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The connections between general and reproductive senescence and the evolutionary basis of menopause

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We consider the relationship between the factors responsible for the general biology of aging and those that specifically influence the aging of the reproductive system. To understand this relationship it is necessary to be clear about the evolutionary forces acting on both sets of factors. Only in this way can the correct causal connections be established. Of particular significance is the existence in some species of a distinct period of postreproductive life. This is most striking in the case of the human menopause, for which a particular combination of biological and sociobiological factors appear to be responsible.

Keywords: aging; evolution; menopause; life history; reproduction; senescence

Introduction

The aging process is commonly defined as a progressive decline within adult organisms of the functional capacity of most, if not all, organ systems, resulting in an age-specific increase in mortality rate and a decline in fertility.[1] An increase in mortality and decline in fertility are detrimental to Darwinian fitness. Thus, aging should be selected against and its widespread occurrence has long been regarded as a key puzzle in evolutionary theory. The fact that longevity is clearly under genetic control raises the interest in understanding the evolutionary roots of aging.[2] A clear contrast between this control of organismal *survival* and an aging program, which involves regulation of mechanisms for organismal *death*, is essential for this understanding. Linked with this is the need to understand the connections between the longevity of reproductive viability and the length of life itself.

At a superficial level, the forces governing general and reproductive senescence are commonly seen to be causally interconnected according to a rather loose logic that has characterized some of the popular thinking around these questions. This has caused enduring confusion. The answer to why aging occurs is often answered by suggesting that once an organism runs out of reproductive viability, or even when it has fulfilled some necessary "quota" of reproduction, it is surplus to requirement and may die. This extends even to the suggestion that postreproductive survival is a drain on a species' resources and therefore that there is likely to be active programming of the aging process in order to get rid of superfluous consumers. These ideas are founded, for the most part, on an inadequate understanding of how natural selection operates and they deserve mention here only on account of their perennial resurfacing, like weeds in a garden. There are, however, deep interconnections between the biology of general and reproductive senescence that merit careful attention. In addressing these intriguing questions it is of paramount importance to organize the logic into the correct causal sequence. In this review, we summarize first why aging is thought to occur at all. We then consider the implications of the evolutionary theory of aging for the mechanisms affecting reproductive senescence. Finally, we address the significance within this framework of postreproductive survival and in particular of the menopause.

Why general senescence occurs

There is general acceptance today that underlying the evolution of aging is the inescapability of

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death from extrinsic hazards, such as predators, challenging environmental conditions, and infectious disease.[3,4] As a result, the cumulative probability of surviving to older and older ages grows smaller and smaller.[5] As Medawar[5] pointed out, and others have elaborated more formally,[6,7] it follows from this empirical observation that, if traits affecting evolutionary fitness are expressed in an age-specific manner, the power of natural selection to affect the evolutionary fate of these traits will gradually diminish with increasing age.

From this recognition of the waning power of natural selection, *even in the absence of original senescence*, it follows that the door is opened to the evolution of specific factors that might cause senescence to arise. There are two "classical" formulations of how this might occur. In the first, the "mutation accumulation" theory, deleterious alleles that affect survival or reproduction only very late in life, when selection is weak, could accumulate in the genome over evolutionary time by mutation pressure checked only weakly by mutation-selection balance.[5] In the second, alleles with "antagonistically pleiotropic" effects, such that they enhance fitness early in life when selection is strong, but depress it late in life when selection is weak, can be favored by natural selection. The reasoning is that the early beneficial effects will, as a direct result of the differential weighting caused by the action of extrinsic mortality, count for more than the later deleterious effects, even when the early effects are smaller in absolute magnitude than the later effects.[8]

