PLEIOTROPY, NATURAL SELECTION, AND THE EVOLUTION OF SENESCENCE [1]

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Senescence is a widespread phenomenon, but it has been largely neglected by non-medical biologists. This neglect may be attributed to a number of causes. One is that the process seldom presents itself to students of natural populations, since recognizably senile individuals are not often found in the wild. Another, perhaps, is an emotional difficulty associated with aging, a situation that was hardly helped by the early clinical association of senescence with sex hormones. Another is the existence of theories that have gained tacit acceptance, despite their conceptual obsolescence and poverty of factual support. The most injurious of these is the identification of senescence with the "wearing out" that is shown by human artifacts. A moment of serious consideration should convince a biologist of the fundamental dissimilarity between these two processes. The breakdown of human artifacts is strictly mechanical and is readily cured by mechanical repairs. The system is a static one, since the same material is continuously present, and there is no endogenous change with the passage of time. An organism, on the other hand, is an open system in a state of material flux. Even such structures as bones maintain constant exchanges with the environment. Moreover, an organism produces itself by a morphogenetic process. It is indeed remarkable that after a seemingly miraculous feat of morphogenesis a complex metazoan should be unable to perform the much simpler task of merely maintaining what is already formed.

It is true, of course, that some parts of organisms do literally wear out. Human teeth, for instance, show wear similar to that of any tool subjected to friction, but this wear is no more a part of senescence than is the wearing away of replaceable epidermal cells. The senescence of human teeth consists not of their wearing out but of their lack of replacement when worn out.

August Weismann (1891) was the first biologist of the evolutionary era to advance a theory of senescence. He believed that organisms must inevitably show a decline analogous to that of mechanical devices, but that, in addition, there was a specific death-mechanism designed by natural selection to eliminate the old, and therefore wornout, members of a population. He did not clearly indicate how such a mechanism could be produced by natural selection. He was likewise dubious about the exact nature of the death-mechanism, but indicated that it might involve a specific limitation on the number of divisions that somatic cells might undergo.

Weismann's theory is subject to a number of criticisms, the most forceful of which are: 1) The fallacy of identifying senescence with mechanical wear, 2) the extreme rarity, in natural populations, of individuals that would be old enough to die of the postulated death-mechanism, 3) the failure of several decades of gerontological research to uncover any death-mechanism, and 4) the difficulties involved in visualizing how such a feature could be produced by natural selection.

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Point number one was discussed in the opening paragraph, and points two and three will be documented in connection with my own theory. Point number four is concerned with the obvious conclusion that, other things being equal, a long-lived individual will leave more offspring than a short-lived one. If there is no specific death-mechanism, it is just as obvious that an individual that deteriorates slowly would be favored over one that deteriorates rapidly. Natural selection should ordinarily proceed towards lengthening life, not shortening it. Such selection, at the individual level, could conceivably be countered by selection at the population level, if senescence somehow favored group-survival. This suggestion was made by Allee *et al.* (1949: 692). The efficacy of such selection depends upon a rather complicated series of assumptions with respect to population sizes, degree of isolation, and relative strengths of the selective forces (Wright, 1945). A theory based on the simpler and more widely applicable principle of selection within a group would be preferable, unless the assumption of effective between-group selection proves to be necessary.

The neglect of senescence by modern biologists has not, of course, been absolute. Recent years have seen the publication of a number of reviews, the most valuable of which are those of Comfort (1954, 1956). Also there is an increasing awareness of the decline of selection pressures with increasing age. This principle, a central part of the theory developed here, is first recognizable in the work of Bidder (1932), and has since been stated or implied by Haldane (1941), Medawar (1953), and Comfort (1956). The principle is implicit in the currently recognized definition of a lethal gene as one that results in death before the reproductive period. However, the relationship of age to selection has never been precisely formulated.

Comfort is severely critical of Weismann's theory, and offers in its place the theory that senescence is selectively irrelevant. He argues (e.g., 1956: 39) that senescence is outside the developmental program that concerns natural selection, since almost no wild organisms ever attain the senile stage. I believe that this theory is incorrect. Its fallacy lies in the confusion of the process of senescence with the state of senility, and in an inaccurate conception of the relationship of age to selection pressures. No one would consider a man in his thirties senile, yet, according to athletic records and life tables, senescence is rampant during this decade. Surely this part of the human life-cycle concerns natural selection. The rate of senescence, as measured by life tables, is known to be subject to genetic variation (Gonzales, 1923; Kallman and Sanders, 1948). It is inconceivable in modern evolutionary theory that senescence, such as operates in man between ages thirty and forty, is selectively irrelevant.

I shall assume initially, therefore, that senescence is an unfavorable character, and that its development is opposed by selection. To account for its prevalence, therefore, it is necessary to postulate another force that favors its development in such a way that the observed variations in senescence reflect variations in the balance between these two forces. I believe that this other force is an indirect effect of selection, and results from the selection of genes that have different effects on fitness at different ages.

