Does Aging Stop?

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Abstract: Human mortality data show stabilization in mortality rates at very late ages. But human mortality data are difficult to interpret because they are affected by changing medical practices and other historically variable causes of death. However, in the 1990s, data from a variety of labs showed that the mortality rates of medflies, fruit flies, wasps, yeasts, and nematodes also stabilize at very late ages. These reproducible "mortality-rate plateaus" forced biologists to develop theories for their existence. There are two main theories of this kind. "Lifelong heterogeneity" theories suppose that highly robust subcohorts are more abundant at later ages because less robust subcohorts have mostly died off. On this type of theory, aging does not stop; aging continues inexorably in all individuals. In contrast, in evolutionary theories for mortality-rate plateaus, based on the eventual plateaus in Hamilton's Forces of Natural Selection at late ages, aging does indeed stop. A variety of experiments have cast doubt on lifelong heterogeneity theories as explanations of mortality-rate plateaus. A few experiments have corroborated the Hamiltonian theory. This has the important corollary that it appears to be possible for aging to stop, at sufficiently late ages, at least among some populations. The implications of this result for aging research are profound. Most importantly, it suggests the possibility that the physiology of adults undergoing aging may be substantially different from the physiology of life after aging.

Keywords: Aging, late-life, lifelong heterogeneity, force of natural selection.

INTRODUCTION

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

$$\mu(x) = Ae^{\alpha x} \qquad (1)$$

where x is age, $\mu(x)$ is age-specific mortality rate, and the positive-valued parameters A and α are background mortality and aging rate, respectively. In equation (1) A and α are estimated from observed data, normally without any *a priori* foundation [e.g. 1]. With increasing chronological age, equation (1) predicts an exponential increase in mortality rates, which Gompertz [2] described physiologically as "the average exhaustion of man's power to avoid death gained in equal proportion in equal intervals of age." The pattern of accelerating adult mortality predicted by equation (1) is generally known as aging, or more specifically "demographic aging." While aging has been studied demographically for almost two centuries, its underlying mechanistic causes and its ultimate source have been topics for persistent debate among scientists [vid. 3].

One of the few points on which there was general agreement among scientists until the early 1990's was the assumption that mortality rates should continue accelerating until all members of a cohort die off [e.g. 4, 5]. While equations such as equation (1) were produced by actuarially fitting human data, they intuitively suggest that aging is an inevitable and accelerating process of deterioration. Thus, it was generally supposed that aging constituted an unremitting process of deterioration, a biological analog of the Second Law of Thermodynamics.

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Yet since 1992, this "limited life span paradigm," as it has been called [e.g. 6], has come under increasing attack from demographic studies in which large cohorts have been followed up until very late ages [see also 7, 8, 9]. These studies suggest that at very late ages equation (1) fails to predict true mortality rates, a limitation that Gompertz himself included in his presentation of the theory. This article addresses general implications of these recent studies for aging research. Most importantly, the question is posed whether aging can be said to stop at very late ages, both demographically and physiologically.

DOES AGING SLOW OR STOP IN AGGREGATE DEMOGRAPHY?

Human Mortality Rates Decelerate at Very Late Ages

For decades, demographers analyzing European demographic data noted that late-age mortality rates did not conform to Gompertzian aging patterns of progressively accelerating mortality rates [e.g. 10, 11]. That is, in humans, age-specific mortality rates stopped increasing exponentially at late ages (e.g. Fig. **1**). These observations were commonly dismissed because reasonable hypotheses could be made to explain away the human demographic data, such as differential treatment of the very old with the advent of nursing homes and modern medicine [e.g. 12]. Another complication with human data is that older people sometimes lie about their age, a practice that demographers sometimes call "age misstatement" [13]. Historically variable causes of death, such as war and pandemics, further complicate human cohort data. Thus the mortality rate deceleration observed in human data would need to be replicated in experimental systems to receive its due attention.

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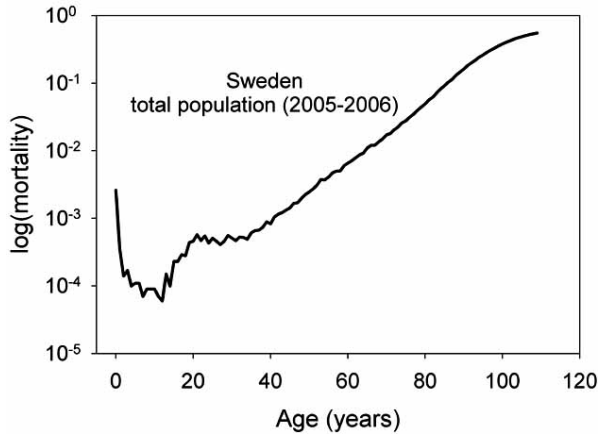

Fig. (1). Mortality for the Swedish population based on 2005-2006 census data. Human Mortality Database. University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). Available at www.mortality.org or www.humanmortality.de (data downloaded on 22 January 2008).