These classical theories for the evolution of senescence are essentially "mechanism-free," in the sense that they postulate only the age-specific character of the hypothetical alleles. This is both a strength of the theories, in that they are neutral with respect to the specific nature of the molecular and cellular mechanisms, but it is also a limitation, in that their predictions are of only a general kind. This limitation was overcome in a subsequent theory that was based on recognizing the physiological costs of an organism's long-term maintenance. The "disposable soma" theory[9,10] recognized that such maintenance is costly and from this derived an integrated hypothesis explaining both why and how aging is caused. Taking account of the attrition in survival caused by extrinsic mortality, somatic maintenance needs only to be good enough to keep the organism in sound physiological condition for as long as it has a reasonable chance of remaining alive in the wild environment. For example, since more than 90% of wild mice die in their first year,[11] a mouse that invests in mechanisms for survival beyond this age has only a 10% chance of receiving any benefit—clearly not a worthwhile return. Nearly all of the mechanisms required for somatic maintenance and repair (DNA repair, antioxidant systems, protein turnover, etc.) require metabolic resources. Resources are scarce, and organisms must tradeoff investment in maintenance and repair with other physiological demands, such as reproduction[12] and immunity.[13]

An abundance of empirical evidence has accumulated in support of these theories. A prediction of classical theories is that interference with the schedule of either reproduction or mortality may impact upon the actions of natural selection on the determinants of longevity. This has been verified through a series of artificial selection experiments, most notably in the fruit fly *Drosophila melanogaster* where selection for late reproduction increased longevity[14–16] and imposing different mortality regimes resulted in the expected effects on longevity.[17] Additional support is provided by "natural experiments," such as the longer lifespans observed in island than mainland populations of opossums that had higher rates of mortality presumably as the result of greater predation pressure.[18] Furthermore, these selection experiments and a variety of comparative studies[19,20] have confirmed repeatedly that, in line with the predictions of the disposable soma theory, increased longevity is associated with an increased investment in the mechanisms underpinning somatic durability and maintenance.

The status of an "aging program"

Although the logical and empirical underpinnings of the evolutionary theory of senescence are extremely strong, there has continued to be a tendency to seek explanation of aging in terms of some kind of adaptive genetic program that specifically limits the individual's lifespan. This has led to recurring misunderstandings about the genetic basis of aging and longevity.[21] It is beyond doubt that genetic factors are important influences on the length of life. This is indicated by the interspecific differences in species' lifespans, the discovery of mutations affecting lifespan, and by the clear heritability of human longevity.[22,23] However there is an essential distinction between this well-established genetics of aging

and longevity, which recognizes that genes influence the mechanisms that underpin longevity, and the genetics that is inferred for an aging program, which would involve genetically specified mechanisms that actually result in the destruction of living systems. This distinction was articulated as long ago as 1982:

> The issue that distinguishes programmed from nonprogrammed ageing is not *whether* the factors that determine longevity are specified within the genome, but rather, *how* this is arranged. An organism which undergoes programmed ageing is regarded as having a specific mechanism to limit its duration of life, whereas an organism which is not programmed in this way does not. In the latter type of organism, duration of life may be determined, for example, simply by the efficiency of somatic repair (p. 114).[24]

The attractions of the program concept are easily understood. First, aging is phylogenetically a very widely distributed trait and in species where senescence occurs, it affects every individual that lives long enough to experience its adverse impacts on fertility and vitality. To many, it therefore seems to make sense that aging exists "for a purpose." Second, there are, as already observed, clear genetic effects on longevity and this leads naturally to supposing that the relevant genes specify some kind of "aging clock." Third, in a postgenome era, when new evidence of genetic causality is being uncovered in many realms of biology, the default assumption that aging is *caused by* gene action preexists in the minds of most of those who come afresh to considering why aging occurs, although this argument is undercut by recent observations that regulation of gene expression deteriorates with age.[25] Finally, and despite the evidence that the details of the aging process are intrinsically variable from one individual to another, there is sufficient broad reproducibility about the manifestations of senescence that it naturally lends itself to the intuition that it has somehow to be programmed. It may reflect the fact that the idea of programmed aging is so apparently intuitive that few attempts have been made to develop a formal logic to support this idea. The commonest suggestions are that possession of a fixed limit to lifespan (i) is beneficial, or even necessary, to prevent the species from overcrowding its environment,[26] or (ii) promotes long-term evolutionary fitness by securing the necessary turnover of generations that allows novel adaptations to be selected.[27]

