

# Aging is No Longer an Unsolved Problem in Biology

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**ABSTRACT:** For much of the 20th century, the accumulation of a considerable amount of information about the processes of aging did not reveal the underlying mechanisms. Toward the end of that century, the biological basis for aging became very much clearer. It became apparent that the best strategy for animals' survival was to develop to an adult, but not to invest resources in maintaining the body, or soma, indefinitely. In their natural environment, animals do not survive environmental hazards (predators, disease, starvation, and drought) to reach a long life span. There is thus a trade-off between the investment of resources in reproduction, and the survival time of the soma. At a stroke, this solves the problem of different rates of aging in different species, because those that develop and reproduce fast also have short life spans, and those that develop and reproduce slowly have long life spans. This difference is due to actual resources invested in the maintenance of the adult soma. There is now much evidence that long-lived mammals have much more efficient maintenance mechanisms than short-lived mammals. Thus, aging can be defined as the eventual failure of maintenance. It also became apparent that many different maintenance mechanisms exist, and that these depend on very many genes and a considerable investment in metabolic resources. Most individual theories of aging revolve around the failure of a given maintenance system, but as there are many of these, it is likely that most of the important theories have some degree of truth. A broad interpretation of the different degenerative changes during senescence should therefore be adopted, with the major conclusion that aging is multicausal. It is also evident that the evolved design of many components of complex animals is incompatible with indefinite survival. We can therefore conclude that this evolved design is intrinsically related to the fact of aging. This in turn means that aging cannot be reversed, although it may be modulated, as, for example, by calorie restriction.

**KEYWORDS:** evolution; maintenance; repair; damage; longevity

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## INTRODUCTION

In 1951, Peter Medawar delivered an inaugural professorial lecture at University College, London, entitled "An unsolved problem in biology." The unsolved problem was aging. The content was wide ranging and the published lecture became very influential.<sup>1</sup> Medawar appointed Alex Comfort to carry out research on aging, and as an aid to research he wrote a book, *The Biology of Senescence*, published in 1956.<sup>2</sup> Later, revised editions<sup>3,4</sup> were published in 1964 and 1979, and this third edition cited approximately 1,750 references. Many other reviews on aging have been published but most notable among these was that by Caleb Finch, *Longevity, Senescence and the Genome*, published in 1990, with nearly 700 pages of text and approximately 4,000 references.<sup>5</sup> Neither Comfort's nor Finch's books came to any strong conclusions about the biological reasons for aging. Indeed, during most of the second half of the 20th century, the field could be said to be in an unsatisfactory state. One reason for this was that there were many different theories of aging that seemed to be competing with each other. Moreover, a single theory of aging implied that there was a single cause, and as time went on this became less and less plausible. There was a huge amount of information from a large variety of experimental systems, but much of this was hard to interpret. One puzzling feature of mammalian aging was the fact that the senescent phenotype of different species was quite similar, even though the longevity of these species varied by about 30-fold. Thus, similar chemical or biochemical changes, such as the cross-linking of collagen, were occurring at very different rates.

Then, at the end of the 20th century, all this information began to fall into place, and the biological reasons for aging became very well understood. It was no coincidence that three books on aging were published in the mid-1990s, which all had positive titles. These were Hayflick's *How and Why We Age*,<sup>6</sup> Holliday's *Understanding Aging*,<sup>7</sup> and Austad's *Why We Age*.<sup>8</sup> There was also a more popular book: Kirkwood's *Time of Our Lives*.<sup>9</sup> These books are by no means similar, but they all reach the same conclusion, namely, that biologists now well understand the biological reasons for aging in animals. It is therefore no longer an unsolved problem of biology.

Some scientific discoveries are accepted almost immediately, and good examples are the discovery of the structure of DNA by Watson and Crick, and the polymerase chain reaction (PCR). Other discoveries lie latent for many years before they are recognized. This was the case for Wegener's proposals about continental drift, and even more well known, Mendel's discovery of the laws of inheritance. Unfortunately, the solving of the problem of aging will come into this second category. It is unlikely that it will be widely recognized either by scientists or the public at large, and people will go on speculating about the mysteries of aging for a long time to come. A lot that is written about aging now is biological nonsense, and that will undoubtedly be true in the future as well.

