An Evolutionary Perspective on Senescence

Chapter · January 1987

DOI: 10.1007/978-94-009-3391-0_4

1 author:

Randolph M Nesse
Arizona State University,
238 PUBLICATIONS **13,372** CITATIONS

SEE PROFILE

RANDOLPH MARTIN NESSE

AN EVOLUTIONARY PERSPECTIVE ON SENESCENCE

At the heart of gerontology, there is an important scientific problem that is now ripe for solution. The problem is: "Why does the phenomenon of senescence exist?" Not why, in the sense of the mechanisms that cause damage. Gerontology has studied dozens of such mechanisms and the resulting mass of information has proved most difficult to integrate. The question to be addressed here is not *what* the mechanisms are but, instead, *how* they have come to exist. In organisms shaped by natural selection, why is there aging and why do individuals inevitably die by some specific age? These crucial questions have not been systematically considered. An answer to the question of how natural selection has affected the traits that influence aging would bring together many current findings of gerontology and would offer a new perspective on what aging really is and its place in the pattern of life. An evolutionary understanding of aging may also shed new light on related ethical and personal issues.

PROXIMATE *vs.* EVOLUTIONARY EXPLANATIONS

Two different kinds of explanations are needed in order to understand fully a biological phenomenon like aging. One kind is the proximate explanation, and the other is the evolutionary explanation ([20], pp. 67–76). This distinction requires elaboration with a few examples. In order to explain any biological phenomenon, we must, of course, give a proximate explanation of the mechanism and how it works. The proximate explanation of the heart, for example, must include its structure, how the valves work, how the contraction is coordinated and regulated, and how the heart rate is controlled. The proximate explanation must include the details of the mechanism at every level. In addition to this proximate explanation, however, a separate, evolutionary explanation is necessary. We must also explain the adaptive function of the heart and the natural selection forces that have shaped these mechanisms. It is not hard to see the function of the heart – it circulates the blood so that each cell is nourished and wastes are removed.

Stuart F. Spicker, Stanley R. Ingman, and Ian R. Lawson (eds.),
Ethical Dimensions of Geriatric Care, 45–64.

As a second example of these two kinds of explanations, let us consider the momentary glow of a firefly. The *proximate* explanation includes the anatomic and neurochemical mechanism that mediates and controls the flash of light. It also includes the developmental process that begins with a DNA code and results in the specific structures of the mechanism. The *evolutionary* explanation, in contrast, specifies the adaptive function that the capacity serves, the selective forces that have shaped it, and, insofar as it is possible, its phylogenetic history. The proximate explanation accounts for the workings of the mechanism; the evolutionary explanation accounts for its existence as a result of natural selection. It is quite possible to formulate testable hypotheses regarding evolutionary function. Does the firefly's flash serve to frighten predators or to locate food? No, both of these hypotheses are false. The function of the glow is to locate mates. A firefly that lacks this trait will survive, but it will not be likely to reproduce, so its genes will be lost.

The cough reflex is a third example. The proximate explanation includes the details of the anatomy and function of the sensory nerves from the respiratory tract, the brain's processing of neural impulses, the motor nerves from the brain to the respiratory tract and diaphragm, and the mechanism by which neural impulses influence muscular action. The evolutionary explanation is that this reflex functions to clear foreign substances from the respiratory tract, and this decreases the likelihood of disease and death. Individuals with an intact cough reflex have a selective advantage over those who do not, and the genes that code for this trait have therefore spread and become universal. Of course, many genes are involved, and natural selection actually shaped the cough reflex gradually over millions of years, not all at once.

The distinction between proximate and evolutionary explanations is well accepted, but some people remain concerned that evolutionary explanations based on the function of a trait are somehow not really a part of science. Biologists, too, were at one time suspicious of questions involving function. The victories over vitalism and teleology were not yet secure, and reductionism and imitation of the methods of physics were the order of the day. Now, however, consideration of a trait's adaptive function is required in every area of biology. The way was paved first by anatomists and physiologists, and then by Tinbergen and other ethologists, who had to account for patterns of behavior observed in various species [27]. More recently, Ernst Mayr has argued, in his book *The Growth of Biological Thought*, that this distinction defines two separate biologies:

The two biologies that are concerned with the two kinds of causation are remarkably self-contained. Proximate causes relate to the functions of an organism and its parts, as well as its development, from functional morphology down to biochemistry. Evolutionary, or historical, or ultimate causes, on the other hand, attempt to explain why an organism, in contrast to inanimate objects, has two different sets of causes, because organisms have a genetic program . . . ([20], p. 68).

No biological problem is fully solved until both the proximate *and* the evolutionary causation has been elucidated. Furthermore, the study of evolutionary causes is as legitimate a part of biology as is the study of the usually physical–chemical proximate causes ([20], p. 73).

The importance and legitimacy of the distinction between proximate and evolutionary explanations are steadily better appreciated by scientists, although interesting questions remain about this distinction, and the methods appropriate for testing evolutionary hypotheses. Space limitations preclude further discussion of these issues here. Instead, the distinction will be used to better understand the phenomena of senescence.