Mortality Rates in Other Organisms also Decelerate or Plateau at Late Ages

In the early 1990s, demographers and aging researchers were surprised with the result that mortality rates in two dipteran species, medflies (*Ceratitis*) and fruit flies (*Drosophila*), plateaued at late ages [7, 6, see Fig. (**2**) and Fig. (**3**)]. Initially there was considerable doubt concerning these findings, in particular because of possible density effects, since densities were not kept constant in some of these experiments [14, 15]. Although density may have been a factor in the original observations [6, 7, 16], changes in density were explicitly ruled out as the sole explanation for decelerating mortality in both *Ceratitis* [17] and *Drosophila* [18].

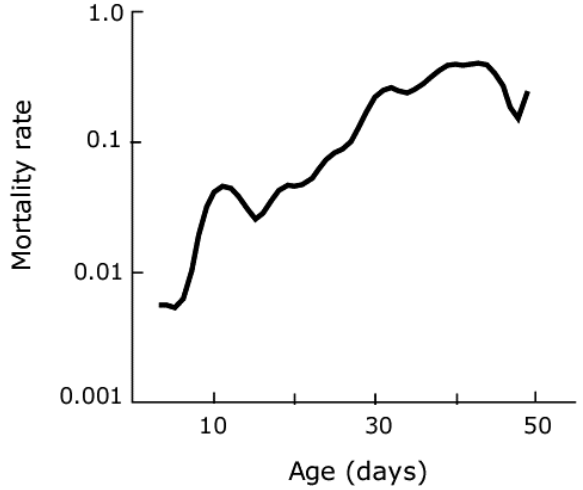

Fig. (2). Late age mortality rates appear to plateau in this graph of the age-specific mortality in a population of inbred *Drosophila* (after Fig. (**2**) from Curtsinger *et al.*, 1992).

Since the initial observations of mortality rate plateaus were published, mortality rate deceleration and mortality rate plateaus have been found experimentally in a variety of organisms, suggesting that late-age mortality deceleration occurs generally among aging organisms [16, 19, 20, 21, reviewed in 8, 22, 23]. In some cases, late-life mortality rates clearly fall [e.g. 7, see Fig. (**2**)]. These findings seem to suggest that old individuals age more slowly, stop aging, and sometimes experience "negative aging." The period of adult life in which mortality rates stop increasing exponentially has been called "late life" [reviewed in 24].

It is worth noting that observed cohort 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, A in equation (1). In other species, such as the medfly, the late-life mortality rate is not as high relative to A [7]. In such species, it is conceivable that many adult organisms achieve late life in laboratory cohorts.

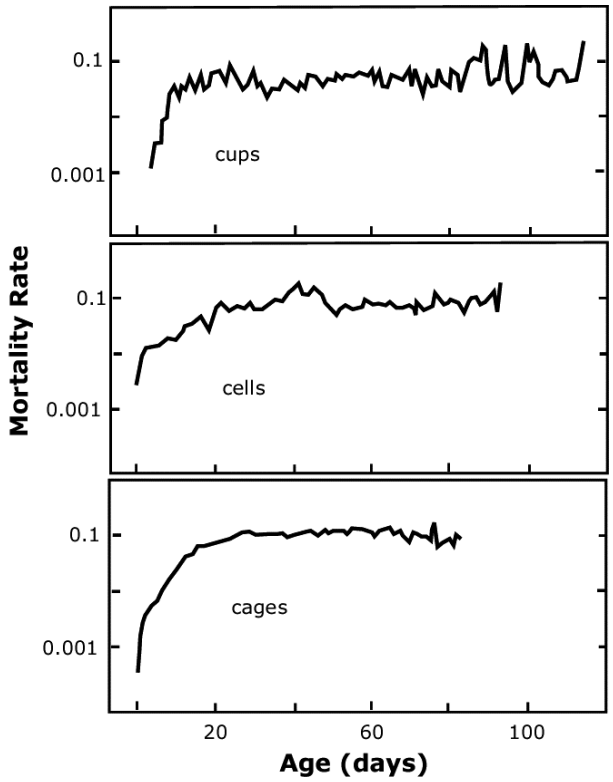

Fig. (3). Late age mortality rates appear to plateau in this graph of the log of mortality rate as a function of age in the Mediterranean fruit fly, *Ceratitis capitata* (after Fig. (**1**) from Carey *et al.*, 1992).

