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Late Life: A New Frontier for Physiology

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ABSTRACT

Late life is a distinct phase of life that occurs after the aging period and is now known to be general among aging organisms. While aging is characterized by a deterioration in survivorship and fertility, late life is characterized by the cessation of such age-related deterioration. Thus, late life presents a new and interesting area of research not only for evolutionary biology but also for physiology. In this article, we present the theoretical and experimental background to late life, as developed by evolutionary biologists and demographers. We discuss the discovery of late life and the two main theories developed to explain this phase of life: lifelong demographic heterogeneity theory and evolutionary theory based on the force of natural selection. Finally, we suggest topics for future physiological research on late life.

Introduction

The contrast between physiological research devoted to adaptation and that devoted to aging is striking. In the first type of research, natural selection acts intensely, producing a fine-tuned physiology that can be studied much as a car company’s engineers might dismantle a sedan produced by a competitor that makes more reliable vehicles, say, Lexus or Honda. Much of biology is concerned with this type of research: unpacking the cell or organism from the standpoint of efficient biochemical and biophysical engineering.

With the second type of physiological research, on aging, natural selection is waning in influence. From the standpoint of evolution by natural selection, the physiological features of aging can be viewed as the consequences of the progressive loss of adaptation with age, as a result of the weakening of the force of natural selection with adult age (Hamilton 1966; Charlesworth 1980; Rose 1991). The physiological investigation of this problem has been proceeding from the diverse perspectives of cell biology (cf. Finch 1990; Clark 1999; Fossel 2004), genetics (e.g., Rose and Finch 1993; Guarente 2003), and evolutionary biology (e.g., Rose et al. 2004). While aging leads to the progressive loss of many physiological adaptations, there is some degree of synchronization among individual aging mechanisms, mediated by the generalized effect of the falling force of natural selection and by pleiotropic genetic effects (Rose 1991, pp. 166–168).

It might be thought that adaptation and aging exhaust the contexts in which particular physiological mechanisms evolve. However, research with dipteran species in the early 1990s (Cayre et al. 1992; Curtsinger et al. 1992) suggested that the period of age-related deterioration eventually comes to an end, leaving a residual post-aging period. Further research has shown that this pattern occurs among other aging organisms as well (e.g., Vaupel et al. 1998). Apparently, evolution sometimes produces a third life-history phase, which we call “late life” here. While this phase of life is becoming better known evolutionarily (e.g., Mueller and Rose 1996; Charlesworth and Partridge 1997; Rose and Mueller 2000; Rose et al. 2002; Rauser et al. 2003, 2005), it remains largely unknown physiologically. In this article, we introduce the experimental and theoretical background to the study of late life and indicate the possibilities for its study by physiologists.

Biological Immortality

It might seem paradoxical for very late ages to be characterized by a cessation of aging, when the continued acceleration of physiological impairment might seem inevitable. But this pattern of nonaging is in fact well known from research on fissile species. Both Bell (1984) and Martinez (1998) have shown that increasing death rates do not arise in symmetrically fissile aquatic invertebrates. This pattern conforms to evolutionary expectations: if there is no differentiation of parent and offspring during fission, then there is an absence of the kind of age structure that is expected to lead to the evolution of aging (Charlesworth 1980, 1994).

The data that are available for such species are sometimes anecdotal. Comfort (1979, p. 110) described cases of long-standing cultures of fissile sea anemones in which no pattern
of senescence was detected, in some cases for the better part of a century. Bell (1984) provided more quantitative data concerning the age dependence of mortality rates, finding an absence of detectable increases in age-specific mortality rates in a handful of fissile aquatic invertebrates.

For the present purpose, the primary interest of the study of nonaging fissile organisms is that it has shown both that aging is conditional on the life cycle and that the observed existence or nonexistence of aging conforms to the expectations of evolutionary theory (Hamilton 1966; Charlesworth 1980; Rose 1991).

Demographic and Evolutionary Theories for Aging

Since 1825, aging has been interpreted in terms of the equation for age-specific mortality proposed by Benjamin Gompertz:

\[ \mu(x) = Ae^{rx}, \]  

where \( x \) is age, \( \mu(x) \) is the age-specific mortality rate, and the positive-valued parameters \( A \) and \( r \) are fitted to the observed data. For age-specific mortality data collected from reproductive adults, equation (1) and equations of related form can be fitted to observed patterns of aging quite well (Finch 1990). It was not of particular concern that this equation generally did not fit mortality during development from egg or seed to very early adulthood because it was viewed as a model for the aging process, and the developmental period has generally been viewed as nonaging. As evolutionary theory also confines the definition of aging to the adult period (Rose 1991), this failure to fit early mortality data was not regarded as problematic for evolutionary biologists either.