A number of workers have postulated that senescence might result from processes that are favorable early in life but have cumulative bad effects later on. Medawar (1953) expressed this concept in genetic terms by suggesting that linkage and pleiotropy might be involved in keeping favorable and unfavorable traits together, but he failed to elaborate on either possibility. Pleiotropy plays an essential role in the theory developed in this paper, but not linkage. Linkage might keep traits together for a time in a single line of descent, but I fail to see how it could contribute to the develop-

ment of senescence in a population as a whole unless crossover values were infinitesimal. Such a condition would approach pleiotropy and no special theory based on linkage need be elaborated.

The Theory

Four factors are initially assumed:

(1) A soma that is essential to reproductive success but no part of which is passed on in either sexual or asexual reproduction.

(2) Natural selection of alternative alleles in a population.

(3) Pleiotropic genes of a special sort. It is necessary to postulate genes that have opposite effects on fitness at different ages, or, more accurately, in different *somatic environments*.

Convincing examples are hard to find, because we seldom know the total survival value of a gene in a wild population, let alone its values in different parts of the life cycle. The best examples I can offer are at the *black* and *speck* loci in *Drosophila melanogaster*. Most laboratory mutants decrease longevity, but these two increase it, at least in the males under laboratory conditions (Gonzales, 1923). *Black* and *speck* are rare in nature, despite their beneficial effect on vigor late in life. The wild alleles of these genes must confer some earlier advantage that offsets the later disadvantage. Other possible examples exist. Caspari (1952) lists a number of genes of Drosophila and the moth Ephestia that have conspicuous effects on adult characters and also alter the rate of development. Bridges and Brehme (1944) list a number of mutants of *Drosophila melanogaster* that are named for conspicuous effects on the adult but which also alter the larval phenotype in some way. Examples are *glass* and *sparkling*, which alter the size, shape and texture of the eye in the adult and the color of the malpighian tubules in the larva. Quite conceivably these different effects at different times could have opposite influences on survival. However, there seems to be little necessity for documenting the existence of the necessary genes. Pleiotropy in some form is universally recognized, and no one has ever suggested that all the effects of a gene need be equally beneficial or harmful, or that they must all be manifest at the same time.

(4) Decreasing probability of reproduction with increasing adult age. An individual entering a population has a *reproductive probability distribution* (fig. 1, solid curve). For an organism such as

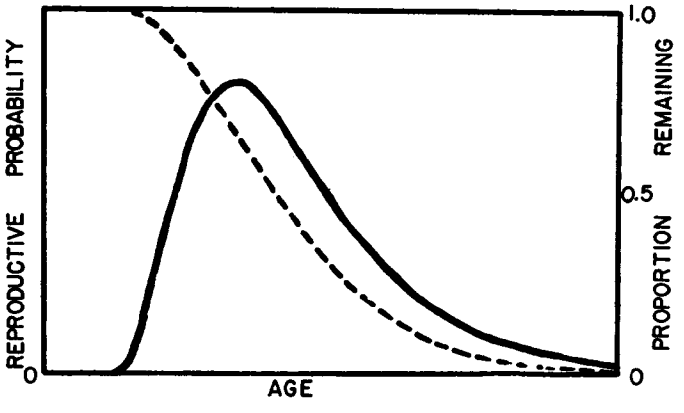

Fig. 1. Relationship of age to probability of reproduction. The solid curve is the reproductive probability distribution. The dashed curve indicates the proportion of the total probability that remains after any given age.

man, who has no definite breeding season, there would be a rise from zero just befor sexual maturity to a peak value shortly thereafter. Then there would be a decline due to a number of factors in man, among them senescence. But even in the complete absence of senescence there would always be a cumulative probability of death. This would produce a decline in reproductive probability, because the probability of reproduction at any age is a function of the probability of surviving to that age. No matter how low the mortality rate there is always a greater chance of surviving to age A than to age $A + 1$.

The fourth assumption need not imply that an individual of age A has a greater likelihood of reproducing itself than an individual of age $A + 1$. If an individual has, in fact, survived to age $A + 1$, the factor of probability does not apply. Medawar (1955) has proposed a mathematical formulation of the reproductive potential of an individual of a certain age in a species characterized by senescence. It was proposed as a measure of the extent of senescence at that age. The fourth assumption relates only to zygotes, and does not imply that senescence is operative.

The reproductive probability distribution of a seasonal breeder would have not one but a series of modes, one for each breeding season. Once maximum fecundity has been reached, however, each successive peak would be lower than the preceding one, due to the probability of death between the two seasons.