To date, almost all research on aging has been designed to provide proximate explanations. Textbooks describe the many changes that occur with age, the dozens of mechanisms that may be responsible, and evidence for and against each of these mechanisms [9]. The diversity and number of these facts and theories are a significant fact in its own right. Limits to cell division may play a role [14]. There may be errors in DNA replication, damage by free radicals, damage from the immune system, irreversible protein cross-linkages – the list goes on and on ([6], [22]). Not only is there no straightforward way to decide what contribution is made by each mechanism, it is not even clear which are mutually exclusive possibilities and which may make overlapping contributions. Something is missing here. An evolutionary perspective may provide an important theoretical framework.

There are four possible relationships between natural selection and aging. First, there is the possibility that genes have nothing to do with aging, and natural selection is, therefore, irrelevant. Second, it could be that aging is somehow adaptive, and has been selected like any other trait. Third, it is possible that the genes that induce aging have never been exposed to natural selection because animals in the wild never live long enough for the genes to pose any serious disadvantage. Finally, there is the intriguing fourth possibility that the same genes that are responsible for the problems of aging also have beneficial effects earlier in life, so that they are, therefore, selected and maintained in the gene pool. These four possibilities will be considered one at a time.

WEAR AND TEAR

Many people think of aging as "wearing out." It is true that parts of the body do wear out and that this contributes to aging. Some parts, however, never wear out or are continually replaced. We never run out of red blood cells, for instance; they are continually replaced. Teeth wear out, but they could be regularly replaced since that happens once already for every human. A lizard can regrow its whole tail if necessary. The effect of aging is manifested not in wear itself, but in the body's limited and diminishing capacity to protect and replace its parts. These capacities, or lacks of capacities, are determined by the genes. Wear and tear cannot explain aging. Both protective and detrimental genetic factors are involved in aging, and we must offer an evolutionary explanation for their presence.

AGING AS AN ADAPTATION

The second theory considers aging to be an adaptation. Is aging itself somehow useful? This idea appears first in an 1881 article by August Weisman:

> Worn out individuals are not only valueless to the species, but they are even harmful, for they take the place of those which are sound. Hence, by the operation of natural selection, the life of our hypothetically immortal individual will be shortened by the amount which was useless to the species ([28], p. 24).

There are many variations on this idea [24], but all of them propose that the individual ages and dies for the sake of the group or the species. This mechanism of group selection was once accepted by many biologists in order to account for phenomena that seemed to have no other possible explanation. However, William Hamilton advanced evolutionary theory considerably in 1969 when he formulated the principle of kin-selection to account for the seemingly self-sacrificing behaviors that had previously been used as prime examples of traits thought to have been selected as a result of their benefit for the group or the species [13]. It is not possible to pursue this interesting story in more detail here, except to say that kin-selection does not explain senescence in general, and that group selection has now been discounted as an evolutionary

mechanism, except in very special situations. The problem with a theory that proposes an adaptive value for aging is quickly clear if we imagine an evolutionary competition between an individual who ages and dies, with an individual who does not age at all. If the individual who does not age lives longer and has more offspring, then the individual that ages, and that individual's offspring, will have relatively fewer of their genes represented in subsequent generations. This process would systematically eliminate genes that caused aging, even if they benefitted the group or the species. Aging is not an adaptive trait in itself. This second possible explanation for aging is as wrong as the first.

SELECTIVE IRRELEVANCE

The third explanation is based on the idea that the genes involved with aging are beyond the reach of natural selection because their effects never have any real disadvantage for individuals in the wild. Even if there were no senescence, a certain proportion of individuals would be killed each year by accidents, predators, disease, starvation, and other forces. Depending on the species and the conditions that it encounters, the mortality rate may be 3% per year or may be 50% per year. Whatever the mortality rate is, after some specific number of years there will be no individuals left. Any genetic effect that poses a disadvantage only after this age will be beyond the reach of natural selection. When individuals of this species are placed in a protected setting, they will live beyond the age that most live to in the wild, and the effects of aging will be seen. Death may then inevitably occur by a certain age because the body can no longer maintain homeostasis during the slightest stress. The core of this proposal is the accumulation of deleterious mutations with effects later in life, because selection cannot eliminate them.

