*BOOK REVIEW ARTICLE*

# The Biological Basis of Aging and Death

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**A Means to an End:**
**The Biological Basis of Aging and Death**
*William Clark*
Oxford University Press

*A Means to an End: The Biological Basis of Aging and Death* by William Clark deals with senescence, the process by which our vulnerability to disease and death increases steadily with age.

One chapter discusses the evolutionary basis for differences in lifespan. We may be tempted to say that naturally living organisms wear out, as do machines, and we should not be surprised when tissues grow old and fail to function. However, this process for similar tissues occurs at quite different rates. At the microscopic and biochemical level, the cellular processes in a mouse and a human are quite similar. Yet the maximum lifespan of a mouse is only 3.5 years while for a human it is 122 years. Clearly, the tissues of some species are engineered to function longer than those of other animals. Why do different species have such different lifespans?

Clark points out that part of it seems related to the age of reproduction. Animals whose function declines before reproduction would be out reproduced by animals whose bodies lasted longer. What has prevented human bodies from evolving to last longer is that most of us have finished rearing our young by the time really serious deterioration has set in (say age 65). While we would like to live longer, living into retirement age contributes little to the number of descendants we leave. Thus, if the price of this living longer is fewer

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children born at younger ages, there is likely to be selection against the genes for body maintenance.

While Clark argues that we have genes for senescence (as well as genes that retard it), he never is quite clear on why those that delay senescence (and hence have a longer reproductive life) do not out reproduce those experiencing earlier senescence. The missing detail is that delaying senescence probably has costs (possibly from diverting energy to cell maintenance and repair). Individuals that divert resources from bodily maintenance can use these resources to avoid being eaten, to fight parasites, or to find mates. The individuals that leave the most descendants accept a shorter lifetime in exchange for other benefits that contribute to leaving descendants. Arking (1998) provides a better discussion of theories of aging.

That an organism's length of life can evolve in response to selection for early or late reproduction has been shown in several experiments. When each succeeding generation of fruit flies was grown from eggs laid late in the life of the fly, the lifespan of fruit flies was increased.

In Trinidad, it was found that guppies from the lower pools reproduced earlier and had a shorter lifespan than those from the upper pools. In the lower (further down the river) pools the main predator ate guppies of reproductive age. In the upper pools the main predator ate immature guppies. In the later case, once a guppy had survived to reproductive age it would leave more offspring if its body survived longer. Thus, the guppies had evolved to live longer. When breeding stock from the pools where lifetime was short were introduced into pools where the predators neglected the older fish, the guppies evolved towards an older lifespan. Finally, when predators that went after the older fish were introduced into the pools with the originally short lived upper pool stock, these guppies evolved shorter lifespans.

Thus, it appears that in these two species at least, and probably in other species, including humans, the gene pool contains genes for a longer life span. In human populations (races) evolving in different circumstances, lifespans could be different. Miller (1994) has argued that in climates where male provisioning of the young is necessary for children to survive, selection for a long life has been stronger than in tropical areas.

The evolutionary mechanism that produces the correlation between lifespan and age of reproduction could also operate within humans. This inspires some speculations that are mine, not Clark's. Several

studies suggest a correlation between socio-economic status and lifespan. In recent generations, the start of reproduction has been later is the higher socio-economic classes. This would produce selection for longer lives. Socioeconomic status is also a surrogate for intelligence. Especially interesting is the Whitehall study in which the mortality rates were found to decrease steadily as one ascended the ranks of the British Civil Service. This was puzzling since all subjects had basically sedentary desk jobs with the same medical care (the British National Health Service). Peak earnings in jobs that involve brain power occurs later than in jobs that require merely muscles. This is probably because experience (and education) results in higher earnings for brain power jobs, while a similar effect is not found in muscle power oriented jobs. Because higher earnings provide a better choice of mates for males, reproduction appears to have started later in those that earned a living by their brains for many generations. This may have gone on long enough for natural selection to have caused the genes for longer life to be concentrated in those also carrying the genes for intelligence. Some evidence that the intellectual classes have been preferentially marrying within themselves for many generations is provided by Weyl's (1990) finding that people with the last name Clark (derived from medieval people who were clerks) are over represented among lists of successful Americans.

Clark's primary message is that the body must contain a relatively small number of genes that produce senescence as well as genes that retard it.

The argument that there are only a few genes that contribute to senescence comes from the existence of a small number of rare genetic diseases characterized by the early appearance of characteristics of the aged. While rare, these are scientifically interesting because they may help unravel the causes of normal aging. These diseases affect a large number of different types of tissues in the body. Clark argues that the defects that produce these diseases must be in housekeeping genes that carry out the same functions in all cells. In this way a single gene defect can produce symptoms that look like accelerated aging in many different tissues.