For either of these suggestions to work, it is a necessary prerequisite that intrinsic aging should make a sufficient contribution to natural mortality that the hypothesized selection process is feasible. If an individual dies before senescent effects are apparent, it makes no difference whether or not that individual is endowed with genes that program aging. Such a program can only be fashioned by selection acting to realize the hypothesized benefits of a program for aging *in those individuals who survive to an age when the program takes effect*. It is therefore a problem for program theories of aging that although some degree of senescence (age-related functional decline and increase in mortality rates) has been reported in many natural populations of species that show evident aging in a captive setting, relatively few individuals survive long enough to be affected by it.[28,29] The exception occurs in semelparous species, such as Pacific salmon, that have evolved a life history plan in which there is only a single bout of reproduction. In such species, death of the parent usually occurs rather quickly after reproduction. Indeed, an important source of misunderstanding of the evolutionary theory of aging has been to regard postreproductive death in semelparous species as an instance of programmed aging, when in fact its evolutionary explanation appears likely to be very different.[30]

How reproductive senescence relates to general senescence

As Weismann[31] recognized, there is often an important distinction in multicellular animals between the cells that constitute the reproductive lineage, or "germline," and those that make up the rest of the body, or "soma." It is an essential requirement of the germline that it can propagate itself indefinitely, or the branch of life that it represents would quickly die out. The essence of the disposable soma theory is the recognition that Weismann's soma/germline distinction has deep implications for investments in the long-term maintenance of the soma. These investments are predicted to be limited, leading to somatic senescence. In effect, the primary function of the soma is to support the germline in its all-important reproductive role.

The necessary immortality of the germline raises interesting questions about its relationship to reproductive senescence. Although the germline must be protected from the long-term accumulation of faults that would lead, over generations, to its eventual failure, it does not follow that in an individual organism reproductive function needs to be sustained indefinitely. The gonads, which include somatic as well as germ cells, are vulnerable to broadly the same kinds of molecular damage that affect other organs. There can be little adaptive value in securing a nonaging reproductive system while every other system of the body is falling apart, except where reproductive success is unaffected by somatic failure, which is generally unlikely. The important quality of the germline is simply that while reproductive viability is sustained, germ cells should as far as possible be free from molecular defects that might compromise the viability of offspring. Babies need to be born young, not old.

How the germline secures its immortality involves a combination of factors and is not completely understood. The overproduction of gametes provides a mechanism to select only the most viable cells and it is possible that such selection acts to screen out significant numbers of potentially defective germ cells from contributing to reproduction.[32] Selection also acts at all stages of pregnancy from implantation of the fertilized egg through to *in utero* and neonatal mortality, which further helps to reduce the threat of accumulating faults in the germline.[33] There also appear to be elevated levels of maintenance and repair in germ cells, as compared with somatic cells.[34] This is evidently the case with the enzyme telomerase, which acts to maintain telomeres in germ cells but which is commonly switched off or downregulated in somatic cells.[35] A specific prediction of the disposable soma theory was that for reasons of energy efficiency there should be a switching off of the mechanisms responsible for high fidelity maintenance "at or around the time of differentiation of somatic cells from the germ-line" (p. 303).[9] It is therefore striking that exactly such a process has been reported when mouse or human embryonic stems cells undergo early differentiation, which is accompanied by a general reduction in the levels of key cellular maintenance systems, such as DNA repair and antioxidant defenses.[34,36]

Although the germline maintains its potential for immortality throughout the fertile period, it is clear that the germ cell population does indeed undergo significant aging from a statistical point of view, even while reproductive viability is maintained. In the case of the human ovary the rate of follicular loss accelerates from around age 35,[37] and male fertility begins to decline, at a more gradual rate, from around age 40.[38] There is also an increase in the frequency of chromosomal abnormalities in newborn children as a function of maternal and, to a lesser extent, paternal age.[39] Nevertheless, healthy children born to older parents are not prematurely aged, although there is some suggestion that daughters' (but not sons') longevity is adversely affected by advanced paternal age.[40] The specific molecular mechanisms underlying age-related deterioration in the germ cell population need to be better understood. For example, oocytes from aged humans show a decline in the ability to segregate chromosomes synchronously,[41] and studies in mice are investigating the underlying reasons for this (M. Herbert *et al.*, unpublished observation).