This theory was first proposed by J. B. S. Haldane in his 1942 book, *New Paths in Genetics* [12]. "In man there is good evidence that arteriosclerosis and some other senile diseases are largely genetically determined. It is natural that such genes should accumulate as a result of mutation, for there is no selection against genes which act after the reproductive period" ([12], p. 113). Haldane deserves credit for originating the idea, but there are two problems that come from his focus on the end of reproduction instead of the inevitable demise of a certain number of individuals each year. First, any species that provides care or

resources for its young will be subject to selection until the period of contribution to the offspring is over. A second more basic error is that Haldane assumes that an age limit to reproduction is inevitable. It is not. If reproduction ceases after a certain age, this must either be because changes of aging have disrupted the reproductive capacity or because the limit to the period of personal reproduction is somehow adaptive. This second possibility will be considered later. First, the theory of mutation accumulation must be illustrated. If there were a mutation that, for instance, caused steady, very slow deposition of calcium in the skin so that the skin became brittle by age 500, then there would be no direct action of selection to eliminate this gene because all individuals are dead from other causes long before this age. If another gene caused clouding of the cornea, but the resulting poor vision never became a problem until after the age at which essentially all humans had died when they lived under natural conditions, then selection could not eliminate or modify this gene. This theory of mutation accumulation is probably accepted by more gerontologists than any other evolutionary theory of aging.

Many give credit for the idea to P. B. Medawar who elaborated it in his 1946 article, 'Old Age and Natural Death' ([21], pp. 17–43). He claims in this article that he is only adding "a few extra guesses woven in among Weisman's original hypothesis of aging" ([21], p. 40), but this is far from the case. Medawar correctly notes the importance of the smaller number of old individuals and its relationship to the reduced force of selection. In this article, he clearly anticipates the pleiotropic theory, the fourth possibility considered here:

> It is by no means difficult to imagine a genetic endowment which can favor young animals only at the expense of their elders; or rather at their own expense when they, themselves, grow old. A gene or combination of genes that promotes this state of affairs will, under certain numerically definable conditions, spread through a population simply because the younger animals it favors have, as a group, a relatively large contribution to make to the ancestry of the future population ([21], p. 38).

He fails to develop this idea, however, until his 1952 article, 'An Unsolved Problem in Biology' ([21], pp. 44–70). Even here, however, he instead emphasizes the fact that natural selection will tend, as the result of modifier genes, to push a deleterious genetic effect to later and later expression in the life cycle. He clearly delineates the appropriate method for recognizing the effect of senescence on a wild population. He points out that if organisms at each age are subject to the exact same

rate of mortality, then the survival curve will show an exponential decline and a semi-logarithmic plot of survivors versus age will be a straight line. If, however, older individuals are more subject to predation and other dangers as a result of senescent changes, then the rate of mortality will increase with increasing age, and the semi-log plot will instead be a downward, sloping curve. Medawar notes the lack of life-table evidence for wild populations, then, without more ado, states that senescence is not observed in nature but only in laboratory settings. He apparently bases this on the absence of observations of decrepit animals in the wild, even though his own thinking clearly emphasizes that this is by no means the crucial datum on which to make a decision about the presence of senescence in wild populations.

Alex Comfort adopted this position in his enormously influential book, *The Biology of Senescence*, now in its third edition [4].

> Death from senescence is itself in many species so rare in the wild state that failure to senesce early, or at all, has little value from the point of view of survival. In many forms the cessation or reduction of group breeding capacity happens well before senescence proper – with certain exceptions in social animals. What happens later, in the post-reproductive period, is theoretically outside the reach of selection, and irrelevant to it ([4], p. 96).

There are two problems here. First, there is no explanation for the cessation of reproduction; an effect of senescence is presumed to be its cause. Second, when Comfort says "death from senescence," he apparently means natural death, but this is, again, not the issue. The issue is whether declining fitness makes an organism increasingly vulnerable to death from any number of causes. Few people have ever seen a very old rabbit in the wild, but this does not mean that aging is unimportant for them. If a one-year-old rabbit can run just slightly faster than a fox and a two-year-old rabbit can run just slightly slower, then foxes will catch many more two-year-old rabbits than one-year-old rabbits, aging will be a major cause of death, and it will be subject to a strong effect of natural selection. If this is the case, and for many species it may well be, then natural selection is acting strongly on aging, and the mutation accumulation theory is an insufficient explanation for the existence of genes that cause aging.

What actual evidence of mortality rates at different ages for a variety of species is available? Remarkably little. In an era that spends millions on research in basic science and millions, for that matter, on aging research, we still do not have field data on the mortality rates at

different ages for more than a few species. Gathering this data should be a high priority because it will indicate how strongly selection is working on aging, and, therefore, the plausibility of the mutation accumulation theory of aging.

Some data are available. The easiest to interpret is that which shows the rate of mortality per unit time, at different periods in the life span. For humans, the data are good, at least for modern times. It shows that the force of mortality increases from age two on, and increases exponentially, doubling every eight years, starting at about age 30 ([10], pp. 28–29). Senescence is occurring steadily and causing increased susceptibility to death, even in the '30s and '40s. A more comprehensive view of aging in a given species is provided by the life table – a summary of the number of surviving individuals at any given age. If there were no senescence, then the curve should show a steady decline of a certain percent of individuals each year. When senescence is present, the curve becomes progressively more rectangular.