## AGING AND THE NATURAL ENVIRONMENT

In his lecture Medawar<sup>1</sup> was the first to point out that animals rarely become senescent in a natural environment, because they normally die from predation, disease, starvation, or drought. The life span of small ground-living mammals is particularly short. Even in gray squirrels, which can escape predators by climbing trees, survival after 1 year is only about 30%, and after 4 years is about 6–7%.<sup>7,10</sup> In the protected environment of a zoo, these animals can live for up to 20 years. Darwin well understood that mortality is very high in natural environments, and that only a proportion of animals survive long enough to breed. His theory of natural selection is based on the principle of the survival of the fittest. As we will see, the mortality of mammals in their natural environments varies considerably between species, and this determines evolutionary trends.

## THE MULTIPLE CAUSES OF AGING

In protected environments, animals can reach their maximum life spans, and it is now very clear that their senescence, aging, and death have multiple causes. These include the accumulation of genetic damage or mutations in genes, chromosomes, and mitochondria; the deposition of lipofuscin and advanced glycation endproducts (AGEs) in many cell and tissue locations; the cross-linking of collagen and elastin, other abnormal modifications of proteins, and the accumulation of insoluble aggregates; damage by reactive oxygen species (ROS) in many contexts; loss of immune functions and autoimmunity; a decline in muscle strength; osteoporosis and osteoarthritis; inflammatory damage to tissues; hormone imbalance and a decline in homeostasis; epigenetic abnormalities, including the loss or gain of DNA methylation, and finally, a greatly increased incidence of tumors. All these can bring about a failure of major organ systems, such as the heart and major blood vessels, the brain and sensory organs, and so on. It is striking that the major theories of aging relate to particular causes of aging, such as the free radical theory, the somatic mutation theory, the mitochondrial theory, theories that relate to the accumulation of abnormal proteins, the immunologic theory, and several others.<sup>4–7</sup> If we accept the fact that there are multiple causes of aging, then it follows that many of the important theories of aging have some truth, and it is important to have a global view of both theories and causes of aging.

Aging is also directly related to the evolved design of the organism. It is clear that mammals and birds, as well as many of their precursors during evolution, have tissue and organ systems that can “last a lifetime,” but certainly cannot last indefinitely. For example, the heart is a very efficient pump, but both it and the major blood vessels have very limited capacity for repair. The brain consists of innumerable neurons, most of which cannot be replaced. Eventually, brain

cells are lost, and there is accumulation of abnormal peptides in plaques, as well as neurofibrillary tangles. The lens of the eye consists of crystallins that cannot be replaced, and eventually lose transparency. The retina continually turns over photoreceptors, and the ability to remove all this material eventually becomes impaired, with loss of retinal function. Joints cannot maintain a steady state, and often become damaged through continuous use. Finally, the wearing out of teeth provides an instructive example. Many herbivores, such as horses, have teeth that wear out through a lifetime of grazing. They are genetically programmed to last a lifetime, but suffer from wear and tear. This illustrates the fact that there is no real distinction between so-called programmed aging and the aging that is due to wear and tear. In humans, of course, the wearing out of teeth is circumvented by dental care, and some herbivores have incisor teeth that grow continuously throughout life.

It has been suggested that some vertebrates that continually increase in size, such as some large fish and reptiles, avoid the features of aging found in mammals and birds. This is open to serious question because age-related changes in these long-lived animals are poorly documented, and it cannot be disputed that their actual life spans are a tiny fraction of evolutionary time. A crucial feature of the evolved design of mammals and birds, as well as invertebrates, such as many insects and nematodes, is that post-mitotic cells cannot be expected to survive indefinitely. There are many events that can end the life of a cell, and it is therefore unreasonable to expect any to remain alive for ever.