Evolutionary biology has tended to view equation (1) and its congeners as a consequence of the fall in the force of natural selection acting on mortality first intuited by Haldane (1941) and Medawar (1946, 1952) but actually derived for the first time by Hamilton (1966). This force is given by \( s(x) \), where \( x \) is again chronological age and \( T \) is a measure of generation length. The function \( s \) at age \( x \) is given by

\[ s(x) = A \sum_{y=x+1} e^{-ry}m(y), \]  

where \( r \) is the Malthusian parameter, the eventual growth rate of a population with the specified \( f(y) \) survivorship and \( m(y) \) fecundity functions. The variable \( y \) is a dummy variable that is used to sum up the net expected reproduction over all ages after age \( x \). In effect, the \( s(x) \) function represents the contribution of the future reproduction by an individual of age \( x \) to its fitness. In more intuitive terms, \( s(x) \) gives the “fitness value” of expected future reproduction. Before the advent of reproduction, \( s \) is equal to 1. After the cessation of reproduction, for all postreproductive ages, \( s = 0 \). During the reproductive period, \( s(x) \) strictly falls, never rising, although it may have brief “steps” in which it does not decline, especially in seasonal breeders. Figure 1 shows an example of an \( s(x) \) function.

Rose (1991, p. 171) offers a typical evolutionary explanation of the connection between \( s(x) \) and the Gompertz equation: “the ‘Gompertz’ form of mortality among iteroparous species may be due to a broad conformity of mortality under good conditions to the intensity of natural selection on age-specific mortality rates.” However, patterns of pleiotropy connecting mortality and fecundity at different ages are expected to quantitatively obscure such patterns, making age-specific mortality conform to the waning force of natural selection only crudely.

The Discovery of Late Life

For decades, demographers and gerontologists noticed that late-life human data did not fit Gompertz models (e.g., Greenwood and Irwin 1939; Comfort 1964, fig. 18, p. 90; Gavrilov and Gavrilova 1991): there was a shortage of deaths. More specifically, the exponential increase in age-specific death rate seemed to slow down considerably, if not cease. However, since these were human data, it was possible to dismiss the violation of Gompertzian patterns by reasonably hypothesizing that the treatment of the very old was different in human populations, especially with the advent of nursing homes and modern medicine.

A crushing volume of data from two dipteran species, one being the key model organism Drosophila melanogaster, showed that the mortality pattern of very old animals did not fit an

![Figure 1. Force of natural selection acting on mortality calculated from equation (2). Natural selection is high at early ages and declines throughout the reproductive period, starting at the first age of reproduction, \( b \), until the last age of reproduction in the population's evolutionary history, \( d \), when it converges on 0, remaining there thereafter. Increases in mortality rates are predicted to slow and plateau sometime after age \( d \) because of the negligible effect of natural selection at these late ages (Rose and Mueller 2000).](image)
overall Gompertz pattern (Carey et al. 1992; Curtsinger et al. 1992; review in Charlesworth and Partridge 1997). Figure 2 shows data obtained in these early studies from populations of medflies. While some were concerned about possible artifacts in these data (e.g., Nusbaum et al. 1993), the results obtained with Drosophila in particular have been vindicated in multiple rounds of replication from multiple laboratories (e.g., Fukui et al. 1993; Curtsinger et al. 1995; Drapeau et al. 2000). Still other organisms have been tested for a flattening of mortality rates at late ages (reviewed by Vaupel et al. 1998; Carey 2003), and the available data can now be considered definitive: at very advanced ages, age-specific mortality rates no longer increase exponentially, if at all. In some cases, late-life mortality rates fall (e.g., Carey et al. 1992). This period of the life span we call “late life” here.

The mortality levels during the late-life period vary widely. The late-life age-specific mortality rates of some animals, humans being one example, are sometimes very high relative to the baseline mortality rate, \( \alpha \). In other species, such as the medfly, the late-life mortality rate is not as high relative to \( \alpha \) (Carey et al. 1992). In such species, it is conceivable that many adult organisms achieve late life in the wild. The distinctive, and reliable, feature of late life is the transition from rapidly accelerating mortality rates to a rough “plateau” of mortality. This is easily the single most important finding of aging-related research since 1990.