Werner's syndrome is one such disease. Victims have a generally aged appearance, early gray hair, and early cataracts, cancer and diabetes. When removed from the body their fibroblasts show a number of divisions that is much less than in non-diseased individuals of the

same age. The symptoms resemble accelerated aging in many different tissues. Werner's syndrome has been recently been found to be caused by a defective helicase gene. This gene is believed to play a role in the repair of genetic damage.

Several highly technical chapters discuss the cell cycle and how the reproduction of the cell is regulated. A single cell growing when it is not supposed to can produce a cancer that kills the whole body. A fascinating chapter deals with number of divisions a cell removed from the body can undergo before it stops growing. This number of divisions is called the Hayflick limit, after its discoverer. It is greatest for cells removed from embryos and least in those removed from the old. It appears greater in long lived species than in short lived species. It is also reduced in several of the progeria, or diseases of aging. Thus, it appears that this limit on cell replication somehow reflects the cellular processes that cause aging, even though most of the cells that under aging in the body do not divide in adulthood. The hope is that if many of the problems of aging can be traced to the actions (or lack of action) of a small number of genes, it may some day be possible to slow down aging.

So far only one process has been found to slow down mammalian senescence. This is caloric restriction. When rodents (and various other experimental animals) are fed much less than they would normally eat in laboratory conditions (i.e. with food readily available), they live substantially longer than laboratory animals normally do. For instance, in one study rats were fed from weaning on only 40% of the calories unrestricted rats received. At maturity they weighed only a third as much as the other rats, but they lived almost twice as long. If the caloric restriction is started in adulthood, the effect is less striking, but still significant. Most of the aging processes in rodents are slowed down by such caloric restrictions. In particular, cells removed from such calorie deprived rodents will undergo more divisions than cells from non-caloric deprived animals.

Unfortunately, it is not known whether this would work in humans. Experiments are now underway to see if caloric restriction works in monkeys, which are closer to humans than rodents are. So far, the monkeys have reached the age where normally fed monkey would be developing diabetes, and diabetes has not yet appeared. It looks as if calorie restriction does indeed slow aging in monkeys.

It would be very interesting to know if this would work in humans.

Clark leaves the question open, but one researcher on caloric restriction, Walford has argued it should work in humans and written a popular book (Walford 2000) and a professional book (Weidruch and Walford, 1988) suggesting adoption of such very low calorie diets for humans.

A natural question is why caloric restriction prolongs lifespan. Clark, like other experts, suspects it is because restricting calories reduces the amount of oxygen used by the cell, and hence the amount of reactive oxygen species produced. These are believed to damage cells in various ways, including oxidizing the lipids in cell membranes, and damaging the DNA in the cells. Cells have developed various mechanisms for reducing such damages, typically through various antioxidants. Both vitamin C and vitamin E are antioxidants. There is considerable evidence that these reduce oxidation damage.

This is not a manual for improving health and Clark does not make recommendations. However, his summary of the evidence on cancer and heart disease suggests that some benefits would be derived from taking such anti-oxidants and he notes that "Reducing mortality from heart disease and cancer would be expected to have at least a modest effect on average lifespan".

The senescence that people fear most is that of the brain. Clark devotes a chapter to brain senescence, with an emphasis on Alzheimer's. Oxidative damage apparently plays a role in brain senescence. Oxidized proteins increase in the brains of aged gerbils. Gerbils maintained on an anti-oxidant made the same number of errors (four) on a maze test as young gerbils did, an error rate that is half that of old gerbils (eight errors). The same antioxidant worked on a senescence-accelerated strain of mice.

Of course, other authors, especially those writing popular books, are less cautious, and argue for taking supplements of various antioxidants (see for instance Carper, 2000; Papas, 1999). It should be realized that whether a particular treatment extends life in humans or other animals is logically distinct from the question of whether one should use that treatment in an effort to extend life. The latter decision depends on whether the estimated benefits exceed the estimated costs. If the benefits are potentially large (a few more years of life) and the costs small (say expending a few dollars on supplements, or changing eating behavior), the expected (in a statistical sense) benefits could exceed the costs even though the odds favored the treatment having no

effect. For instance, many of us would be willing to take supplemental anti-oxidants if the risk of damage was low (as it appears to be) even if the odds that they extended life were only one in four. In this case it would be correct to say the evidence was against the treatment being effective, but to still conclude that the treatment should be adopted. Unfortunately, given the amount of time (and expense) needed to test a life extending measure in humans, there are many measures which appear likely (or which plausibly could) extend life judging from animal experiments or epidemiological evidence, but which have not yet been shown to actually be able to extend life. The empirical problem with research on human life extension is that many measures that slow human deterioration might have to be utilized from an early age onward. Whether they were having an effect would not be known until that cohort had passed their normal age of death, perhaps fifty or seventy five years later. Studies over that time period are hard to organize and expensive to conduct.

