as it is to reducing the risk of age-related diseases and disorders. Thus, those living significantly beyond the average life expectancy today may have genes and environments that reduce the causes of earlier mortality, or better allow them to survive after experiencing some of the age-related disorders that manage to kill the majority of us before we reach 80 years of age. In brief, the cause of the reduced rate of rise of mortality rates at older ages may be due to a change in IMR, rather than a change in MRDT. While this issue remains unresolved, those who live considerably beyond a normal life expectancy at least point to the possibility of increasing the average age at death for those of us who do not reach it yet.

Another reason for thinking that we have not yet maximized our life expectancy comes from the studies (described in Chapter 1) of mortality rates for 80-84 year olds in the United States during the 20th century. Their mortality rates have continued to decline throughout the last century, indicating an ongoing improvement. These reductions in death rates at older ages probably are related to a number of interventions that do not necessarily slow senescence per se, but delay, reduce, or cure such age related diseases as cancer, heart disease, and pneumonia. Better nutrition probably also has helped, as has the adoption by some of healthier life styles. Again, most of these changes may be more related to changes in IMR than in MRDT, so they may not relate to any actual slowing of the rate of aging itself.

A third reason for thinking that humans are not at a lifespan limit, and one that is more likely to be directly related to senescence rates, is that some species are much better than we are at avoiding aging from oxidative damage and sugar cross-linkage, two of the major underlying causes of aging described in Chapter 9. The major role played by free radicals and other reactive oxygen variants generated by metabolism in our cells in producing senescence is universally recognized, as we have discussed in Chapter 9. A bit of background will help us to understand what is happening in these animals that seem to do better than we do at avoiding the damage related to aging.

An oversimplified view of aging once claimed that we died because of simple wear-and-tear. In an older car we can easily see the wear and tear in symptoms ranging from increased oil consumption to rusting body. It once was thought that animal aging was for similar reasons—simple wear-and-tear. It was thought that, just as we look at mileage in a car as a measure of age, we could measure heartbeats in an animal. In a typical human lifetime, the heart beats over two billion times. That number was taken as a measure of our total allowable lifetime metabolism, as the pumped blood supplied the oxygen needed for that metabolism.

While we now view wear-and-tear as an oversimplified view of aging, we do know that, as we extract energy from the food we eat, we produce damaging oxidative byproducts, and that these are major contributors to senescence. One of the main reasons that a simple, wear-and-tear view of senescence is invalid is that, as noted in Chapter 9 when our “pact with the devil” was discussed, we have repair and maintenance systems that protect us against free radical damage. The higher the level of repair and maintenance systems, the more calories we can burn in a life time. What I wish to emphasize now is that, if humans were at some kind of a limit in potential life expectancy, these protective systems should be at a maximum in us, and our total, lifetime metabolism (calories burned per weight) should be as high as any animal.

Such is not the case, and there is good evidence that our level of protection against oxidative and free radical damage can be greater. Thus, we probably are not at a lifespan limit because we know of other species that burn more calories per gram than we do in a lifetime. Among these are birds and bats (Holmes and Austad, 1995). Most animals the size of small birds and bats live short lives—two to three years or so. Birds and bats are off-the-curve for animals of their size, with some living for several decades. For example, the little brown bat weighs as little as 8-14 grams (less than half an ounce), and can live at least 32 years. During that time, they are expending a lot of energy flying, and also to keep warm because their small body size contributes to high rates of heat loss.

Because they can fly and escape predators more easily than other small creatures, many birds and bats have lower mortality rates, once they are old enough to fly, and have thereby evolved lower aging rates than other animals of their size and body temperature. Many even manage to survive with about twice the glucose concentration of humans in their blood, a level that, in us, would soon cause diabetes and produce other damage due to a greater level of sugar cross-linkages. Evolution has built these flying creatures to live longer by increasing levels of repair and maintenance. That birds and bats are even better than we at avoiding the ravages of metabolism and high blood sugar, suggests that we have room for improvement well beyond 80 to 85 years, if we can just further enhance our repair and maintenance processes.

Summary and Conclusions

Genetic studies of worms, flies, and mice show the possibility for increasing life span in a variety of animals. Caloric restriction studies in animals show that environmental manipulation also can slow the rate of aging. Thus, there is a growing case to be made that, since we can extend life expectancy in model organisms, humans might be next (Arking, 2003). Many of these cases reinforce the idea that levels of repair and maintenance genes contribute to our rate of senescence.

Our knowledge of birds and bats, combined with studies of the oldest humans, suggests the real possibility of extending human life expectancy. This is where my estimate of at least 150 years average longevity for humans comes from. Since these animals can burn at least twice the calories per gram that we do in a lifetime, we should be able to live twice as long at our present rates of calorie burning, with the right level of maintenance systems in place.

There seems to be a consistent story that carries the same theme as in earlier chapters--that up-regulation of an organism's repair and maintenance genes could bring us additional healthy, productive years. This chapter concludes the description of, and evidence in favor of, the notion that we are very close to at least a doubling of human life expectancy. Before considering in detail the consequences of such an advance for individuals and society, perhaps a cautionary note about the long history of false claims of fountains of youth, is in order. The next chapter serves that purpose.