

# The Essence of Aging

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## Abstract

The idea that aging is a purposeful, programmed series of events is intuitively appealing based on its many conserved aspects and the demonstrated feasibility of modifying life span by manipulating single genes or pathways. Yet, the case for a nonadaptive basis of aging is strong and now all but generally accepted in the field. Here, we briefly review why the case for programmed aging is weak, with a focus on the lack of possible evolutionary beneficial effects.

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Only the gods can never age, the gods can never die. All else in the world almighty Time obliterates, crushes all to nothing.  
[Oedipus to Theseus]  
*Oedipus at Colonus* by Sophocles

Aging must have fascinated humans almost immediately after the gradual emergence of consciousness and complex thinking about 100,000 years ago in Africa [1]. Naturally, the first recorded attempts at explanation were entirely in terms of religion. Aging was seen as something

that befell humans but spared the gods. Possibly because of this religious trigger to immortality, aging came to be seen as an active program of decay that could be prevented provided one could discover the correct way to do it. This point of view never went away and is now with us in the form of aging as a process genetically programmed in our DNA. That is, genetic information in the organism does not only specify its development but also its demise. This is sometimes called adaptive aging (which we use interchangeably with programmed aging) because the process is supposed to have emerged during evolution as a series of germ line mutations that were selected on the basis of a particular gain in fitness. Hence, according to this idea each of us has a biological clock set to go off at a particular time to signal our bodies first to age and then to die. The trick is to find the key to switch it off. This is obviously a very attractive concept to most people. Indeed, it is very difficult to accept that the elegant series of developmental switches and checkpoints that creates an organism is so crudely interrupted by a seemingly random, aimless process that leads to our demise. Yet, the great majority of experts in the science of aging believe that this is exactly what is happening. Aging is not programmed based on adaptive evolutionary change because evolution optimizes for fitness, not for longevity. Indeed, life as it emerged, diversified and perpetuated over almost 4 billion years has no vested interest in healthy aging or immortality, but merely in reproduction. In this view-

point, we re-emphasize the logic of the consensus theory in light of arguments that are still being made for aging as a genetically programmed series of events that increases the fitness of the individual.

For the ancients the teleological component of an aging program was always clear: to keep humans in their place. Modern scientists, of course, require something more than a divine whim. However, the logic of programmed aging also appeals to scientists, especially biologists. Biology always was a purposeful science par excellence and the introduction of molecular biology with its signaling pathways and genetically controlled functional networks made it even more so. Naturally, aging could only become a topic of study when explained as a series of signaling steps that bring life to a close. Moreover, recent results with model organisms providing evidence that aging can be affected by manipulating single genes or through the administration of single drugs (see below) have greatly strengthened deterministic positions and make the issue of programmed aging topical and relevant. We will see, however, that the relative ease by which aging is genetically modulated can support both programmed and nonprogrammed aging.

It is not difficult to find examples of animals that appear to undergo programmed aging. Indeed, there are many such organisms that have a semelparous life cycle. Death following reproduction has been documented in various species from a wide diversity of taxa, across bacteria, plants, and almost all animal classes. According to some, the term comes from Sémélé, a strikingly beautiful princess of the ancient Greek city of Thebe and the lover of Zeus, the king of the Greek gods. Somewhat unwise, she insisted on witnessing her lover's full power, which cost the tragic princess her life. Since she was pregnant and Zeus was always careful with his offspring, he sewed the infant in his thigh and a few months later Dionysus was born.

There are multiple explanations for a semelparous life style, all based on logical evolutionary reasoning [2]. Natural selection should favor physiological processes that enable individuals to maximize the number of offspring. In species with a low probability of reproducing more than once, for example, because they only have a brief life span or due to long migration, as in certain eels or in different species of salmon, selection should favor an extreme mobilization of the resources for reproduction in order to maximize the number of offspring. The rapid decline and death of such individuals would be merely a consequence of their intense reproductive effort. Whether or not this is truly accelerated aging is debatable, but

there is no reason to assume that the process is itself a selectable trait offering a competitive advantage to the individual and/or its offspring.

In some respects, semelparity is easier to explain than iteroparity, in which adult members of a species reproduce repeatedly during life, often with great variation in breeding schedule. Intermittent reproduction is associated with organisms, such as humans, with fairly long life spans living in environments that can vary drastically over time, such as seasonal environments. Still, not maximally using the first breeding opportunity and spreading out reproduction over time is evolutionarily intriguing because of the risk of not surviving. It is beyond the scope of this essay to detail these different reproductive strategies and the reader is referred to the excellent overview by Finch [3] in his book *Longevity, Senescence, and the Genome*.