Systematic consideration of the importance of senescence in wild populations requires a quantitative assessment of its strength in various species, but such techniques have not been available. The effect of senescence acting on a wild population can, however, be quantified as the coefficient of selection that acts on the traits comprising senescence. The arithmetic is very simple. Treating each sex separately, the mortality rate is determined during the period of early maximum reproduction. The actual survivorship curve is then compared to a hypothetical one which is based on the assumption that the force of mortality does not increase at all with increasing age, that is, that there is no senescence. If one further assumes, as is generally correct if there is no senescence, that the reproductive rate remains constant with increasing age, then the number of reproductive life-years lost to individuals who senesce, as compared with those who hypothetically do not, can be readily identified. The coefficient of selection acting on senescence then can be seen to be equal to the decrement in reproductive life years caused by senescence, divided by the total number of reproductive life years for a population which does not senesce, but instead loses members at a steady rate. This technique will be described more comprehensively elsewhere, but this simplified version shows the potential for comparing the effects of senescence on a variety of species. A sample calculation based on data published for the red deer population on the Isle of Rhum

[5] shows a very high coefficient of selection of 0.65. Collection and analysis of data for a variety of species would be of great benefit.

In 1957, Gertzing summarized the available data on senescence in wild fish populations [11]. This is of particular interest because many fish continue to grow and to increase their reproductive capacity throughout their lifespan, so they would be less likely than other species to demonstrate senescence. Nonetheless, his data show clear-cut evidence of increasing mortality with increasing age in several wild fish populations that had not been exploited by man. Data for small birds, on the other hand, seem to show a very rapid, steady mortality that is uninfluenced by senescence, so far as we can tell with the available data ([4], pp. 141–142). For tsetse flies, there is excellent evidence for the effect of senescence on mortality rates in the wild during the rainy season, but not during the dry season [18]. In plants, the importance of senescence is substantial [19]. Unfortunately, data of this sort are scarce, and what is available has not been analyzed from this point of view. It seems that scientists were so convinced that aging is not a factor for wild populations, that many opportunities to answer the question have been missed. A small institute, say, ten people funded for ten years, would take us a long way toward answering this very important question.

Separate from the problems of the available life-table data, there are also theoretical problems with the mutation accumulation theory. First, there is a problem of how the genes that affect aging could spread and become universal in the gene pool if they were indeed irrelevant to survival and reproduction. If they were not increased in frequency by natural selection, then how did they spread? The concept of genetic drift ([31], [3]) is a possibility, but it seems hard to imagine that this could account for the large number of genes that are involved in senescence and their remarkably uniform effects, both within members of the same species and between closely related species. Although the importance of drift is the subject of a complex technical debate, that cannot be pursued here.

The theory of mutation accumulation faces still other problems related to basic observations about aging and life span. If aging genes have not been subject to selection, one might expect that the effects of aging would be substantially different in different people, that different effects would become manifest at different rates, and that the length of life in a protected environment would vary considerably. What we find,

however, is that the effects of aging are very similar in different individuals, that the rate of decline in reserve capacity in a variety of organ systems is identical [26], and that length of life for many species in a protected environment varies by only a small amount. Fries and Crapo have extrapolated current human mortality trends to estimate that, if premature causes of death were eliminated, 95% of people would die within 8 years of age 85 ([10], p. 71).

Finally, proximate studies on senescence challenge the idea that selection has not affected the genes which influence aging. Proximate research has vividly demonstrated the way in which the effectiveness of a variety of defenses against aging is correlated with the life spans of diverse species. The ability to repair DNA, the level of protection against damage from superoxides, the number of cell divisions possible – all of these show substantial correlations with the life span of the species considered ([6], pp. 45–57). The proponents of these theories have used this data to argue that each of these mechanisms contributes to the effects of aging. For laboratory studies, this may be correct, but an evolutionary perspective suggests that these protective mechanisms have been shaped by natural selection to be just as effective as they must be to protect these species during their usual life spans in the wild. They cannot provide more protection, because natural selection has no effect at ages not encountered in the wild. In combination with the other arguments advanced above, these facts pose serious problems for the hypothesis that aging is caused by the effects of genetic mutations that have accumulated outside the range of natural selection.

Although the accumulation of mutations is probably incorrect, the importance of the decreased force of selection with increasing age remains crucial. To go further, however, we must distinguish among three categories of genes. Each will be differently affected by natural selection. First, there are genes that protect against or repair inevitable damage at the molecular level. Genes that code for DNA repair mechanisms are a good example. Second, there are genes which code for mechanisms that allow the regeneration of damaged cells and tissues. The ability to heal a skin laceration, and the ability of a starfish to regenerate appendages are good examples. Third, there are genes whose effects cause tissue damage. Using these categories, it is readily apparent that the declining force of selection with increasing age cannot account for those genes which cause damage, but it can readily explain why the effects of various mechanisms that protect the body at the

molecular and cellular level may not prove effective beyond the usual life span. With this perspective, it appears that wear and tear can cause aging because selection has not been able to create mechanisms that protect the individual long enough, or because the creation and maintenance of such protective mechanisms exacts a continuing cost to the organism which is not worth the benefit of improving the protective mechanism, given the limited life span of a species in the wild.