Wright (1956) has proposed the following model of the natural selection of a gene with mixed effects on fitness:

$$(1) \quad W = (1 + S_1)(1 + S_2) \ldots (1 + S_n)$$

where W is the selection coefficient of a gene and S_1, S_2, etc. are the advantages or disadvantages associated with its separate effects. Such selective effects consist of two factors. One is the direction and magnitude of the effect itself. The other is the proportion of the total reproductive probability influenced by the effect. This second factor would depend upon the amount of time during which the influence operates, but the relationship would not be a simple proportionality with time. The reproductive probability per unit time in the affected period would also be important.

Equation (1) can therefore be restated as:

$$(2) \quad W = (1 + m_1p_1)(1 + m_2p_2) \ldots (1 + m_np_n)$$

where m is the magnitude of an effect and p is the relevant proportion of the reproductive probability. Obviously a gene that conveyed a slight increase in fitness with a high p-value might be favorably selected in spite of a serious decrease in fitness with a low p-value. This, I believe, is the key to understanding the evolution of senescence, because any genic effect that arises late in life will have a low p-value. Natural selection may be said to be biased in favor of youth over old age whenever a conflict of interests arises. Medawar (1952) reached precisely this conclusion by a somewhat different line of reasoning.

If a genic effect influences the survival of the soma in any way, it will alter the value of the entire reproductive probability that follows the onset of the effect. This is true even if the effect is expressed for only a short period. An influence on the likelihood of coming successfully through the birth process would be an example. It would alter the probability of survival to any age subsequent to birth, and therefore of reproduction at any age subsequent to birth. For such an effect, coming at any time before the reproductive period, the value of p would be unity. Altering the order of such effects would alter the order but not the values of the factors to be multiplied in equation (1) and this would have no influence on the product.

An effect on survival coming during the adult period, however, would alter only

that part of the reproductive probability that follows the age of onset (dashed curve in fig. 1). This proportion, the maximum value of p for any given age, is therefore a measure of the selective importance of that age. Since p starts to decline at the age of reproductive maturation, this point should theoretically mark the onset of senescence.

Some genic effects might influence only fertility or some other strictly reproductive function having nothing to do with somatic survival. This would alter the value of the reproductive probability only for the duration of the effect, because it would not influence the probability of survival to subsequent ages. For such an effect the value of p would be determined by the duration of the effect and by the average reproductive probability per unit time in the affected period.

One of Comfort's main criticisms of Weismann's theory is that it assumed initially what it purported to explain, a declining vigor with increasing age. This is not true of the present theory, since no senescence is assumed to be initially present in the population. Each new gene, however, is judged on the basis of the current reproductive probability distribution. Any previously established genes that cause senescence will increase the rate of decline in p and make it easier for other such genes to become established. In this way senescence becomes a self-aggravating process. It must be emphasized, however, that senescence is an unfavorable character. The direct action of selection will always be opposed to it. The establishment of an important "senescence gene" in a population would cause the favorable selection of other genes that would reduce or delay the unfavorable effects. As a hypothetical example we might imagine a mutation arising that has a favorable effect on the calcification of bone in the developmental period but which expresses itself in a subsequent somatic environment in the calcification of the connective tissue of arteries. If the gene becomes established in the population and if this later effect is eventually deleterious, a selective premium would be placed on any gene that might suppress this arterial calcification. As the suppression approached completion, however, the selection pressure for further suppression would diminish. Complete suppression would probably never be realized. Senescence might be regarded as a group of adaptively unfavorable morphogenetic changes that were brought in as side effects of otherwise favorable genes, and which have only been partly expurgated by further selection. There are therefore, two opposing selective forces with respect to the evolution of senescence. One is an indirect selective force that acts to increase the rate of senescence by favoring vigor in youth at the price of vigor later on. The other is the direct selection that acts to reduce or postpone the "price" and thereby decrease the rate of senescence. The rate of senescence shown by any species would depend on the balance between these opposing forces.

The theory advanced here covers the senescence of genetically defined individuals only. It does not refer to the decline of renewable parts, such as leaves and erythrocytes, but some mention of the senescence of parts seems appropriate. It might be supposed that permanence of functional efficiency is a desirable characteristic of any part of an organism, but that it is not the only consideration. Given the necessary selective forces, it might be possible to evolve a potentially immortal erythrocyte, but some compromises would be necessary. A gene that favored erythrocyte longevity might be far from ideal for the maximization of oxygen-carrying capacity, to say nothing of unrelated functions of other systems that the gene might affect. The selective advantage of an erythrocyte that could last forever over one that could last "a very long time" might be so slight that genes favoring erythrocyte senescence might creep in because of other advantageous effects they might produce. Thus the senescence of renewable parts can also be

attributed to the natural selection of pleiotropic genes.

Testable Deductions from the Theory

The remainder of this paper will be devoted to a consideration of some expectations that follow from the theory, most of which can be tested in a preliminary way by reference to information contained in the literature. I believe that this information, although nowhere conclusive, is quite favorable to the theory.