While there can be no doubt that in semelparous organisms, specific, genetically controlled processes bring life to a close shortly after reproduction, the existence of a similar mechanism is much less clear for iteroparous organisms. There are two key problems here. First, the process takes a long time and it remains unclear why evolution could not come up with a cleaner, more rapid process to end life (as it evidently did with semelparous organisms). To drag it on like this seems to serve no purpose. Second, aging as a selectable trait is difficult to act on by natural selection because the force of natural selection significantly weakens with age (see below) [4]. Before we discuss the various arguments that have been proposed as to why senescence itself is an adaptive trait, we will now briefly present what is considered the consensus point of view as to why aging exists.

Ironically, nonadaptive theories of aging started with what is probably the most adaptive theory of aging ever proposed. This idea that aging is a beneficial trait, evolved to cleanse the population of old worn-out individuals, originally came from the German evolutionary biologist August Weismann (1834–1914). Weismann is best known for his germ plasm theory, in which he for the first time distinguished a germ line from the soma. As pointed out by Kirkwood and Cremer [5], Weismann often came to reject some of his own earlier positions, and his adaptive theory of aging may have been one of them. Indeed, Weismann was keenly aware that natural selection can only work when a phenotype is relevant to fitness and realized that aging by itself is unlikely to have an advantage, which contradicts his earlier idea of a beneficial cleansing mechanism.

Weismann's early ideas set the stage for the later realization by the great quantitative geneticists Fisher, Hal-

dane and Hamilton that the chance of individuals to contribute to the future ancestry of their population declines with age [4]. Eventually, this would lead to the often cited lecture by Peter Medawar [6], delivered at University College, London, in 1951, in which he argued that aging, at least in sexually reproducing organisms with a difference between the soma and the germ line, is a result of the declining force of natural selection with age. Medawar proposed that aging was the necessary result of constitutional mutations, accumulated in the germ line over evolutionary time, that reduce fitness late in life. However, Medawar's concepts by themselves are not sufficient to explain aging. A strong argument as to why genetic variants with adverse effects late in life can emerge, leading to symptoms of senescence at ages frequently reached even in the wild, is antagonistic pleiotropy, i.e., when the same gene variant controls a phenotypic trait with beneficial effects at early age and adverse effects later. There are many examples of such antagonistic pleiotropy. Still the best example was provided by the father of the antagonistic pleiotropy theory, the late George Williams [7]. He hypothesized that a gene for rapid bone calcification during development would be selected in spite of the fact that this could also lead to depositions of calcium in the arterial walls, an age-related phenotype already occurring at middle age or earlier. Of note, experimental evidence supporting the 'evolutionary theory of aging' has been obtained for several animal species, including animals in the wild [8, 9].

It is often pointed out, especially by proponents of programmed aging, that there are some isolated cases that seemingly contradict the evolutionary theory of aging [10]. However, biology is often confronted with exceptional cases. But even these exceptional cases can almost always be explained within the boundaries of evolutionary logic. Indeed, evolutionary theory itself is also easily exposed to seemingly contradictory evidence that at the end of the day is always logically explained without the need of intelligent design or creation, two alternatives that are neither logical nor supported by a similar mountain of scientific evidence as evolution theory. Nevertheless, it would be imprudent to immediately rule out aging as a possible object of selection, and we will now critically discuss some of the arguments that aging is an adaptive trait.

Proponents of programmed aging often argue that the process of organismal degeneration and death has all the hallmarks of evolved adaptation. It is controlled by genes that have often been conserved across extensive phylogenies and shows pathophysiological changes that are of-

ten very similar from species to species. While this is not in conflict with nonadaptive explanations for aging, it is true that at first glance it seems more compatible with programmed aging. The first and easiest way to explain aging as an adaptive trait is to invoke group selection, in this case meaning that aging of the individual occurs for the benefit of the group, which shares genetic alleles. As we have already seen, Weismann was the first to propose that aging evolved to get rid of weak, worn-out individuals to preserve resources for the healthy young who still need to reproduce. There are two problems with this. First, as noticed almost immediately by Weismann himself, this hypothesis seeks to explain the problem of aging by aging itself, an obvious example of circular reasoning. The second problem is the controversy about group selection. As explained in very clear terms by the great evolutionary biologist Ernst Mayr [11], the object of natural selection is first and foremost the individual. Mayr does not rule out group selection, i.e., when there is a relationship between the fitness of an individual and the properties of the group. Indeed, one could imagine that certain characteristics, such as the emergence of sentinels to warn of predators, could be subject to group selection because the fitness of individuals belonging to such a group may be higher than that of individuals from nonsentinel groups. However, as pointed out below, it is difficult to find such an advantage for altruistic aging.

Mitteldorf [12] proposed that a major target of natural selection at the group level is demographic homeostasis. As he argued, aging could have evolved based on its contribution to stabilizing population dynamics, helping prevent population growth overshoot. Later, this same author proposed a group benefit of senescence in limiting the spread of infectious epidemics through the regulation of population dynamics [13]. This makes sense because overpopulation often results in famine or epidemic disease, which could wipe out the entire population. Aging, then, could have evolved as a means for the group or even species to control its death rate. While the problem remains that the process simply takes too long to be of any use, especially in wild populations where most members of a species die of age-extrinsic causes, it is difficult to see why young adults are not at least equally well suited as targets in this model.