The limited ability of the body to regenerate damaged tissues is a somewhat different issue. Such limitations are imposed partly by the rarity of opportunities to repair some specific forms of damage. For instance, it would be extremely rare for an individual to live very long after trauma which damaged brain or heart tissue, so that the capacity to regenerate these tissues would offer little survival advantage. In addition, the benefits of complex organizations of tissue that can be achieved most efficiently with a single irreversible and unrepeatable process of differentiation may outweigh the costs of being unable to regenerate some tissues. Finally, the ability to regenerate damaged tissue must involve some risk of uncontrolled cellular replication. This risk of cancer may also be a cost that limits the selection force for mechanisms that allow regeneration of damaged tissue.

Two of the three categories of genes that influence aging can, therefore, be understood without too much difficulty. Natural selection has shaped mechanisms that protect cells and that repair damaged tissues, but these mechanisms cannot be perfectly efficient, both because of compromises that must be struck with inevitable costs, and because some of the damaging events are either rare or occur after the age at which essentially all individuals of the species have died in the wild environment. The third category of genes, those whose effects cause damage themselves, cannot be explained by the evolutionary mechanisms outlined so far.

THE PLEIOTROPIC THEORY

The fourth evolutionary theory of aging is usually called the pleiotropic theory. It was first formally stated by George Williams in 1957 [29]. He emphasized the decline in numbers of individuals with advancing age, even in the absence of senescence, and then he pointed out that the larger number of young individuals have, by the simple fact of their number, many more genes on which selection can act, than the smaller

group of old people. Natural selection acts more strongly on genetic effects that are expressed in youth than it does on those effects expressed in old age, simply because there are more individuals for it to act upon. Pleiotropy refers to the fact that a single gene may have many different manifestations, and, in this case, that these are likely to be different, or to have different significance, at different ages. The idea is similar to that advanced by Haldane and Medawar, but Williams states it much more clearly, recognizes its central importance, and draws several interesting inferences.

An example offered by Williams will illustrate the theory. If there were a hypothetical gene that made bones stronger in early adulthood, this would offer a selective advantage, and the gene would spread in a population and become nearly universal. If this same gene caused steady deposition of calcium in the arteries, so that some people had strokes or heart attacks, even during the life span observed under natural conditions, then that gene would also pose a serious disadvantage. If the disadvantage were equal to the advantage – say, for instance, that the stronger bones increase survival by one percent per year in early adulthood, and the arteriosclerosis resulted in the death of one percent of older people per year, then the gene could still be selected for and could spread in the gene pool because there are so many more young people than old people for selection to act on. It is a simple, but brilliant idea. A gene with an early advantage will be selected, even if it causes a serious disadvantage or death at a later age. This theory, in contrast to the other three, can explain, in evolutionary terms, the existence of genes which cause tissue damage associated with old age.

A few more hypothetical examples will further illustrate the theory and its potential importance. If an individual with especially delicate structures in the lung could transport oxygen and carbon dioxide more rapidly, this would offer a significant advantage in the ability to flee from predators or to run after prey. If this same trait resulted in more fragile tissues that were more susceptible to damage and less susceptible to repair, this would pose a significant long-term disadvantage and might well mean that, after some age, the lungs could not be expected to function well enough to support life, even in the resting state. Even so, this gene would be selected and would become a part of every individual because those individuals who had it would survive better and reproduce more in youth (at a time when there are more individuals alive), while natural selection would not act nearly as strongly on the deleteri-

ous effects later in life. An individual who did not have this trait would contribute fewer of his genes to the next generation than an individual who had the trait, and the trait would become nearly universal. Whether this proposal is correct or not, it should not be surprising that pulmonary function steadily declines with increasing age.

As another example, let us consider a hypothetical mutation that resulted in a larger milk supply from the breast that would allow more offspring to survive in periods of famine. Even if this same gene caused a tendency to have breast cancer later in life, the gene might well be incorporated in the gene pool by natural selection. As a final example, consider the advantages that a particularly aggressive immune system would offer against possibly lethal infections. A gene which made such an aggressive immune system possible would be selected, even if it resulted in autoimmune damage that accumulated steadily with age.

William Hamilton has mathematically analyzed the pleiotropic theory of senescence [14]. After considering mathematical models for natural selection of pleiotropic genes, he concludes that "for organisms that reproduce repeatedly, senescence is to be expected as an inevitable consequence of the working of natural selection" ([14], p. 26). Pleiotropic effects must account for some of senescence. The pleiotropic theory avoids the problems of the other theories and accounts for phenomena which other theories cannot. It explains how there can be genes that cause the changes of aging, it explains why their effects are in synchrony, why mortality rates increase exponentially, and why the maximum life span is so rigidly fixed in many species.