Most popular scientific books leave one with the feeling that the area being discussed is important and worthy of further support. Thus, it is no surprise that this book shows that much progress has been made on understanding senescence, and that further support is likely to result in more progress. Indeed, it does appear that we could find ways of greatly extending human life through senescence research. What is not realized often is that this potential is much greater than for most disease research. The reason is that the major killers (cancer, heart disease, pneumonia, Alzheimer's etc.) kill mainly the old. Someone saved from one of these diseases would usually die in just a few years from another cause. Indeed, because death rates rise so rapidly with age, progress against one of the age related diseases will soon be followed by an increase in the population's average age that returns death rates to their previous levels.

However, if senescence itself can be defeated, or slowed up, gains in life expectancy would be greater than would be achieved by such medical miracles as the conquest of heart disease or cancer. While much research aimed at curing specific diseases must be conducted on humans and by expensive medical doctors, most research on senescence can (and practically must be) conducted on short-lived species such as worms, yeast, fruit flies, mice, rats, and monkeys. Research on these species can be conducted by less well paid biologists and biochemists working in university laboratories.

The possibility that human life could be extended by calorie restriction below that which keeps people at a normal weight appears worthy of extensive research. While the time needed for an experiment to see if human lives can be extended is very long, projects that closely monitor various biomarkers for aging may be possible and could give results in perhaps ten years.

If severe calorie restriction works in humans, the required diet will be very hard for people with normal appetites to stay on. For those with sufficient will power it may involve continually feeling hungry and thinking of food. The experience of those currently dieting shows that.

Thus, it would appear desirable now to support research on means for reducing appetite. If a very calorie restricted diet eventually is shown to prolong life, we would have the tools in place to actually implement it. If that degree of restriction proves not to be worth implementing, the ability to control appetite could still prolong life. The new knowledge could be very useful to those who are now obese, and whose health is currently suffering because of it.

Several lines of interesting research come to mind from tidbits of information. The reproductive potential of cells (fibroblasts) of rodents undergoing calorie reduction feeding is greater than for control rats. Similar work in humans might be possible, possibly using subjects from poor countries or from Okinawa. Weidruch and Walford, (1988) mention Okinawa as an area whose numerous centenarians may be due to a historically low calorie diet.

Clark states that large breeds of dogs have longer life spans than small breeds. It is easy to see how selection for size would have also selected the genes that promote longevity since a large animal will take more time to reach maturity. If the breed does not also undergo selection for a longer lifespan, it will be out-reproduced by dogs of the same breeds that live longer. When the dog has been genotyped (Celera is doing this), there should be a range of breeds with different lifetimes available for study.

There is another reason for adding a carnivore, such as the dog, to the rodents traditional used in senescence studies. In the wild, most rodents are killed by predators and selection for a long life is weak. Only a few rodents would make it to an age where death from old age was important. Species that are predators, not prey, would be expected to undergo stronger selection for a long life, and to resemble humans more.

I cannot help but suspect a politician who put conquering death on his platform and explained that it required more research on senescence could win elections.

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# Reproductive Perspectives: A Review of Some Recent Books on the Ethics of Manipulating Human Genes

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The author reviews nine books published during recent years which discuss, from widely different points of view, the ethical impact of Mankind's new ability to manipulate the genetic heritage of posterity.

**Key Words:** Genetics, human reproduction, reproductive ethics, eugenics, cloning, dysgenics, happiness, eliminating disease

**Genethics: Moral Issues in the Creation of People**
*Heyd, David*
Berkeley: University of California Press. 1992

In *Genethics: Moral Issues in the Creation of Life*, David Heyd claims that "Theoretical interest in genesis problems has emerged only after being forced on us by the new dilemmas of demography, genetic manipulation, 'wrongful life' cases, and self-imposed threats to the very future of the human race. Do we have an obligation to bring new people into the world? Do we have a duty to have children? to avoid having miserable children? Is there a right to be born, or a right not to be born, or a right to be born healthy? Can moral principles guide us in artificial genetic molding of humans? Is a world with $n$ happy persons morally better than a world with no persons at all? than a world with 1/2 $n$ equally happy persons? than a world with $2n$ persons who are only mildly happy? Is there a value in the existence (and perpetuation) of the human species as such, regardless of the quality of life of its members? These are some of the questions involved in genesis situations, or at least implied (or presupposed) by them."

This book is an excellent introduction to the philosophical questions facing eugenics and genetic engineering, but like any book based on philosophical questions it can raise more questions than it answers and it too often assumes people have attitudes and wishes that may not be universal, a tendency of most philosophical works. That is,