The first four deductions relate to the phylogeny of senescence. Especially important is the implication that phylogenetic variation in senescence should be predictable on the basis of phylogenetic variation in the reproductive probability distribution. The next four relate to the physiological expectations that follow from the theory, and the last concerns the expected outcome of artificial selection for increased longevity.

(1) *Senescence should be found wherever the conditions specified in the theory are met, and should not be found where these conditions are absent.* There are organisms in which the distinction between soma and germ-plasm may not exist, but the other assumptions of the theory would seem to be inevitable for any organism, at least for any that has a clear distinction between soma and germplasm. The theory regards senescence as an evolved characteristic of the soma. We should find it wherever a soma has been evolved, but not elsewhere.

There should, therefore, be no senescence of protozoan clones. Some clones die out after a limited time, but there is reason to believe that clonal deterioration is fundamentally different from metazoan senescence. There are some strains that can apparently be propagated asexually for an indefinite period and others that cannot. Within a single species both conditions have been reported, and even among the individuals arising from a single pair of exconjugant ciliates, some will die after a few divisions and others can be propagated asexually for as long as favorable environmental conditions are maintained. No such intraspecific variation is known among metazoans. The difference between temporary and permanent clones of protozoans may apparently be due to a very few genetic factors. These various aspects of protozoan "senescence" have been reviewed by Comfort (1956: ch. 3) who concludes (p. 119)

> It is in any case probably misleading to identify the decline of protozoan cultures with the metazoan senescence which it superficially resembles. . . . There is no special reason, upon the present evidence, why the "senescence" of *Paramecium* should continue to figure as extensively as it has done in treatises devoted to gerontology.

While asexual clones should not show senescence, asexually reproducing individuals may be regarded as having somas and they should, according to the theory, show senescence. Fissile animals would appear at first sight to lack a soma, but often the products of fission are not altogether similar. It may be physiologically justified to regard one as parent and the other as offspring. The asexual reproduction of turbellarian flatworms, for example, is often termed fission, but the division is transverse and separates a head end from a quite different tail end. In some, moreover, the two parts are very unequal in size. Sonneborn (1930) interprets the division of the flatworm *Stenostomum incaudatum* as budding. Each worm gives off a small and largely undifferentiated posterior bud and retains most of the specialized tissues. The series of anterior products of division can therefore be regarded as an individual soma giving off buds. Conditions specified in the theory are met, and eventual senescence is expected of the anterior series. This appears, in fact, to be true. Sonneborn was able to keep most of the clones composed of successive posterior ends continuing for long periods of time, and none gave clear indications of death from endogenous causes. Lines of suc-

cessive anteriors, however, all died out after a limited number of posteriors had been given off.

There is a problem as to just what constitutes "the individual" in an asexual clone. From a physiological standpoint, each functionally independent system is an individual, but to natural selection, all such systems of the same genotype collectively comprise a single individual, no matter how numerous and scattered they might be. So it might be best to regard a flatworm clone as an individual and anterior series as its expendible parts.

An analogous problem exists with respect to the soma of higher plants. It is physiologically reasonable to think of a single tree as a separate individual and its demise as the death of a mortal soma. Many of the cells of a tree, however, may give rise to shoots bearing sexual cells or to structures passed on in asexual reproduction. Such potential germ cells are scattered throughout a plant. It may be that the great majority of the living cells of a plant are potential parts of the germline, because even rather specialized cell types can dedifferentiate and give rise to reproductive structures (Buvat, 1944). From the standpoint of selection and the theory developed in this paper, it would be better to regard a clone of higher plants as an individual and the separate cellulose edifices as its expendible parts. This theory demands that there be no senescence of the clone (genetically defined individual) although there should be senescence of its expendible parts (physiologically defined individuals). There is no doubt that physiologically defined individual plants undergo senescence, but the senescence of plant clones is a matter of some controversy. When Molisch wrote his classic review of plant senescence in 1928 (Molisch and Fulling, 1938), he expressed the conviction, with some reservations, that plant clones eventually deteriorate and cannot be maintained indefinitely. When the subject was reviewed again by Crocker (1942), it was indicated that many of Molisch's examples of clonal senescence had been attributed to exogenous causes. Some clones, for instance, deteriorated because of virus diseases that were passed on in asexual reproduction but not through seeds. In regions that were free of these diseases, the clones continued to thrive.

It will probably be a long time before this matter is completely settled. Nevertheless, it can be concluded that if a plant clone undergoes senescence at all, it must be very slow compared with the senescence of the separate individuals of the clone. As Crocker pointed out, many horticultural varieties, which live as isolated plants for only a few years or decades, have been propagated asexually for centuries and are still vigorous.