In view of the centrality of reproduction within the organism's life history, it is natural that there should be intercommunication between the gonads and the rest of the body that may have important consequences for senescence. This is seen dramatically in the case of semelparous species, where the entire life cycle is geared toward maximizing success during the one and only bout of reproduction. The rapid deterioration of Pacific salmon after mating is a byproduct of a life history that has been geared by natural selection to stake everything on the success or failure of a single bout of reproduction. The first phase of a semelparous life history is devoted to growth and to acquiring the resources necessary for reproduction. As soon as the signal to reproduce is triggered, a massive effort is made to mobilize all available resources to maximize reproductive success, even if this leaves the adult so severely depleted or damaged that death ensues. Once a species has evolved down the pathway that results in semelparity (this is most likely to occur where ecological circumstances decree that the chance of surviving to breed again would in any case be small), there is no reason to hold back resources for postreproductive adult survival. Although instances may conceivably occur where the death of the adult directly benefits its young,[30] there is little evidence that semelparous organisms are *actively* destroyed once reproduction is complete. They are, in effect, extreme examples

of the "disposable soma." It is striking that in Pacific salmon, removal of the gonads before reproduction can occur results in significant extension of lifespan.[42] In iteroparous species, castration has less dramatic effects on senescence although there is some evidence that male castration reduces or removes the longevity disadvantage experienced by males in humans and some domesticated species.[43] Elegant studies using germ cell ablation by direct or genetic methods have shown that in the nematode *Caenorhabditis elegans*, germ cells exert significant effects on somatic aging.[44,45] As with the studies in semelparous species, these experiments reveal not that the reproductive system actually programs aging per se but that the allocation of resources between reproduction and maintenance may be tuned to signals that take account of the organism's status with respect to its physiological and maturational status. A further interesting example of interplay between the reproductive and general somatic systems that well illustrates the connections between resource allocation and senescence is seen in the case of rodent dietary restriction. During periods of food shortage, mice (and to a slightly lesser extent rats) switch off fertility and appear to divert any resources thereby saved into increased somatic maintenance. There is some evidence that such a switch in resources is the result of a selective adaptation,[46] which delays general and reproductive senescence while deferring fertility until the environmental is more favorable.

Natural selection and postreproductive life

A period of postreproductive life is seen when either there is a specific shut-down of fertility well ahead of general biological senescence or when reproductive system-specific senescence leads to a decline in reproductive function faster than general senescence leads to mortality. Even if reproductive system-specific senescence runs, on the average, no faster than general senescence, variation in the relative timing of senescent effects in different organ systems will mean that postreproductive individuals may be found who are observed to be alive but no longer fertile. Since reproduction is physiologically demanding, it is unlikely that organisms will remain fertile up to death. These considerations mean that the biological significance of, and reasons for, postreproductive survival need to be reviewed with care (e.g., Reznick *et al.*).[47] This is particularly relevant for female postreproductive survival, since in many species the store of potential oocytes is fixed early in development and postreproductive life begins once this store has been exhausted. Artifactual postreproductive survival may occur when disease accelerates ovarian depletion, or, as seems likely to have happened in laboratory rodent strains, intensive breeding has selected for increased early fecundity leading to more rapid ovarian exhaustion than would occur in natural populations.[48]

If a significant period of postreproductive survival is seen in a majority of surviving individuals within a population, this raises intriguing challenges to explain why such a state should exist. Two general observations help to focus the analysis of such examples:

Observation 1. There is little or no advantage to be gained from an organism's survival after its reproduction is complete unless the survival of the adult contributes to the success of its offspring, in which case survival is not strictly postreproductive since parental care is an integral part of the package. "Offspring" may, in social organisms, be generalized to include genetic kin and their progeny as well as direct descendants.