The Explanation of Late-Life Mortality: Lifelong Heterogeneity

Of course, science is much more than the documentation of amazing facts. It is preeminently their explanation in terms of significant, ideally quite general, predictive theories. Late life has been explained by two main kinds of theory: lifelong demographic heterogeneity theory and evolutionary theory based on the force of natural selection.

The first theory offered to explain late life was lifelong demographic heterogeneity (Vaupel et al. 1979). This theory has the required generality, because granting only a few seemingly natural assumptions leads to a robust prediction of decelerating age-specific mortality late in life. The heterogeneity theory assumes that we can model cohorts as a collection of subsidiary groups, each of which has its own characteristic Gompertz function that defines its mortality pattern. Thus, one group might have a very low initial mortality rate, formally a small value for \( \hat{A} \), which will reduce its age-specific mortality rates throughout life relative to groups that have higher values of \( \hat{A} \), but the same value for \( \alpha \), the parameter giving the acceleration in mortality with respect to age. Under this model the average age-specific mortality rate is

\[
\bar{\mu}(x) = \frac{\hat{A}e^{\alpha x}}{1 + [\sigma^2\hat{A}(e^{\alpha x} - 1)]\alpha^{-1}}, \tag{3}
\]

where \( \hat{A} \) is the average value of \( A \) and \( \sigma^2 \) is proportional to the variance in \( A \). At advanced ages, the average mortality rate of equation (3) approaches a plateau equal to \( \alpha \sigma^{-2} \).

Alternatively, a group might have a different value for \( \alpha \) that makes its pattern of mortality rate acceleration distinctive (Pletcher and Curtsinger 2000). Note that this distinction among groups is based on the implicit premise that groups have predetermined lifelong mortality patterns. This type of heterogeneity-in-\( \alpha \) model is substantially more difficult to analyze. Pletcher and Curtsinger (2000) examine the age-dependent changes in the variance of the natural log of mortality rates. Mueller et al. (2003) use this model to make predictions about the expected numbers of very long-lived individuals in populations of Drosophila. It is a straightforward corollary of the assumptions built into the lifelong-heterogeneity theory that the individuals that survive to later ages will come from groups with lower values of \( \alpha \) and \( A \). Thus, whenever this type of lifelong heterogeneity arises, we can expect a deceleration in mortality at late ages. However, lifelong heterogeneity does not necessarily
lead to mortality rate decelerations that will be as pronounced as those observed during late life in cohorts of Diptera and other species. It will only do so if there is a great deal of lifelong heterogeneity.

The Explanation of Late-Life Mortality: The Force of Natural Selection

A completely different theory of late life is implicit in Hamilton’s (1966) original theory for the evolution of senescence. It is apparent from Figure 1 that \( s(x) \), the scaling function for the force of natural selection acting on age-specific mortality, declines throughout the reproductive phase of adult life. For species that have a finite life span in nature, this scaling function inevitably converges on 0, remaining at 0 thereafter. This implies that the intensity of natural selection reaches a minimum value of 0 at late ages. But it does not require that age-specific survival rates must reach 0 as well. Any beneficial effect that is not age dependent will continue to benefit individuals who remain alive after the force of natural selection has converged on 0. And after that age, the intensity of natural selection will no longer depend on chronological age. If there are any age-independent genetic benefits, they will be favored by natural selection acting at early ages, with a pleiotropic echo benefiting later ages.

The theoretical possibility of age-independent beneficial effects has been treated explicitly by Mueller and Rose (1996), as well as by Charlesworth (2001). Their numerical and analytical modeling demonstrated that mortality plateaus can arise as a consequence of the force of natural selection in age-structured populations. Mortality plateaus evolve when age-specific survival is determined by either mutation accumulation or antagonistic pleiotropy, as shown in Figure 3. These evolutionary models also predict a Gompertzian increase in mortality rates before the onset of late life. Models of heterogeneity simply assume an underlying Gompertz kinetics to age-specific mortality. Evolutionary models generate both Gompertzian aging and subsequent late-life mortality plateaus from first principles, not by assumption.

There have been several critiques of the evolutionary theories of late life (Pletcher and Curtsinger 1998; Wachter 1999). Additional theoretical research on these models would no doubt improve them.