(2) *Low adult death rates should be associated with low rates of senescence, and high adult death rates with high rates of senescence.* Cumulative adult mortality is the primary reason for decline in reproductive probability with the passage of time. If, as I have indicated, the rate of this decline determines the balance of selective forces acting on senescence at any given age, we should be able to predict rates of senescence on the basis of adult mortality rates.

This expectation is obviously realized, if it is legitimate to compare widely different kinds of organisms. Active adult insects have mortality rates of the order of ten percent per day (Lack, 1954: 102), and maximum longevity is of the order of a few weeks (Comfort, 1954: 57). Mortality rates of adult man in extremely primitive situations probably never averaged more than ten percent per year, and man's maximum longevity may include as many years as that of the insects includes days. In wild populations generally, it probably seldom happens that senesence has more than a slight modifying influence on mortality. The death rates of young adults are usually such that very few individuals will live long enough to suffer any gross debilitation through the process of senescence (Lack, 1954).

The critical comparison would be be-

tween organisms that have approximately similar life cycles except for adult mortality rates. Birds have lower adult mortality rates than mammals of similar size (Lack, 1954; Blair, 1948; 1951), and, as expected, greater potential longevity (Comfort, 1956: 160). The difference in senescence rate has been attributed to some fundamental difference between the physiological organizations of birds and mammals, perhaps to differences in the manner of growth limitation (Comfort, 1956: 160). For reasons discussed below, however, I believe it is unlikely that any single physiological difference is responsible. The evolutionary cause of the low rate of bird senescence must be that birds can fly, are thereby less liable to predation and accidents, and therefore have lower mortality rates. Decisive evidence would come from a detailed investigation of the rates of senescence of flightless birds, for which high rates of senescence would be expected, and flying mammals, for which low rates would be expected. No such investigation has been carried out, but the evidence, although meagre, is extremely suggestive. Of 45 non-passerine birds for which Comfort (1956: 50) lists reliable age maxima, only two, the ostrich and the emu, are flightless, and these are among the four with the lowest age maxima. Large animals are usually longer-lived than small ones, and on this basis the ostrich and emu should live longer than any of the other birds in Comfort's list. If such age maxima are a reliable basis for comparison of senescence rates, a causal relationship between flightlessness and rapid senescence is clearly indicated.

The most volant mammals are the bats. There are no reliable records of bat age maxima, nor studies of mortality rates in the wild. Ringed bats, however, have been recovered after as long as seven years (Lack, 1954: 100), a period that exceeds the age maxima of other small mammals such as rodents and insectivores (Comfort, 1956: 47). Bats must be significantly longer-lived than other mammals of comparable size and developmental rates.

Other special life-history features can affect mortality rates, and such features should therefore influence the evolution of senescence. The shells of turtles presumably reduce their vulnerability to predation and fatal injury. This may account for their great longevity compared with other reptiles, even with very large ones like crocodilians. Relatively small tortoises have a maximum life-span of twice that of the alligator (Comfort, 1956: 51–2). Such factors as homing and territoriality could also affect adult mortality rates and the balance of selective forces acting on senescence. If an animal has occupied an individual niche for a long time it is likely, by virtue of the long-continued survival of the animal, that the niche is an especially favorable one. The probability that it will continue to be favorable for one more year increases with each passing year. Such factors as these would act to lower mortality rates for the higher age groups and intensify the selection against senescence. Such a declining adult mortality rate has been demonstrated for territorial lizards (Stebbins, 1948).

According to the theory, death rates prior to maturation have no influence on the evolution of senescence. The larger fishes and the very prolific marine invertebrates have enormously high mortality rates in the young stages, yet such organisms may live for a long time in captivity (Comfort, 1956: ch. 2).

(3) *Senescence should be more rapid in those organisms that do not increase markedly in fecundity after maturity than those that do show such an increase.* Many organisms, such as rotifers, most insects, and warm-blooded vertebrates grow very little after reaching maturity. Others, such as mollusks, most crustacea, and most cold-blooded vertebrates continue to grow at an appreciable rate long after sexual maturity, perhaps throughout life. Such an increase in size is accompanied by an increase in fecundity. An

old carp may produce ten times as many eggs as a recently matured one (Carlander, 1953). An increase in fecundity has the opposite effect from mortality. It tends to increase the reproductive probability for the more advanced ages and thereby intensify the selection against senescence. This, I believe, is the basic evolutionary reason for the apparent association between rapid senescence and determinate growth (Comfort, 1956: ch. 5).