DOES DEMOGRAPHIC AGING SLOW OR STOP FOR INDIVIDUALS?

Lifelong Heterogeneity Theories Assume that Aging does not Stop

Since its discovery, the late-life period of decelerating mortality rates has been explained by two main kinds of theory: lifelong demographic heterogeneity theory and evolutionary theory based on the force of natural selection. Only these two major theories are discussed in this article. Several minor theories have also been proposed to explain late life; these are reviewed by Olshansky and Carnes [25].

The first theories offered to explain late-life mortality decelerations were demographic lifelong heterogeneity theories in which cohorts are modeled as collections of subsidiary groups, each with its own characteristic Gompertzian function of accelerating mortality rates [26, 27]. In lifelong heterogeneity theories, individuals that are less robust throughout life are expected to die off at earlier ages, compared to individuals that are more robust throughout life. Therefore, it is supposed that at very late chronological ages, individuals with life-long superiority in robustness will be present in larger numbers than more frail individuals. It is hypothesized that the survival of the most robust individuals then translates into a slowing in demographic mortality rates at late ages when the less robust individuals are no longer around to affect mortality rates, as shown schematically in Fig. (**4**).

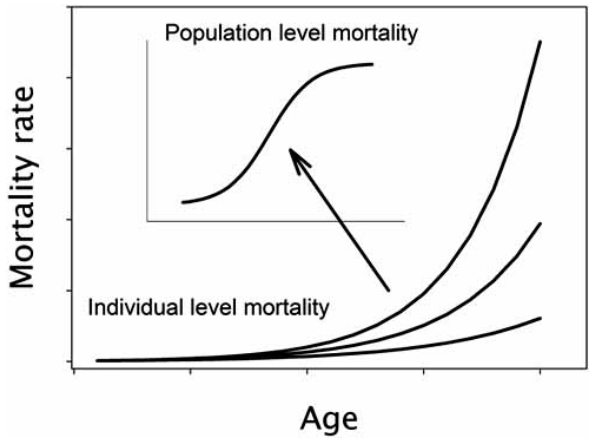

Fig. (4). Suppose individuals have exponentially increasing (Gompertz) rates of mortality but vary due to genetics or the environment. This figure shows that mortality plateaus may appear as a consequence of this heterogeneity.

The idea of demographic heterogeneity predates the definitive discovery of late-life mortality-rate plateaus. Beard [26] derived mathematical models for mortality that assumed heterogeneity in Gompertzian mortality patterns. His mortality models included variables that hypothesized sustained individual differences in "vitality" [28]. He later suggested that these supposed differences in vitality could be the underlying cause of the slowing in late-age mortality rates observed in some human demographic data [29].

Lifelong heterogeneity theories of late life can be readily characterized in terms of equation (1). Two groups with the same value for α, the parameter which defines acceleration in mortality with respect to age, but with differing values for A, the initial mortality rate, will experience different rates of age-specific mortality rates throughout life. Alternatively, a group might have a different value for α, which makes its pattern of mortality-rate acceleration distinctive [30]. Note that this distinction among groups is based on the implicit premise that groups have predetermined lifelong mortality patterns. Heterogeneity in α models are substantially more difficult to analyze than heterogeneity in A models [31].

In lifelong heterogeneity theories, late-life plateaus are aggregate demographic effects. In these theories, all individuals in a population are assumed to undergo exponential aging until death. In these models there is an unending acceleration in the process of organismal deterioration, and thus aging does not stop until an organism dies. In a sense, these models supply the most "conservative" interpretation of the finding of aggregate demographic plateauing of mortality rates in late life.

Experimental Evaluation of Lifelong Heterogeneity Theories

Given the use of the term "heterogeneity" in the name of this theory, it might be supposed that lifelong heterogeneity is a necessary corollary of the mere fact of genetic and environmental variance for adult life-history characters [e.g. 32]. There is a considerable amount of literature showing that survival probabilities vary within populations [reviewed in 1, 5, 33, 34]. This abundant variation for life-history characters might be interpreted as showing that the heterogeneity model is well-founded.

But sporadic or intermittent heterogeneity that affects some, but not all, adult age classes is different from the lifelong heterogeneity required by these models. In lifelong heterogeneity theory, differences between individuals are assumed to arise early in life and remain fixed throughout the life span. Lifelong heterogeneity theories of late life specifically require strong positive correlations between survival probabilities among adult ages; there is evidence that this particular assumption is not true [reviewed in 5, 35].