Some other proposed theories of aging are tacitly based on pleiotropy. For instance, it has been suggested that limits to the number of fibroblast replications may serve the adaptive function of limiting the growth of atherosclerotic plaques. Although this proposal is unlikely, it is more clear when recognized as a possible pleiotropic mechanism to explain limits to cell division.

In his discussion of the pleiotropic theory, Williams proposes an ingenious explanation for menopause ([29], pp. 407–408). At first glance, it appears that cessation of reproduction must be a manifestation of senescence; it certainly seems to pose a disadvantage for maximizing the number of one's genes in the next generation. However, Williams notes that, in species that offer parental care to their young, selection continues to operate so long as this care is provided. After all, the offspring have many genes identical to the parents. He proposes that the

senescent changes associated with increasing age make child-bearing more risky, and this threatens not only the life of the mother but also her ability to care for her existing offspring who carry replicas of her own genes. Thus, women who have menopause might have a selective advantage because more of their offspring will grow to reproductive maturity as compared with those mothers who continue to have children and risk the survival of the children already born. This proposal is difficult to test by the comparative method, because the duration of child care in humans is so much longer than in other species. Nonetheless, the possible evolutionary benefits of menopause may be of importance, especially to women and to gynecologists.

Are there specific data that support the pleiotropic theory of aging? We have already seen life-table data that show that aging is a factor in the mortality of wild populations. If further studies show that it is a major factor, that is, that the coefficient of selection is high in a variety of species, then this cannot be explained by the other theories. Once again, important data are not available.

The other main support for the pleiotropic theory of aging comes from breeding studies. If one allows fruitflies to breed only at advanced ages, then presumably this procedure will select against pleiotropic genes that tend to shorten the life span. This is exactly the experiment done by Rose and Charlesworth [23]. They found that this selection process increased longevity and late reproductive output, but that it decreased early reproductive output and decreased total reproductive output. They conclude, "It seems reasonable to suggest that senescence in *Drosophila* is due to the late-acting deleterious effects of genes which are favored by natural selection because of beneficial effects at early ages" ([23], p. 142).

Sokal performed the opposite experiment [25]. He bred 40 generations of flour beetles from eggs laid very early in the life span. He found that this breeding procedure produced significantly shorter life spans, and he concluded that this resulted from either the accumulation of mutations or from selection from pleiotropic genes. If he had measured changes in reproductive capacity, it might be possible to better use his data to support the pleiotropic theory.

A full consideration of the evidence that bears on the pleiotropic theory of aging is beyond the scope of this presentation. It should be clear, however, that it is a sensible theory, and that it has some experimental, as well as theoretical support.

The importance of pleiotropic effects will differ substantially for different species. A phylogenetic perspective offers intriguing predictions. If a species has recently, say in the past million years, been exposed to increasing predation or competition for food and shelter, this would decrease the average life span, and one would expect to find relatively few genes directly influencing this shorter life span in the wild, most of which would likely be pleiotropic. For such a species, average and maximum life span in a protected setting should show moderate variation. If, however, mean lifespan in the wild has recently increased because a species has been released from predation and competition, as appears to be the case for man, then one would expect to find a large number of pleiotropic and other senescent effects clustered tightly together by natural selection in a brief period at the end of life. Selection for increased efficiency of various protection mechanisms should be proceeding. There should be selection against pleiotropic genes, and this might cause susceptibility to diseases or other decreases in vitality early in the life span. For such species, mortality rates should show an increase during the usual adult life span, and there should be a fixed maximum life span with relatively little variation in the mean age of death in a protected environment. These conclusions follow from the principle that senescent effects will pile atop one another at a specific period late in life span, because, instead of predation and starvation causing a steady drop off in the number of individuals so that selection cannot operate, it is senescence itself that causes most mortality. There could be no selection for modifier genes that would push senescent effects beyond the age at which most individuals had died as a result of multiple senescent changes. In the same way that a sand dune is built from millions of grains that are carried to the top and then dropped where the peak blocks the force of the wind, the expressions of a multitude of discrete senescent effects are pushed by natural selection to the end of the life span where they collect atop one another because the force of natural selection is blocked by the sudden drop-off in population that is caused by senescence itself. This explains why the "Wonderful One-Hoss Shay" of Oliver Wendell Holmes:

> Went to pieces all at once, –
> All at once, and nothing first, –
> Just as bubbles do when they burst. [17]

IMPLICATIONS

An evolutionary perspective on aging has important implications for basic attitudes and ideas about aging and death, for gerontology and research on aging, for ethics and social policy, and finally, for our more personal feelings about our own aging and death. The most important implications are those which have to do with our basic understanding of what aging is. Aging is not an accident. Aging is not an adaptation. Aging is not a disease, and it will not be cured. Medicine and changing social conditions have substantially extended the average life span, so many people hope, illogically, that it will extend the maximum life span. Relatively few people are aware that the maximal life span has not changed, at least in the last century ([10], pp. 72–77). Even fewer people realize that we will not be able to significantly extend the maximum life span. The effects that cause senescence are not only too numerous and separate from one another to be susceptible to much manipulation, but many of them also are part and parcel of what makes our bodies work. If they are disrupted, there are likely to be disadvantages in youth. Substantial disruption might well interfere with crucial parts of the body's machinery. An evolutionary perspective suggests that there is no clock that controls the rate of aging from some central point. Aging is the sum total of a multitude of changes. It *seems* coordinated, but this is explained by the action of natural selection, not by some central organizing mechanism. For once, the evolutionary biologists can warn their proximate biologist colleagues about teleological thinking. There is, in fact, no coordinated mechanism governing senescence; there are just many senescent effects that are expressed concordantly, because natural selection has pushed them together at the end of life.