(4) *Where there is a sex difference, the sex with the higher mortality rate and lesser rate of increase in fecundity should undergo the more rapid senescence.* Males of many animals are exposed to greater risks than females. They may fight each other or spend much time in conspicuous courtship displays, and they may be more conspicuously colored than the females. All these factors would increase the dangers from predation, and any actual combat. of course, may be dangerous in itself. A greater adult mortality rate of males is known for a number of wild populations of species to which these considerations apply (Haskins and Haskins, 1951; Krumholz, 1948; Lack, 1954: 111–12) although female mortality rates seem to be higher in birds (Lack, 1954: 107–11). Likewise, the number of offspring produced by a male is presumably less dependant upon body size than it is in the female, at least where there is internal fertilization. All these factors would make the rate of decline in reproductive probability more rapid in males than in females. The balance of selective forces should therefore result in more rapid senescence in the males of species in which these conditions are found, and in which the genetic and hormonal mechanisms provide for sex differences in such characters.

Throughout the animal kingdom it is a general rule that females are longer-lived than males; so it would appear that the theoretical expectations are realized. There are some possible exceptions, and unfortunately both the rule and exceptions are based on scanty data (Comfort, 1956: 30–4). It is certain, however, that the females of really well studied animals, such as man, farm animals, and the fruit-fly are longer-lived than the males. The theory of senescence as a function of the reproductive probability distribution may explain sex-differences in vigor in old age, but it does not explain the frequently observed differences in vigor early in life, such as the greater fetal and infant mortality of human males.

(5) *Senescence should always be a generalized deterioration, and never due largely to changes in a single system.* The earlier an adverse genic effect, the greater will be the associated p-value and the intensity of adverse selection. So if the adverse genic effects appeared earlier in one system than any other, they would be removed by selection from that system more readily than from any other. In other words, natural selection will always be in greatest opposition to the decline of the most senescence-prone system. If, for instance, degenerative changes in the endocrine glands were the primary cause of human senescence, there would be little selection against the deterioration of other organs. The selective forces against senescence would be directed primarily against that of the endocrine system. This selection and the accumulation of harmful genetic effects in other systems would cause the senescence rate of the other systems to approach that of the endocrine glands.

Formerly it was believed that mammalian senescence was largely a hormonal phenomenon. Miraculous rejuvenation was anticipated from the implantation of young gonads into aged people, but the miracles were never realized. It was also thought by some that a deterioration of the nervous system was the primary cause of senescence in certain insects. Comfort has shown, however, that there is little evidence for these beliefs. For insects he lists (1956: 96–7) several known types of senile deterioration, including "general senile decay." In mammals and especially man it is now realized that senescence

characterizes many organs and systems, perhaps all (Comfort, 1956: ch. 6; Lansing, 1952: ch. 8–30). More evidence is needed for other organisms, however.

Comfort (1956: 98) points out that death in insects that do not feed during the imaginal stage must eventually result from a depletion of food reserves. This is true, but according to my theory there should be other degenerative changes in addition to the food depletion. It would be expected that death in natural populations would result from these other changes about as often as from the food depletion. Otherwise there would be intense selection favoring greater food reserves. It would also be predicted that artificial replenishment of food reserves would not lengthen life to any significant degree.

Basic research in gerontology has proceded with the assumption that the aging process will be ultimately explicated through the discovery of one or a few physiological processes. Medawar (1955) clearly expressed this basic assumption. He envisioned the essential task of gerontologists to be that of distinguishing cause from effect among the multitude of observable changes in aging organisms, and eventually isolating the presumably few ultimate causes. Any such small number of primary physiological factors is a logical impossibility if the assumptions made in the present study are valid. This conclusion banishes the "fountain of youth" to the limbo of scientific impossibilities where other human aspirations, like the perpetual motion machine and Laplace's "superman" have already been placed by other theoretical considerations. Such conclusions are always disappointing, but they have the desirable consequence of channeling research in directions that are likely to be fruitful.

(6) *There should be little or no post-reproductive period in the normal life-cycle of any species.* This prediction is a special case of the one immediately preceding, since sterility is the selective equivalent of death. If most of the senescence-influenced removal of individuals from the breeding population were due to a deterioration of the reproductive system, there would be a greater selection against this deterioration than any other. The population would evolve towards increased reproductive and decreased somatic longevity.

At first sight it appears that this prediction is not realized. Long post-reproductive periods are known in many domesticated animals and in man himself. In man it may even be longer than the reproductive period. However, these observations lose much of their seeming importance when it is realized that they are largely artifacts of civilization. In very primitive conditions, such as prevailed throughout almost all of man's evolution, post-reproductive individuals were extremely rare. Of 173 paleolithic and mesolithic skeletal specimens whose age at death could be determined, Valois (1937) found only three who were over fifty, and none was much older than this. It is safe to conclude that senile sterility became an important factor in removing individuals from the human breeding population only in recent historical times.

The term *post-reproductive* needs clarification with respect to man. There is more to reproduction than producing viable gametes. In man there is a very long period of dependance after conception. Any individual, of whatever age, who is caring for dependent offspring is acting in a way that promotes the survival of his own genes and is properly considered a part of the breeding population. No one is post-reproductive until his youngest child is self-sufficient. So the post-reproductive period in man begins not with senile sterility, but at least a decade later.