Observation 2. There is little to be gained by causing the death of a postreproductive adult except where such survival adversely affects the success of its offspring, as defined in 1.

Both observations may be further qualified by the fact that any potential advantage of either postreproductive survival or death will be strongly modulated by the strength of selection acting at the relevant ages. This is particularly relevant in iteroparous species where the force of selection declines throughout reproductive life. In the case of semelparous life histories, the force of selection is maximal until reproduction commences. This is because even though many individuals will die before this can happen, all reproduction is still in the future until this point and therefore any differences between alternative genotypes will feel the full force of natural selection. Immediately after semelparous reproduction is completed, the force of natural selection reduces to zero, except where parental care is operative (although, as noted above, in such cases it can not yet be said that reproduction is actually completed). Thus, there is a spectrum of possibilities that is seen across the range of semelparous organisms. In some instances, death and

reproduction are intimately linked, for example if the adult body is consumed as a food source by the young. In the mite *Adactylidium* the young hatch inside the body of the mother and eat their way out.[24] In other cases, the parent indulges in short-term parental care before dying, as in the female *Octopus hummelinckii* that propel water over their eggs to ventilate them.[24] Often, however, as in Pacific salmon, the semelparous adult simply dies although not necessarily at once, generally from side-effects of extreme reproductive effort, with no obvious benefit being generated either by death or temporary survival. Thus, the first point to note in considering the significance of postreproductive survival across the species range is that the underlying life history pattern, in particular whether it is iteroparous or semelparous, is an essential consideration.

Observation 2 above is relevant to considering whether cessation of reproduction should result in an abrupt increase in mortality. Such a prediction was considered by Hamilton[6] who referred to the possibility as a "wall of death." If reproduction ends, the effect on the force of selection is such that within the terms of the mutation-accumulation theory for evolution of senescence, there should be a steep increase in the number of late-acting deleterious mutations beyond this age. This formal concept is, however, questionable. First, despite significant effort to demonstrate that mutation accumulation contributes to senescence, the great majority of studies have proved negative.[49] Second, as was pointed out by Kirkwood,[9] the concept begs the physiological question of what might be the timing mechanism to control the action of late-acting mutations if we disallow, as previous considerations tell us we must, the notion of a program for aging.

The really interesting question concerning postreproductive life is whether the exceptions noted with respect to Observation 1 are sufficient to make an extended period of survival positively advantageous. This is of greatest interest in social animals where the concept of "inclusive fitness"[50]—namely, the idea that an individual can contribute to the success of its genes not only through its own reproduction but by aiding the reproduction of its kin—comes into its own. Studies in social animals, such as lions, baboons, and killer whales,[51–53] have demonstrated significant survival of postreproductive females in the natural environment. Interestingly, chimpanzees do not seem to have a significant postreproductive survival in the wild and this may also be true in captivity.[54,55] The clearest evidence of postreproductive life follows fertility loss in women (menopause), which occurs at a remarkably similar age—around 50 years—in all human populations,[56] and which is preceded by a period of 10–15 years of declining fertility. When compared with other species, the decline in human fertility and ultimately the menopause happens unusually early in the lifespan.[56,57] Its proximate cause (as in other mammalian females) is the exhaustion of ovarian oocytes, accompanied by degenerative changes in reproduction-associated elements of the neuroendocrine system.[58]