Experimental Evaluation of the Lifelong-Heterogeneity Model

Given the use of the term “heterogeneity” in the name of this theory, it might be supposed that heterogeneity is a necessary corollary of the mere fact of genetic and environmental variance for adult life-history characters (see, e.g., Carnes and Olshansky 2001). There is a considerable literature showing that adult life-history characters vary (reviewed in Finch 1990; Rose 1991; Roff 1992; Stearns 1992). This abundant variation for life-history characters might be interpreted as showing that the heterogeneity model is well founded.

But the manner in which lifelong-heterogeneity theory explains the virtual cessation of aging in late life requires additional assumptions. Specifically, the variance in \( A \) or \( \alpha \) values between groups (within cohorts) must be sufficient to produce an extreme deceleration in mortality rates in the cohorts composed of such groups. It is possible to choose arbitrary Gompertz functions for a hypothetical collection of subsidiary groups and then fit the ensemble of aging groups to extant data (e.g., Kowald and Kirkwood 1993). This is a post hoc calculation. It is also possible to assemble synthetic cohorts from genotypes with very different mortality patterns and produce a slowing in late-life mortality (e.g., Brooks et al. 1994). But such results do not show that actual populations conform to the stipulations of lifelong-heterogeneity theory in fact.

There are several published studies that critically test the heterogeneity theory using experimental data. In principle, heterogeneity between individuals may arise from genetic differences or environmental effects. Fukui et al. (1993) found mortality plateaus with inbred *Drosophila* lines (inbreeding coefficient > 0.99). Thus, genetic variation is not required for plateaus. If the heterogeneity theory is valid, there must be sufficient environmental heterogeneity to account for observed mortality plateaus. An early test suggested that there may be population heterogeneity that affects age-specific survival (Kh-
zaeli et al. 1995), but the authors later retracted their results (Curtsinger and Khazaeli 1997). Khazaeli et al. (1998) created populations of *Drosophila* with differing levels of control of the larval environment. The reduction of environmental variation during the larval period of *Drosophila* had no significant effect on the presence of plateaus, leading the authors to conclude that larval environmental heterogeneity does not make a substantial contribution to mortality deceleration at late life.

Drapeau et al. (2000) compared *Drosophila* populations with differing levels of robustness for late-life plateauing of mortality rate. They found significant differences in mortality rates at early ages but not at later ages. These results did not fit the heterogeneity theory. However, Steinsaltz (2005) has argued that different types of age-specific models applied to the data of Drapeau et al. provide modest support for the heterogeneity hypothesis. In part, these contrasting conclusions arose from Steinsaltz’s decision to censor early-mortality data that did not appear to follow a pattern of increasing mortality with age, while Drapeau et al. used all observations. However, Steinsaltz made an important contribution by noting that the flat-plateau model used by Drapeau et al. is not well behaved statistically and thus must be used with caution.

Mueller et al. (2003) performed a more direct test of heterogeneity theory. They fitted lifelong-heterogeneity models to mortality data from varied *Drosophila melanogaster* populations, deliberately choosing parameter values for the heterogeneity models that fitted the observed data as closely as possible. That is, the parameter values most favorable to heterogeneity theory were chosen. The heterogeneity models that best fitted the overall mortality were, however, quite poor at predicting the late-life mortality pattern, especially the age at death of the last fly to die, as shown in Figures 4 and 5.

At the present time, the published experimental results do not support the feasibility of using lifelong-heterogeneity models to explain the cessation of aging in late life. This does not mean that lifelong demographic heterogeneity never causes some quantitative deceleration in late-life mortality. It is likely to have this effect, though perhaps not always of a magnitude large enough to be detected experimentally.

Experimental Evaluation of the Force-of-Natural-Selection Model

The situation with respect to the experimental evaluation of Hamilton’s force of natural selection as an explanation of late life is different. The quantitative theory of Mueller and Rose (1996) was used to generate predictions concerning the effect of varying the last age of reproduction on the evolution of late life. The basic pattern of these numerical results is shown in Figure 6. As the last age of reproduction varies, the start of the late-life mortality rate plateau covaries positively.

Rose et al. (2002) tested this prediction in three independent experiments, featuring either a 55-d or a 20-d contrast in last ages of reproduction. Data for males from one of these com-

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Figure 4. Probability of surviving beyond a certain age in two different populations (B and O) for both sexes. The probability scales are not identical for all plots. The circles represent the observed probabilities in each group, while the solid lines represent the values predicted by the heterogeneity-in-a model (Mueller et al. 2003). For more of this analysis, see Figure 5.
parisons are shown in Figure 7. There is a statistically significant difference in the day at which late life starts in these populations, when sample cohorts are handled simultaneously and in parallel. This difference is qualitatively in accord with the predictions derived from the Mueller-Rose model. We are not aware of any comparable data from other laboratories. However, these critical tests involved 25 evolutionarily distinct populations, so they are already extensively replicated.