In the human male and in both sexes of other animals, reproductive decline is a gradual process (Comfort, 1956: 177–8), as is the senescence of other systems. In the human female, however, it is rather abrupt, and some special explanation is required. At some time during human evolution it may have become advantage-

ous for a woman of forty-five or fifty to stop dividing her declining faculties between the care of extant offspring and the production of new ones. A termination of increasingly hazardous pregnancies would enable her to devote her whole remaining energy to the care of her living children, and would remove childbirth mortality as a possible cause for failure to raise these children. Menopause, although apparently a cessation of reproduction, may have arisen as a reproductive adaptation to a life-cycle already characterized by senescence, unusual hazards in pregnancy and childbirth, and a long period of juvenile dependence. If so, it is improper to regard menopause as a part of the aging syndrome.

The long post-reproductive periods of domesticated animals are also the products of civilization. The rat has a long post-reproductive period in a man-made environment where blindness, extensive paralysis, and other gross functional impairments do not result in death, but this is clearly not of the same significance as such a post-reproductive period in a wild individual.

A related problem is that of castration. Castration, of course, immediately reduces the reproductive probability to zero, but it is only through selection that such an effect could hasten senescence. If castration were persistently performed at a certain age, it would remove all selection against senescence following that age. After a large number of generations an increased rate of senescence would be expected after the age of castration.

Such an experiment has been performed by nature in the development of uniparous animals and monocarpic plants. For every individual of such species, the immediate reason for reproducing only once is that once it reproduces it dies. Historically, however, it must have been the other way around. The lack of a second period of reproduction in the normal life-cycle removed all selection against senescence following the first reproduction. Eventually this resulted in a uniparous or moncarpic life-cycle through an extremely rapid senescence following the first period of reproduction. Such conditions probably arise gradually. Heavy mortality between the first and second breeding seasons lowers the reproductive probability for the second season relative to the first. This in turn favors the development of senescence between the two breeding seasons, and this further lowers the probability of a successful second reproduction. Eventually the complete loss of the second period of reproduction might not be a serious disadvantage, and might be brought in as a pleiotropic effect of a gene that conferred some slight advantage during the first season. A possible transitional condition is shown by the Pacific steelhead trout, which spawns in the same streams as the salmon *Oncorhynchus kisutch*. The trout, unlike the salmon, does not die right after the first spawning. It may return to the sea and undertake a second spawning migration the following year. The chances of a repeat spawning are low, however. The first spawners were five times as numerous as all other age groups combined in a spawning steelhead population studied by Shapovalov and Taft (1954).

(7) *The time of reproductive maturation should mark the onset of senescence.* Senescence is regarded in this paper as a consequence of the decline of reproductive probability with increasing age. This decline starts at the time of reproductive maturation. So senescence should also begin at this time.

This expectation would be very difficult to test at present, since no precise measurement of senescence has been developed. The life-table demonstration of increasing probability of death with increasing age is subject to some serious criticisms but remains the best available measure of senescence (Medawar, 1955). It is reliable only when different age classes are exposed to the same kinds and degrees of dangers and stresses. Since such factors are seldom completely controlled, the life-table can be relied on only for studying very marked functional impairments with the passage of time.

Moreover, senescence is not the only factor responsible for variations in vigor at different ages. All through development there must be compromises between the need for continuous fitness and the demands of morphogenesis. The modern human mortality rate is extremely high in infancy, a period of rapid morphogenesis. It then declines to a minimum at ages ten to twelve, rises during adolescence, and continues to rise with increasing rapidity thereafter (Comfort, 1956: 16). This distribution of death rates might be taken as verification of the theory, but adolescence is a period of more rapid morphogenesis than that immediately preceding, and this factor may be partly responsible for the increased adolescent mortality. Moreover, the distribution of stresses and dangers is hardly uniform through childhood, adolescence, and early adulthood.

In many primitive human societies the death of teen-age parents must have greatly reduced the survival prospects of any children they might have produced. The care of dependent offspring is as important to human reproduction as the production of gametes. So the rate of decline in reproductive probability in early adulthood must be very slight, and this factor should result in a very low rate of senescence during the first decade of man's reproductive life.

Comfort (1956: 39–40) maintains that any theory of senescence based on natural selection demands that the age of minimum mortality and that of maximum fertility should coincide. He casts doubt on such theories because human life-tables fail to confirm this expectation. This argument is surely fallacious. Vigor at age ten is no less important to human reproduction than vigor at age twenty-five. In fact it is more important. Vigor at ten affects the value of the entire reproductive probability. Vigor at twenty-five affects only the part of reproductive probability that follows that age.