## MAINTENANCE OF THE ORGANISM

Why do mammalian and bird species live as long as they do? The answer depends on the efficiency of cell, tissue, and organ maintenance in each species.<sup>7</sup> Maintenance mechanisms are very extensive, and consume considerable resources. Moreover, as time goes on we learn more about the overall details of each mechanism and its relative importance in preserving the body or soma, and its role in maintaining a potentially immortal germ line. Thirteen separate mechanisms can now be identified:

1. the multiple pathways of DNA repair, which are vital for the removal of spontaneous lesions in DNA;
2. the defenses against oxygen-free radicals, which include antioxidants and enzymes;
3. the removal of defective proteins by proteases;
4. protein repair, such as the renaturation of proteins by chaperones, and the enzymic reversal of oxidization of amino acids;
5. the accuracy of synthesis of macromolecules, which depends on proof-reading mechanisms;
6. the immune response against pathogens and parasites;

7. the detoxification of harmful chemicals in the diet by the monooxygenase enzymes coded for by the P450 gene superfamily;
8. wound healing, blood clotting, and the healing of broken bones and torn ligaments;
9. physiological homeostasis, including temperature control;
10. the epigenetic stability of differentiated cells, and the defenses against neoplastic transformation;
11. apoptosis, which is the means of removing unwanted or damaged cells;
12. the storage of fat, to allow animals to survive in the absence of food; and
13. grooming of fur or feathers, which removes external parasites, dirt, and debris.

All these mechanisms depend on a large number of genes. For example, at least 1,000 genes are required for the immune system (P. Hodgkin, personal communication), and 150 genes for DNA repair (T. Lindahl, personal communication). Also, most of the maintenance mechanisms are the matter of scientific disciplines in their own right, so their understanding all depends on considerable biological and biochemical knowledge.

### THE ALLOCATION OF RESOURCES

The energy and metabolic resources available to any animal must be divided between three fundamental features of life. The first comprises basic metabolism, which includes biochemical synthesis; respiration; cell turnover; movement; feeding, digestion, and excretion. The second is reproduction, which depends in mammals on the gonads, gametes, and sex; gestation and development; suckling; care of offspring, and growth to the adult. The third is maintenance, namely all the 13 functions listed in the previous section.

Whereas basic metabolism is essential for all animals, the extent of investment in reproduction and maintenance can vary between species. This is the trade-off known as the disposable soma theory of aging.<sup>11-14</sup> It states that increased investment in reproduction results in less investment in maintenance, and this reduces life span. More investment in maintenance and less in reproduction results in an increase in life span. The evolved balance between the two depends on the life history strategy and ecological niche of the species. It is predicted that there is an inverse relationship between the maximum potential number of offspring a female can produce during her lifetime and the maximum life span in a protected environment. This was confirmed for 47 mammalian species in which adequate data are available.<sup>7,15</sup> Of course, in natural environments females almost never achieve their full reproductive potential, nor do they reach their maximum life span. It should be noted that although this trade-off applies to females, males have the same genotypes (apart from the Y chromosome), so the same evolutionary forces will apply to them.

There have been many comparative studies that demonstrate that long-lived species have more efficient maintenance mechanisms than short-lived species. These have been comprehensively reviewed elsewhere,<sup>7</sup> and since that time more evidence has been published.<sup>16</sup> Only a few examples are mentioned here: the same chemical cross-links in collagen occur much more quickly in bovine than human skin.<sup>17</sup> In rats, carcinomas arise far more frequently than they do in humans, with an approximately 30-fold difference in the rate of onset.<sup>18</sup> Also, somatic mutations in lymphocytes increase about 10-fold during the life span of mice and humans. However, this increase occurs over about 3 years in the mouse, and 80 years in humans.<sup>19</sup> It has been shown that the defenses against ROS in a long-lived bird, the pigeon, are much more efficient than those in the short-lived rat, a mammal of similar size and metabolic rate.<sup>20</sup> A similar difference is seen between small long-lived birds (canary and parakeet) and the mouse.<sup>21</sup> Many studies on DNA repair and DNA metabolism confirm a relationship between longevity and efficiency of maintenance.<sup>7</sup>

## THE MODULATION OF AGING

It is very well known that calorie restriction in rodents substantially increases their life span, and it also greatly reduces their fecundity. This is probably an evolutionary adaptation, particularly in ground-living mammals which have a variable supply of food.<sup>22-23</sup> When food is absent or limited, it would be disadvantageous for females to breed, and better to invest available resources in maintenance and survival. When food becomes available, reproduction can then occur. The overall effect with a variable or limited food supply is to increase the life span.

Mutations in genes that increase longevity (in so-called gerontogenes) are likely to have deleterious effects on the phenotype, such as loss of fertility. Such animals would not compete with wild-type animals in a natural environment. It is therefore likely that any treatment that increases longevity comes at a cost. For example, there may be ways and means of reducing metabolic rate, or reducing temperature, or increasing sleep, all of which could conceivably increase longevity.