There is no getting around it. Aging is here to stay. Aging is inevitable for individuals, not just in fact, but theoretically as well. Research on gerontology will not cure aging and is very unlikely to postpone it substantially. If we think that more money spent on aging research will accomplish these goals, we are fooling ourselves. Perhaps it is our wish to avoid these facts that has prevented consideration of aging in an evolutionary perspective. It is incredible that we have spent so many millions on senescence research without answering the basic scientific question of why there is senescence. Williams' theory has been available since 1957, but most doctors have never heard of it, and many gerontologists do not understand its significance. This may be a most interesting topic for a philosopher of science.

The next implications of an evolutionary view of aging are those that relate specifically to research and gerontology. As mentioned, almost all research has been focused on the proximate half of the problem. A small investment in evolutionary studies of senescence would pay big dividends in itself, and would also enhance our understanding of proximate mechanism. Proximate gerontologic research is also of great importance. It may not extend life, but it will improve the quality of life and may help us to find the cures for specific disease. Most of the diseases confronted by medicine today are diseases of senescence. There is every reason to believe that proximate research can lead to findings that will help specific individuals with specific diseases.

It is possible that some of the more common changes and diseases of aging may be pleiotropically linked to benefits earlier in life. Alzheimer's disease, atherosclerosis, and osteoporosis may be good candidates. Do people who have these diseases also have some advantages earlier in life? This could be the case despite numerous etiologic possibilities. For instance, even if Alzheimer's disease turns out to be caused by a virus, we might find that inability to resist the virus may be one effect of a gene that offers other benefits to the immune system. These examples are entirely hypothetical, but they illustrate the point.

Are there ethical implications of this view of aging? This is a delicate issue. Those who advocate an evolutionary perspective on human issues have often been criticized for directly drawing moral implications from biological facts. But many biological facts have no direct moral implications. To assume that they do shows the most primitive poor logic. Nonetheless, it seems to be a part of human nature for people to be tempted to take a biological fact and to conclude that what *is*, is what *should* be. They then use this precept as a guide for human choices. This is not only illogical, it is dangerous, because those who control a political system always seek justification for their favored position and their inordinate share of available resources. This kind of pseudobiological rationale is surprisingly seductive for many people.

Even though biological facts are not independently sufficient to provide any ethical guidelines, an evolutionary perspective on senescence provides understanding that is essential for any discussion of ethics associated with aging. When combined with even a simple, ethical principle like "provide the greatest good for the greatest number," they do suggest possible changes in our behavior. In a large university hospital, the issues and contradictions are vivid. A 95-year-old terminally ill comatose woman may be put on a respirator for long enough to

wipe out the savings that might have offered her children new opportunities in life. On the other side, dialysis may not be recommended for a 65-year-old person because of supposed advanced age. Many doctors continue to treat death as the only enemy without knowing why there is aging, or why death is inevitable. Understanding the evolutionary fact of senescence and the inevitability of death might change attitudes and behaviors. It tips the balance toward quality of a life, as against quantity of life as a goal we should strive for. It suggests that physicians should concentrate more on relief of problems that interfere with living, and less on prolonging life. It does not suggest that the elderly should be deprived of curative treatment when that is possible. It may have implications for the increasing proportion of the Gross National Product which is spent on health care and the increasing portion of this expenditure that is spent on attempts to prolong the lives of elderly patients, even as the availability of other resources for the elderly are declining.

Finally, there are personal implications when we learn that there is an evolutionary explanation for aging and for the inevitability of individual death. Death turns out to be simply one move in the mindless but perfectly efficient strategy of natural selection. Graffiti in the University of Michigan Museum of Zoology succinctly summarize the central point:

> Why are we born, only to suffer and die?
> Because those who suffered and died in the past,
> outreproduced those who didn't. [2]

An evolutionary perspective on senescence offers new questions that have important implications for gerontology, research, ethics, and our personal understanding about aging and death. It is one example of the use of evolutionary theory to better understand medicine and biology. Darwin died 102 years ago, but the range and explanatory power of evolution by natural selection is still not fully appreciated. Paradoxically, it appears to be precisely the issues of most crucial human concern that have not been analyzed from an evolutionary perspective. Aging is one example, many other problems are waiting. Each offers us an opportunity to better understand our place in the natural world.