Even though these data corroborating the Mueller-Rose evolutionary model for late life come from our own laboratory, it is nonetheless notable that these results were the first instance of corroboration for any theory of late life. The testing of predictive theories of late life is still in its infancy.

The Evolution of Late-Life Fecundity

The evolutionary theory of late life based on the force of natural selection can be generalized to the evolution of age-specific fecundity. Age-specific fecundity also has an age-specific scaling for the force of natural selection, $s'(x)$, which is given by

$$s' = \exp(-rx)l(x).$$  \hspace{1cm} (4)

All the variables in equation (4) have the same definitions as those in equation (2). This scaling function also reaches 0 in organisms that undergo mortality, provided that the population size is not declining steeply (Hamilton 1966; Charlesworth 1980, 1994).

The same kind of analysis as that applied to mortality during late life carries over to the analysis of late-life fecundity. In particular, the evolutionary theory of late life predicts that late-life fecundity will also reach an approximate plateau at ages later than the age at which $s'(x)$ converges on 0.

We performed the first test of this prediction known to us by measuring mid- and late-life fecundity in three independent populations (Rauser et al. 2003). The results are shown in Figure 8. Statistical analysis reveals that all three of the tested populations achieved stable fecundity plateaus late in life. These fecundity plateaus feature average fecundity levels significantly greater than 0, which is similar to the plateauing of mortality rates at some value less than 100%. Perhaps the reason these plateaus in fecundity had not been observed before our finding is because most studies of fecundity use small numbers of individuals per cohort and thus fail to measure fecundity at later ages accurately. The discovery of plateaus in fecundity is significant for the study of late life because, unlike the case of mortality, physiological aspects of fecundity can be directly measured throughout the lives of individuals that make up a population. Therefore, experimental tests can be done to evaluate theories that assume lifelong heterogeneity in robustness as the cause of late-life plateaus.

The kind of predictions derived by Mueller and Rose (1996) concerning the evolution of late-life mortality rate plateaus can similarly be developed for late-life fecundity. In particular, evolutionary theory suggests that fecundity should plateau according to the age at which $s'(x)$ converges on 0, sometime after the last age of survival in a population’s evolutionary history. Rauser et al. (2005b) tested this prediction in two independent experiments, finding that there is a statistically significant difference in the day at which late-life fecundity plateaus in populations with different $s'(x)$ functions in their recent evolutionary history, qualitatively in accord with Hamiltonian
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Figure 7. Two-day log mortality rates for males from five replicate B populations, cultured with early ages of reproduction for hundreds of generations, and five O populations, cultured with late last ages of reproduction for more than 100 generations. Late-life plateaus in mortality start much later in the O populations than in the B populations, which is predicted by the evolutionary theory of late life based on the declining force of natural selection. These were the first results corroborating any theory proposed to explain mortality patterns in late life (Rose et al. 2002).

Figure 8. Average mid- and late-life fecundity from three independent populations of *Drosophila melanogaster* (dotted lines). The solid line represents the average fecundity from these three populations and shows how fecundity stops declining at late ages. Statistical tests corroborate the inference of a late-life plateau in age-specific fecundity (Rauser et al. 2003).

Late Life Is a New Frontier for Physiology, Too

Almost everything that is well established concerning the third phase of life concerns aggregate life-history characters among populations: age-specific mortality and age-specific fecundity. There are some preliminary results concerning two forms of late-life stress resistance, desiccation and starvation (Drapeau et al. 2000), in *Drosophila*. Unfortunately, these findings lack the quantitative detail of research on mortality and fecundity in late life.

Carey (2003) has raised a number of issues concerning the natural history of late life, particularly from a comparative point of view. Mortality and fecundity have reached 0. From the work on both mortality and fecundity in late life, there is at least some pleiotropic connection with early life. When the last age of reproduction is abruptly changed, the timings of the mortality rate and fecundity plateaus shift evolutionarily over just two dozen generations (Rose et al. 2002; Rauser et al. 2005b). Mortality rate plateaus can change by almost a day for each generation of laboratory evolution. This is a remarkable speed of evolution, essentially unknown among other life-history characters. However, it is explicable in terms of late-life pleiotropic effects of genetic change arising from strong selection on alleles that have beneficial effects early in life.