Lifelong heterogeneity theory is based on an underlying robustness character that is unspecified. Attempts to associate particular measurable characters with such robustness have been unsuccessful [e.g. 9, 36]. However, such experiments can always be criticized on the grounds that they have not identified the 'true' robustness character that determines lifelong heterogeneity. With such an invisible and unmeasured variable, it becomes possible for proponents of lifelong heterogeneity theories to invent new *post hoc* variants of their theory if faced with experimental refutation. Naturally, this opportunity to create such *post hoc* variants will be considered by many scientists to be a clear weakness of lifelong heterogeneity theory. We will, nonetheless, review some of the experimental evidence that has been brought to bear on the question of the validity of the lifelong heterogeneity hypothesis, in order to give the reader some detail concerning its empirical standing.

It is possible to assemble synthetic cohorts of *Caenorhabditis elegans* from genotypes with very different mortality patterns and produce a slowing in late-life mortality [e.g. 16]. Brooks *et al.* [16] found that mortality rates in an isogenic population of the nematode *C. elegans* showed a less distinct plateau than a genetically heterogeneous population. However, the isogenic line studied by Brooks *et al.* [16] was grown at a higher temperature and higher food concentration than the heterogeneous line, complicating the interpretation of the mortality patterns in these experiments [37]. Unlike the *C. elegans* data, experiments with highly inbred lines of *D. melanogaster* have shown that distinct mortality plateaus persist in the absence of genetic variation [6, 19, 38]. Thus, genetic variation is not required for plateaus.

If genetic heterogeneity is not required for the occurrence of mortality-rate plateaus, then the heterogeneity required by

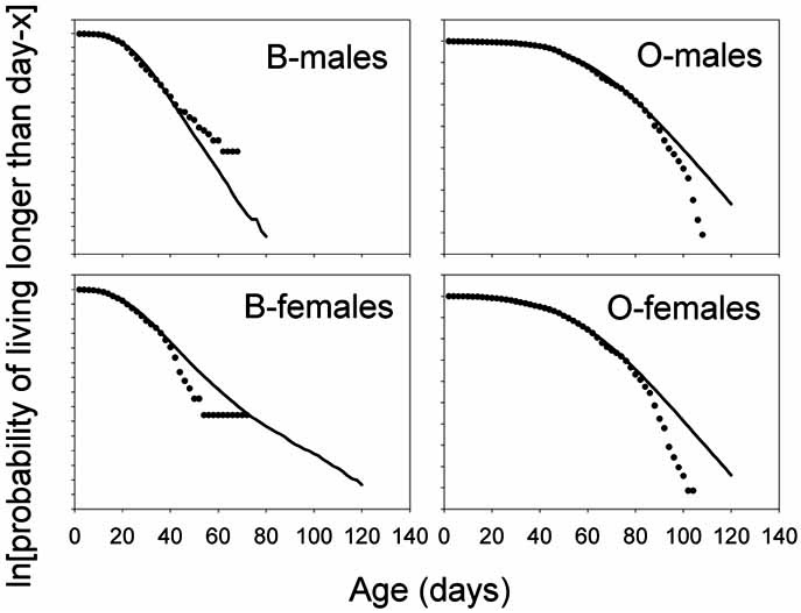

Fig. (5). The probability of surviving beyond a certain age in a long-lived (O) population and a short-lived (B) population and both sexes. The solid circles are the observed probabilities in each group while the solid lines are the values predicted by the heterogeneity-in-a model. Since the model predictions are based on simulated, finite numbers of deaths, they do not always produce smooth curves especially at the advanced ages (after Fig. (**7**) from Mueller *et al.*, 2003).

lifelong heterogeneity theories must come from the environment. That is, it must be possible to generate sufficient heterogeneity entirely from environmental effects. Khazaeli *et al.* [39] reduced pre-adult environmental heterogeneity among individuals from highly inbred *Drosophila* cohorts by manipulating egg laying, larvae collection, pupae selection and adult fly selection. The reduction of environmental variation had no significant effect on the presence of plateaus, leading the authors to conclude that pre-adult environmental heterogeneity does not make a substantial contribution to mortality deceleration in late life.

