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Chapter 6 Evolution and Experiment Show the Way

In this chapter I will present some evidence supporting the idea that the levels of repair and maintenance gene products in a variety of organisms seem to be under common genetic control. If they are, then a reduction in the rate of human aging will be much easier to achieve by tapping into one, or a small number of, genetic control pathways. To make my case, I will examine the story of the nematode, *Caenorhabditis elegans*, with its programmed, longer-lived dauer state. I also will point to fruit flies of the *Drosophila* genus that have been selected for later reproduction. Such artificial selection produces flies that show a suite of life history changes, including longer life spans. I will look at a study showing that opossums on an island without predators evolved longer life spans over a relatively short evolutionary time span. A common feature of all of these studies is the indication of linked expression of those genes that are involved in repair and maintenance, and each of the studies demonstrate that increased levels of expression of such genes can lead to significantly enhanced average life expectancy and maximum life span. The fact that animals, both invertebrate and vertebrate, appear to have links among their repair and maintenance systems and show life span lengthening when such systems are up-regulated, is promising for the extension of human life expectancy.

As the Worm Turns

Nematodes of the species *Caenorhabditis elegans* are popular research subjects that ordinarily live life in the fast lane (Wood, 1988). In just three days, these worms develop from egg to adult, and then live only 2-3 weeks. As adults, they are only about a millimeter (less than 1/20 of an inch) long.

However, if these nematodes experience harsher environments, such as elevated temperatures, overcrowding, or low food supplies (food consists of bacteria, which they consume in large numbers), the young offspring have an alternate developmental pathway. In the middle of development, instead of going on to become adults, they molt into what is called a dauer larva (Wood, 1988). Dauer animals are smaller than adults, crawl actively on the dish, don't reproduce, and can live for extended periods of time—up to months instead of weeks! The dauers are more likely to survive a bad environment than an adult animal. If conditions improve, or an improved environment is found by their exploring, the dauer animals will develop into adults, start reproducing, and live a normal adult life from that point.

The ability of the dauers to survive for months arises, at least in part, from their increased expression of repair and maintenance genes. They are better protected against oxidative damage, heat, dry conditions, etc. We will see in Chapter 10 that we can tap into aspects of this dauer pathway by mutations that allow the adult, reproducing animal to live longer. For the normal nematodes, the dauer state has evolved as a safety feature, allowing survival over more extended periods when their environments threaten survival. Notice that it is advantageous to have the gene expression of many different repair and maintenance process linked in the nematode, so that they can be increased by a single signal. There would be little advantage to increasing the protection against, for example, heat damage without also increasing protection from oxidative damage, unless one

needed protection only from increased temperatures in the environment. By linking the expression of these repair and maintenance genes, the nematodes can enhance protection against a whole range of environmental insults at the same time.

Late-Life Offspring From Flies

A number of laboratories have used artificial selection to generate flies that live longer. The first two reports came from researchers who included Luckinbill, Rose, and Arking (Lukenbill et al, 1984; Rose, 1984). These investigators, and others after them, generated a variety of longer-lived strains of the fruit fly, *Drosophila*. One simple selection mechanism involves the breeding of old adults, generation after generation. The selecting of late offspring, generation after generation, produces animals that demonstrate the kind of trade-offs that were discussed in Chapter 4--delayed reproduction selects for longer-life through the generations.

It is interesting to consider humans in this regard. In the last several generations in developed countries, on average, individuals have been marrying later and having children later. In a sense, we are performing a kind of delayed reproduction selection of our own free choice, but it will take many generations before any significant lengthening of human life might result from such late-reproductive behavior. In the case of flies, where generations pass in a hurry, one can study forty or fifty generations, or more, and examine the changes that occur with late reproduction. The resulting increase in life expectancy, which can be 30% or more of normal life expectancy, is accompanied by a number of other changes. The longer-lived flies are more resistant to a variety of stressors—heat, starvation, drying—just as would be expected if these animals were to have raised general levels of repair and maintenance. Some of the studied strains also took a bit longer to mature and grew to be a bit larger than normal adult animals. This study of evolution in the laboratory shows that longer life expectancy is possible and that the repair and maintenance processes again appear to be linked since the extension of life expectancy occurred in a relatively small number of generations. It would be unlikely that the enhanced life expectancy would have resulted so quickly were there the need to influence a large number of separate gene-regulation pathways. However, in at least some of these long-lived strains, it appears to be IMR that is influenced as well as MRDT.

So far, so good, but I have only discussed two species of invertebrates, worms and flies, which have life spans measured in weeks, not years. A skeptic could argue that it should be much easier to lengthen life for shorter-lived organisms, and might ask what this has to do with mammals. So…

Protected Opossums

Steven Austad recognized a good situation when he saw it and performed a nice experiment with Opossums (Austad, 1993). While these animals do not usually live very long--rarely over two years in the wild—this is much longer than we see with nematodes and fruit flies. Before reaching two years of age, most opossums have been killed, frequently by a predator, and the few that are still living at age two show definite signs of aging.

Austad took advantage of a situation existing on Sapelo Island, off the coast of Georgia. Opossums were on that island, but none of their many mainland predators were

present. Austad expected that, under such conditions, and given enough time for evolution to occur, natural selection would produce opossums that would live longer and age more gradually than mainland ones. Given what we learned in Chapter 4 about why we age, that was a very reasonable prediction, and his studies showed him to be right. Compared to mainland opossums, average longevity in Sapelo opossums was 25% greater, and maximum longevity was 50% greater. One test of the rate at which they were aging, measuring the damage in a major molecule in tendons (collagen), showed that such damage builds more slowly on island opossums than mainland ones, an indication of their lower aging rate, linked to their enhanced life expectancy. Interestingly, the island opossums also had evolved to produce smaller litter sizes. Thus, we again see the linkage between reproduction and aging in this natural experiment on Sapelo Island.

What about humans?

We already have some evidence suggesting that we may be able to adjust our metabolic rate, at least in limited ways. When we shift into an energy-conservation mode, such as when food is scarce or we are dieting, metabolism seems to become more efficient. That is why, under reduced caloric intake in humans, it is hard to continue to lose weight on an extended diet—as we become more efficient in our energy utilization, we are able to do more with less in the way of calories, so we don't need to burn as much of our fat reserves. While that is a good thing in times of true starvation in humans, because it allows us to live longer without food, it is not very helpful for those of us trying to lose weight. The enhanced efficiency of metabolism may be accompanied by reduced oxidative damage to our cells.

An indication of a potential for enhanced repair and maintenance comes from the comparison of our germ cell lines with somal (body) cells. As was discussed earlier, our germ cell lines (sperm and egg producers) appear to have greater protections against the ravages of time that so impact the rest of our body cells. What would be needed to achieve a higher level of repair and maintenance for our body cells? Examining the above cases, it would appear that linked production of repair and maintenance systems may be common among animals. If so, one or a small number of interventions of the right sort should produce the increase needed for a substantial increase in life expectancy. The indication from evolutionary theory is that the ultimate cost to the individual of such an increase might involve such things as a sturdier body and delay in reaching adulthood and reproduction—a sacrifice that many humans might be quite willing to make. The next chapter describes how we might be able to do it.