Two broad hypotheses have been advanced to explain menopause in terms of active selection for a period of postreproductive survival. These are founded on the extreme altriciality of human infants and the extensive opportunities for intergenerational cooperation within kin groups.[8,59–61] The altriciality of human offspring appears to be the result of a compromise driven by the evolution of an increasingly large brain in the hominid ancestral lineage and the pelvic constraint on the birth canal. On the one hand, the human neonatal brain size is near to the limit that is compatible with safe delivery, and even so presents considerable mortality risk to the mother in cases of birth complications. On the other hand, the newborn human infant still requires its brain to grow and develop for a considerable period before it is capable of any kind of independent existence, which renders it highly dependent on adult (usually maternal) attention for its survival. Given that maternal mortality increases with age and that maternal death will seriously compromise the survival of any existing dependent offspring, it appears to make sense to cease having more children when the risks outweigh the benefits. Nevertheless, *Homo sapiens* is unique in the extent to which kin assist in care and provisioning of young.[61,62] Thus, an alternative theory is that menopause enhances fitness by producing postreproductive grandmothers who can assist their adult offspring by sharing in the burden of provisioning and protecting their grandchildren. A further contribution to inclusive fitness may also be made within kin groups if postreproductive women contribute similar support to the survival and reproduction of other relatives.

At the core of any plausible evolutionary hypothesis must be, in addition to a verbal statement of the potential adaptive benefit, a quantitative demonstration that there is indeed an associated increase in fitness under natural fertility and mortality conditions representative of our evolutionary past. This validation is often lacking but without it, the hypothesis remains a matter of speculation. Even to demonstrate, for example, that postreproductive women result in a reduction in grandchild mortality *does not establish that menopause is adaptive unless it can be demonstrated that overall fitness is actually enhanced*. It is therefore highly significant that attempts mathematically to model the fitness benefits resulting from menopause in terms either of the maternal survival or grandmother hypotheses have shown that the magnitude of the contributions from individual sources might have to be unrealistically high to make the necessary difference.[59,63,64] Only when the effects of menopause on maternal mortality and the grandmother contribution were combined, was an increase in fitness observed.[64] Subsequent analysis combining life history modeling with data from a West African population highlighted the importance to fitness of the observed grandmaternal contribution in reducing of grandchild mortality but it also revealed that this contribution was only just sufficient to offset the fitness benefits that might otherwise accrue from continued reproduction of the grandmother herself.[65] Using a different approach, Lahdenperä *et al*.[66] analyzed multigeneration records from Finland and Canada to show that women with a prolonged reproductive lifespan had more grandchildren. There is, however, an important caveat in all such studies that individual variations in material circumstances and health, including exposure to infectious diseases, will tend to generate positive associations between longevity and reproductive success.

The demonstration that menopause can, in quantitative terms, result in enhanced fitness lends support to the idea that there may be something special about postreproductive life in humans. This needs further study. In particular, theory needs to take account of how individuals move between kin groups, since this has a bearing on the degree of relatedness. Cant and Johnstone[67] have examined the situation where intergroup transfer is chiefly via younger women joining the kin group of their male partners. In this situation new arrivals will have little biological incentive initially to contribute effort to the group's fitness but the incentive will increase over time as a result of interbreeding, since, as the female accumulates her own offspring, these will share genes with the group. Lee[68] has proposed that analyses should take account of intergenerational resource transfers in modeling the benefits of postreproductive life. There is less novelty here than at first there seems to be, since what Lee deals with via transfers has already been represented in state-dependent life history models as costs and benefits for the relevant individuals. Nevertheless, the idea of transfers is congruent with data gathered by anthropologists and this may have advantages. More problematic in the specific model developed by Lee[69] is the reliance on mutation accumulation as the process through which effects on senescence are assumed to occur, since there is poor support for such a mechanism.

Finally, an area where much greater attention needs to be focused is on the connections between mechanisms of general biological senescence and reproductive decline. In relation specifically to menopause, Pavard *et al*.[70] point out that the increased failure rate in reproduction resulting from senescence (stillbirths, birth defects, etc.) may result in an age-related decline in offspring quality that undermines the fitness contribution of later born children. Shanley *et al*.[65] have also noted, in line with the disposable soma theory, that the metabolic costs of the extra maintenance that would be required to support reproductive function for longer may be an additional factor contributing to the evolutionary advantages of menopause. It is likely to be through better understanding the mechanisms responsible for reproductive senescence, and the selection forces acting upon them, that further advances will be made.

Conflicts of interest

The authors declare no conflicts of interest.

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