We have only begun to characterize the evolution of late life. But it is already quite clear that it is as different from aging as aging is from development. There are pleiotropic genetic and evolutionary connections between these phases of life, but each phase evolves according to very different rules. Evolutionary biology has a new set of problems to solve.

Late Life Is a Distinct Phase of Life-History Evolution

While late life was first established as a scientific phenomenon by biologists who were interested in demographic theories appropriate to the “oldest old” (see Vaupel et al. 1998), evidence is accumulating that the phenomenon is not a mere sampling effect arising within cohorts. Late life is an evolutionarily distinct phase of life history, evolving according to strictures very different from those that mold both early life and aging.

Late life arises after the forces of natural selection acting on life-history theory. These results demonstrate not only that fecundity plateaus in late life, like mortality rates, but also that it evolves according to the evolutionary theory for late life based on the force of natural selection.

There is no direct extension of the demographic-heterogeneity theory that predicts a plateau in late-life fecundity. It is possible to imagine such lifelong-heterogeneity explanations: perhaps flies that are capable of surviving long enough to reach late life have low, stable fecundities compared to flies that die before reaching late life. This type of lifelong heterogeneity could then generate these data. Note, however, that this is a contingent, post hoc supposition. There is no apparent need for such a universal trade-off pattern. In the literature on such trade-offs in aging, this type of trade-off comes and goes from experiment to experiment (cf. Partridge and Fowler 1992; Leroy et al. 1994; Rose et al. 1996; Rose et al. 2005). Nor is this trade-off observed when looking at individual female fecundity trajectories (Müller et al. 2001).
of view. In addition, it is possible to study the physiology of late life in experimental systems using the approach of evolutionary physiology, with extensive replication and careful discrimination among alternative physiological mechanisms, as has been the case with the study of postponed aging in *Drosophila* (e.g., Rose et al. 2004).

Among the problems that are of interest to us are the following:

1. Do physiological characters that affect mortality and fecundity also plateau when the life-history characters that they underpin plateau? This is not a trivial question. We know that starvation resistance in *Drosophila* is a determinant of senescence, yet the character increases in *Drosophila* females during the aging phase while remaining roughly constant with respect to age in *Drosophila* males (Rose et al. 2004). On the other hand, desiccation resistance determines rates of senescence as well, yet it declines with age in both males and females (Rose et al. 2004). There is thus no general chronological pattern to the physiological mechanisms of aging. We have no idea what the corresponding patterns will be during late life.

2. What kind of physiological connections are there between mortality and fecundity during late life, or are they disconnected? The physiological mechanisms connecting survival and reproduction during aging are complex. Lipid, for example, apparently plays a key role connecting age-specific survival to age-specific fecundity during aging (Pletcher et al. 2002; Rauser et al. 2004; Rose et al. 2004). Will it also mediate the relationship between age-specific mortality and fecundity during late life? Perhaps the onset of mortality rate plateaus at late ages is simply a physiological side effect of plateaus in fecundity. That is, resources once invested in fecundity can be allocated to survival after the onset of the fecundity plateau, resulting in the slowing of late-age mortality rates.

3. How do the environmental and genetic controls on late life interact? We know, for example, that diet and genetic differentiation can modulate aging independently (see Chippendale et al. 1993). We have already shown that both selection (Rose et al. 2002; Fig. 7) and environment (Rauser et al. 2005a; Fig. 9) modulate the start of late life, though not its occurrence. What is the physiology of their interaction?

4. Male fertility should plateau in late life under the evolutionary theory of late life. In addition, the age at which this plateau starts would be subject to change as the strength of natural selection varies.

5. Are high levels of genetic variation in early demographic parameters possible, since such variation is subject to strong natural selection?

**Conclusion**

The discovery of late life in the early 1990s created a whole new area of interest for evolutionary biologists and demographers. However, because theoretical and empirical research has shown that late life is a unique and distinct phase of life very different from aging, it is now important to study and understand the physiology of late life, much as researchers have studied and understood aging and development. In this article, we have set up the theoretical and experimental background for future work on the physiology of late life by presenting what has been theoretically derived and experimentally tested thus far. However, only a careful analysis of the underlying physiological mechanisms shaping late-life mortality and fecundity patterns can provide us with a better understanding of how organisms within a population stop aging. Furthermore, research on aging must now carefully partition studies of the biology of adult life into two phases: aging and late life. Because almost all studies of the physiology of aging, including our own, have not done this, many of the findings of gerontology now need to be reexamined.

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