(8) ***Rapid individual development should be correlated with rapid senescence.*** Reproductive maturation is the most important landmark in the life-cycle for the evolution of senescence. Senescence may theoretically begin right after this stage in development. So the sooner this point is reached, the sooner senescence should begin, and the sooner it should have demonstrable effects. This is, perhaps, another reason for the apparently slow senescence of birds. They grow very rapidly to maximum size, but sexual maturity does not occur until long after this maximum size is reached.

Senescence has long been considered an aspect of morphogenesis (see Comfort, 1956: 7–8, for references), although the precise meaning of this relationship has never been clarified. In this paper I have assumed that genes produce different effects in different somatic environments, and that these effects become progressively less controlled by selection with increasing adult age. If senescence is actually due to the morphogenetic effects of genes, conditions that favor rapid morphogenesis should also favor rapid senescence, not only by reducing the time required to reach maturity, but during the adult stage as well. The rate of recognizable morphogenetic change in the adult, such as the obliteration of bone sutures in man, should therefore correspond to the rate of senescence.

The idea that the rate of senescence depends in some way on the "rate of living" has been recognized for many years. It appears that there is some sort of fixed quantity of vital vigor that can be expended at different rates. Comfort (1956: ch. 5) advanced three hypotheses as to the nature of this life quantity: (1) an unrenewable store of some vital necessity (2) a metabolic quantity, measurable, perhaps, in calories (3) a fixed developmental sequence. Since the first suggestion was not made specific enough to discuss very critically, the choice is mainly between the remaining two. According to my theory, the third alternative is the correct one. It would be expected that if development could be completely arrested, there would be no senescence, and that if development were greatly accelerated,

without a commensurate increase in metabolism, senescence would be accelerated and appear at the usual developmental stage.

Senescence of monocarpic plants can be greatly delayed by preventing them from forming flowers and seeds (Crocker, 1942). The eel may live 55 years in captivity (Comfort, 1956: 53), where conditions necessary for spawning are not found, but wild ones usually spawn and die at about ten years, and never more than twice this age (Frost, 1950). An eel kept for half a century at room temperature surely performs an enormously greater feat of metabolism than a wild one in ten years. If the immediate post-reproductive death of organisms that reproduce only once is considered senescence, and if the pre- and post-reproductive periods are considered morphogenetic stages, these observations on eels and monocarpic plants indicate a causal relation between delayed morphogenesis and delayed senescence.

A direct relationship between rates of morphogenesis and of senescence is also indicated by Lansing's (1947) evidence of a cytoplasmically inherited factor that influences both longevity and rate of development of rotifers.

(9) *Successful selection for increased longevity should result in decreased vigor in youth.* If senescence results from genes that increase youthful vigor at the price of vigor later on, the loss of some of these genes through selection should result in decreased youthful vigor. It does not follow that puny youths are necessarily long-lived, nor that very old individuals were necessarily below average in youthful vigor. Most of the genes or gene combinations that favor vigor early in life probably also favor longevity. Only a small proportion of the genes need be of the sort that produce opposite effects on fitness at different ages, and of these, only a certain proportion would have available alleles that could reduce the rate of senescence. It follows that an individual can not be exceptionally gifted with both youthful vigor and long life. I would predict that no human being who is over a hundred years old was unusually vigorous as a young adult.

Summary

A new individual entering a population may be said to have a *reproductive probability distribution.* The reproductive probability is zero from zygote to reproductive maturity. Later, perhaps shortly after maturity, it reaches a peak value. Then it declines due to the cumulative probability of death. There is a cumulative probability of death with or without senescence.

The selective value of a gene depends on how it affects the total reproductive probability. Selection of a gene that confers an advantage at one age and a disadvantage at another will depend not only on the magnitudes of the effects themselves, but also on the times of the effects. An advantage during the period of maximum reproductive probability would increase the total reproductive probability more than a proportionately similar disadvantage later on would decrease it. So natural selection will frequently maximize vigor in youth at the expense of vigor later on and thereby produce a declining vigor (senescence) during adult life. Selection, of course, will act to minimize the rate of this decline whenever possible. The rate of senescence shown by any species will reflect the balance between this direct, adverse selection of senescence as an unfavorable character, and the indirect, favorable selection through the age-related bias in the selection of pleiotropic genes.

Variations in the amount of fecundity increase after maturity, in the adult mortality rate, and in other life-history features would affect the shape of the reproductive probability distribution and thereby influence the evolution of senescence. Any factor that decreases the rate of decline in reproductive probability intensifies selection against senescence. Any factor that increases the rate of this decline causes a relaxed selection against

senescence and a greater advantage in increasing youthful vigor at the price of vigor later on. These considerations explain much of what is known of phylogenetic variation in rates of senescence.

Other deductions from the theory are also supported by limited available evidence. These include the expectation that rapid morphogenesis should be associated with rapid senescence, that senescence should always be a generalized deterioration of many organs and systems, and that post-reproductive periods be short and infrequent in any wild population.

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