The University of Michigan
Ann Arbor, Michigan

BIBLIOGRAPHY

1. Alexander, R. D.: 1979, *Darwinism and Human Affairs*, University of Washington Press, Seattle, Wash.
2. Alexander, R. D.: 1981, 'Senescence: Explaining the Finiteness of Individual Existence', unpublished manuscript.
3. Bodmer, W. F. and Cavalli-Sforza, L. L.: 1976, *Genetics, Evolution and Man*, W. H. Freeman and Company, San Francisco, Calif.
4. Comfort, A.: 1979, *The Biology of Senescence*, 3rd ed., Elsevier, New York.
5. Clutton-Brock, T. H.; Guiness, F. E. and Albon, S. D.: 1979, *Red Deer: Behavior and Ecology of Two Sexes*, The University of Chicago Press, Chicago, Ill.
6. Cutler, R. G.: 1982, 'Longevity is Determined by Specific Genes: Testing the Hypothesis', in R. C. Adelman and G. S. Roth (eds.), *Testing the Theories of Aging*, CRC Press, Inc., Boca Raton, Fla., pp. 24–114.
7. Dawkins, R.: 1982, *The Extended Phenotype*, W. H. Freeman and Co., Oxford.
8. Dykhuizen, D.: 1974, 'Evolution of cell senescence, atherosclerosis and benign tumors', *Nature*, No. 5476, pp. 616–618.
9. Finch, C. E. and Hayflick, L.: 1977, *Handbook of the Biology of Aging*, Van Nostrand, Reinhold Co., New York, N.Y.
10. Fries, J. F. and Crapo, L. M.: 1981, *Vitality and Aging*, W. H. Freeman Co., San Francisco, Calif.
11. Gertzing, S. D.: 1957, 'Evidence of Aging in Natural Populations of Fishes', *Gerontologia* **1**, 287–305.
12. Haldane, J. B. S.: 1942, *New Paths in Genetics*, London.
13. Hamilton, W. D.: 1964, 'The Genetical Evolution of Social Behavior, Parts I and II', *Journal of Theoretical Biology* **7**, 1–52.
14. Hamilton, W. D.: 1966, 'The moulding of senescence by natural selection', *J. Theor. Biol.* **12**, 12–45.
15. Hayflick, L.: 1980, 'The Cell Biology of Human Aging', *Scientific American* **242**, 58–65.
16. Hinde, R. A.: 1982, *Ethology: Its Nature and Relations with Other Sciences*, Oxford Press, New York, N.Y.
17. Holmes, O. W.: 1857–1858, 'The Deacon's Masterpiece; or, The Wonderful 'One Hoss Shay', *The Autocrat at the Breakfast Table*, Boston, Mass.
18. Jackson, C. H. N.: 1940, 'The Analysis of a Tsetse-fly Population', *Annals of Eugenics (London)* **10**, 22–369.
19. Leopold, A. C.: 1961, 'Senescence in Plant Development', *Science* **134**, 1727–1732.
20. Mayr, E.: 1982, *The Growth of Biological Thought*, Belknap Press, Cambridge, Mass.
21. Medawar, P. B.: 1957, *The Uniqueness of the Individual*, Methuen and Co., Ltd., London.
22. Moment, G. B.: 1982, 'Theories of Aging: An Overview', in R. C. Adelman and G. S. Roth (eds.), *Testing the Theories of Aging*, CRC Press, Inc., Boca Raton, Fla., pp. 2–23.
23. Rose, M. and Charlesworth, B.: 1980, 'A Test of Evolutionary Theories of Senescence', *Nature* **287**, 141–142.
24. Sachar, G. A.: 1982, 'Evolutionary Theory in Gerontology', *Perspectives in Biology and Medicine* **25**, 339–353.

25. Sokal, R. R.: 1970. 'Senescence and Genetic Load: Evidence from Tribolium', *Science* **167**, 1733–1734.
26. Strehler, O. L. and Mildvan, A. S.: 1960, 'General Theory of Mortality and Aging', *Science* **132**, 14–21.
27. Tinbergen, N.: 1951, *The Study of Instinct*, Clarendon Press, Oxford.
28. Weisman, A.: 1881, 'The Duration of Life', in *Essays Upon Heredity and Kindred Biological Problems*, by A. Weisman, E. B. Poulton, S. Sehö, and A. E. Shipley (eds.), trans. A. E. Shipley and S. Schönland, Clarendon Press, Oxford, England, pp. 1–66.
29. Williams, G.: 1957, 'Pleiotrophy. Natural Selection and the Evolution of Senescence', *Evolution* **11**, 398–411.
30. Williams, G. C.: 1966, *Adaptation and Natural Selection*, Princeton University Press, Princeton, N. J.
31. Wright, S.: 1932, 'The Roles of Mutation, Inbreeding, Cross-breeding, and Selection in Evolution', *Proceedings of the 6th International Congress of Genetics*, Ithaca, N.Y., **1**, pp. 345–365.