Programmed aging has also been considered in individual-based models with competition between parents and progeny. Yang [14] presented a model according to which aging is selected to benefit the group in viscous populations, i.e., populations in which offspring stay around rather than disperse. The benefit of aging in this

model is to promote survival of genetically fitter young progenies who would suffer competition from their parents, who had already acquired improved abilities with age. Hence, this basically goes back to the original Weismann hypothesis, but this time based on the benefit of capturing inherited, superior abilities in the progeny rather than the elimination of individuals already damaged by wear and tear to reduce the burden to the group. Yet another model, also based on the competition between parents and progeny, is from Martins [15], who proposed that aging serves as a pruning mechanism to get rid of older individuals harboring less well-optimized genotypes who managed to survive by chance.

In summary, programmed aging theories provide dubious theoretical arguments as to how a process of organismal deterioration and death could have emerged during evolution. None can boast of some serious experimental support. In addition, they all suffer from the fact that aging is a gradual process, without a critical age or threshold when the hypothetical mechanism would kick in to abruptly increase death rate. There is in fact experimental evidence that contradicts programmed aging. Indeed, it has now been established that in multiple species, possibly including humans [16], death rate at extreme old age starts to slow down rather than exponentially increase further as one would expect if aging was programmed. Hence, the conclusion must be that the case for programmed aging is a weak one at best.

Let us now revisit the peculiar finding that it is relatively easy, at least in animal models, to intervene in the aging process and extend the life span of the organism. This seems paradoxical if aging really is the effect of a decline in natural selection and, by extension, likely a highly variable and multifactorial process. Put another way, if aging is caused by the decline in function of many different processes, it would seem difficult to alter the process by one genetic mutation. Yet, it is irrefutable that this is possible. In fact, reduced or ablated expression of hundreds of individual genes (up to 5% of the respective gene sets) leads to life span extension in worms and yeast, and similar observations have been made in flies and mice based on more limited studies to date [17, 18].

One way to resolve this apparent conflict is to propose that while aging is not adaptive, species come preequipped with programs that can be turned on to delay aging. More accurately, they can be turned on for other naturally selected reasons, but when activated delay the aging process. The best example would be dietary restriction, a reduced calorie intake without malnutrition that has been demonstrated in many laboratories to significantly in-

crease life span [19]. A reduction in available nutrients converts species from an unabated focus on reproduction to allocation of resources toward long-term survival, presumably until resources become once again abundant [20]. This re-allocation of resources, which leads to activation of stress resistance and turnover of damaged molecules in cells, may be just the ticket to forestall many features of aging and extend life span. Indeed, many genetic and pharmacologic interventions that delay aging are proposed to phenocopy dietary restriction [18].

From a more philosophical perspective, slowing aging as a means of extending the healthy period of life seems feasible whether aging is programmed or not. If one takes the programmed view, interventions should be sought that disrupt the program, thus avoiding aging. But extending life span may be just as easy from the nonprogrammed perspective. In this case, the most likely strategy would be to find interventions that enhance programs selected to promote health during early adulthood, in other words, improving the function of pro-health pathways rather than disrupting pro-aging ones. This may be less difficult than it seems. Evolution has had billions of years to optimize fitness in species, but at older ages, when the force of natural selection has greatly declined, it may be relatively easy to tweak existing pathways to prolong their normative function and delay aging. This is perhaps consistent with findings that a surprisingly large number of genetic mutations enhance organismal life span [17]. Of course, many of these life span-extending interventions may have deleterious age-extrinsic consequences on important aspects of fitness, making them undesirable particularly outside the laboratory. Nevertheless, it seems from the current perspective that while aging is not likely programmed, it will still be possible to target aging as a means of extending human life span and, more importantly, prevent the onset of a wide spectrum of chronic diseases that are increasingly plaguing humanity [21].

After almost 100,000 years of consciousness, humans are still fascinated with aging, even more so in the last 200 years when we have entered an era where most individuals have to face the prospects of watching their bodies slowly decline with time and the fear that they will be robbed of their very humanity by chronic diseases. Elders are the most rapidly growing segment of the population in most countries in the world and up to 20% of the global population will be over 60 in the not-too-distant future. The 21st century will be defined by these demographics (dare we suggest the term 'Age Age?'), and continued research is likely to change the way we think about aging.

Perhaps findings will re-ignite the programmed aging debate but for now the experimental evidence rests firmly on the side of a nonprogrammed view, with the caveat that it still may be feasible and even easier than we would have guessed to forestall aging and the chronic diseases that aging enables.

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