## THE MODULATION OF AGING BY NATURAL SELECTION

With regard to life span, there have been two very different trends in mammalian evolution.<sup>24</sup> If the mortality increases, perhaps on account of a change in environment or the appearance of a new predator, then the population will decline. There will then be selection for earlier development and reproduction, with an increase in the number of offspring. Usually such animals become smaller. An excellent example of this trend is seen in the carnivores, with the evolution of small stoats and weasels. These develop rapidly, have large and

frequent litters, and in captivity have a short life span. In their natural environment, their high mortality is largely due to shortage of prey. The opposite trend is illustrated by the very well-documented evolution of the horse. Primitive horses were about the size of a hare, but during the course of evolution their size gradually increased. This increase could also be associated with slower development, fewer offspring, and a longer life span. In this case, a reduction in mortality would result in the selection of the longest-living females that have, on average, the most offspring. This trend occurred in pachyderms, large whales, and the higher primates. Thus, the evolution of longevity ultimately depends on environmental mortality, and the ecological niche the species inhabits. It should also be realized that over long periods of time, the different causes of aging will become synchronized by natural selection.<sup>25</sup>

### ANIMAL IMMORTALITY

An immortal animal must have the means to regenerate or replace cells and tissues that become damaged, or show signs of aging. Such regenerative powers are seen in a few simple animals, such as Hydra, some coelenterates, and flatworms. Aging is of ancient origin, since most differentiated invertebrates have finite life span. Many insects, and also nematodes, consist of post-mitotic cells, apart from germ cells. Since their cells cannot be replaced, they have clearly defined life spans. What would be the properties of more complex animals that could live indefinitely? Again, they would have to be capable of regenerating essential parts of the body; for example, with regard to the circulatory system, they would need two hearts and sets of major blood vessels. Then, as one declined in function, the second would start up, while the first would be repaired, then the second would be repaired, and so on. This would provide, in effect, a steady-state system with infinite survival time. It is much harder to see how such repair or regeneration could apply to the brain, in which long-lived neurons encapsulate experience and memory. The fact is that higher animals have simply not evolved that way because many of their phenotypic features demonstrate that many parts of the body have a finite life span. The evolved design of the body means that it has also a limited lifetime, and the reason for this is that it is counterproductive for animals to preserve their body, or soma, in environments where very few of them will survive for a long period. To put it another way, any animal that could preserve its soma indefinitely would have to invest so many resources that its Darwinian fitness would be lesser than that of an animal that has finite survival time.

### CONCLUSIONS

The main conclusion is that after many decades of uncertainty, the biological reasons for aging became clear at the end of the 20th century. There are

multiple causes of aging synchronized by natural selection, and the rate of aging and longevity in any given species depends on the failure of cell, tissue, and organ maintenance. There is now much evidence from comparative studies that efficiency of maintenance is correlated with maximum life span. Also, in mammals there is a clear inverse relationship between fecundity and longevity.

Although it may be possible to modulate life span, it is unreasonable to suppose that all the different causes of aging could be reversed. There is much discussion at present about anti-aging medicine. Ronald Klatz, in *Advances in Anti-Aging Medicine*, writes: "Within the next 50 years or so, assuming an individual can avoid becoming the victim of major trauma or homicide, it is entirely possible that he or she will be able to live virtually for ever."<sup>26</sup> This is biological nonsense, and reveals a complete ignorance of the field of gerontology, and why animals age. Unfortunately, despite our new understanding of aging, people will continue to misunderstand it for a long while to come.

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Our long-term dataset on a wild population of barnacle geese allowed us to examine telomere dynamics on an individual basis, covering almost 80% of the lifespan of this long-lived species. Using this longitudinal dataset, we demonstrate that within each individual, telomeres are well maintained throughout life. Thus, our study adds further empirical support to theories of ageing, predicting a link between efficient maintenance mechanisms and organismal longevity [1, 2]. Previous studies based on cross-sectional estimates of TROC in birds concluded that telomeres of long-lived species are lost ...<sup>Â</sup> Holliday R: Aging is no longer an unresolved problem in biology. *Ann NY Acad Sci.* 2006, 1067: 1-9.