In principle, environmental heterogeneity may affect either of the two parameters of equation (1), A or α [40, 41, 42]. Large-scale changes in the environment, like dietary restriction or the addition of urea to adult food, have been shown to change survival by altering the A parameter of the Gompertz equation; they typically have no consistent effect on α [43, 44]. However, numerical analysis of such environmental effects on A shows that they are unlikely to generate enough environmental heterogeneity to explain mortality plateaus [31]. A Gompertz model with heterogeneity in the age-dependent parameter was chosen by Mueller *et al.* [31] to give the best possible fit to an extensive collection of *Drosophila* data. The best-fitting lifelong heterogeneity model predicted higher survival at late ages than observed (Fig. **5**). There were significantly less very old individuals in experimental cohorts than predicted by the best fitting heterogeneity in α Gompertz model.

Another test of heterogeneity theory uses the age-specific pattern of variance in mortality rates. Models with lifelong heterogeneity predict a unimodal peak in the variance of the log of mortality rates *vs*. age [41]. However, variance estimates obtained from *Drosophila* laboratory cohorts do not show such peaks [31]. Drapeau *et al.* [9] found no differences in late-life mortality between cohorts of flies that had markedly different levels of early robustness, although Steinsaltz [45] has argued that a re-analysis of the Drapeau *et al.* [9] data provides modest support for the heterogeneity theory. However, in his re-analysis, Steinsaltz [45] censored early-mortality data, whereas Drapeau *et al.* [9] used all observations.

Rauser *et al.* [46, 47] found that declining age-specific fecundity in *D. melanogaster* also undergoes a pronounced deceleration at late ages. These late-life fecundity plateaus are not readily explained by lifelong heterogeneity theories [48]. It is possible that flies that are capable of surviving into late life have low, stable fecundities compared to flies that die before reaching late life. This possibility is based on the assumption of trade-offs between reproduction and mortality. But such trade-offs do not always occur, nor do they always have the same form when they do occur [cf. 49, 50, 51]. Opportunely, for *D. melanogaster*, it is possible to measure the propensity to reproduce on a daily basis, allowing a more direct test of lifelong heterogeneity theory for the fecundity character. Rauser *et al.* [48] performed such an experiment and found strong evidence against the explanation of late-life fecundity plateaus using any type of lifelong heterogeneity.

EVOLUTIONARY BIOLOGY ALLOWS THAT AGING MAY STOP DEMOGRAPHICALLY

Evolutionary Theories of Aging and Biological "Immortality"

By the middle of the twentieth century, evolutionary theories of aging were proposed based on the idea that natural selection should operate less effectively late in life [5, 52, 53].

The decline in the force of natural selection arises because, even in the absence of aging, probabilities of survival, and therefore also of future reproduction, will decline with age due to accidental deaths in nature. In evolutionary theories, the physiological features of aging and equations such as equation (1) are consequences of the progressive loss of adaptation with age [5, 54, 55]. Haldane [52] used this idea to explain why Huntington's disease, which has a late onset, is common relative to genetic diseases with earlier onsets, despite its lethality.

In evolutionary theories of aging, age-related deterioration of function is the result of a decline in the force of natural selection. Therefore, for any interval of ages over which there is no possibility of change in reproduction, and therefore in the force of natural selection, there should also be no clear evolutionary tendency to produce changes in mortality. In other words, whenever the force of natural selection is not declining, there should be no continued deterioration with age. This is the case during development when natural selection acts at full force – natural selection is completely effective at eliminating mutations that destroy individuals before they have developed to adult reproductive ages. This does not preclude fluctuations in mortality rates during the developmental period, but it does imply the absence of a strong, persistent, and predictable deterioration in survival rates of the type seen in biological aging.

Some organisms experience natural selection at full force their entire lives and are therefore expected to not age biologically. Examples of this evolutionary pattern come from fissile species. Fissile here does not mean merely asexually reproducing or budding. It is now well known that budding yeast exhibit aging, as does the asexual protozoan Tokophyra. When asexual reproduction is sufficiently asymmetrical, there may be a pseudo 'adult' producing 'juvenile' offspring. When this occurs in a way that can give rise to differential evolution of such adults and juveniles, then aging can evolve. The cases in which aging cannot evolve, according to the theory, are those with strict symmetry between the products of fission. In these cases, if aging were to occur, it would extinguish all the descendant lineages, wiping out any such aging species, because senescent deterioration would then accumulate from cell division to cell division. This outcome would be opposed by natural selection acting with full force, which would halt such aging among surviving species.

As expected by theory, organisms with strictly symmetrical fission do not apparently exhibit aging. Bell [56] and Martínez [57] have shown that increasing death rates do not arise in fissile aquatic invertebrates. These examples show that aging is conditional on the life cycle and that the existence and nonexistence of aging conforms to the expectations of evolutionary theory [5, 54, 55, 58]. Most importantly, these examples suggest that aging is not a result of an inevitable, merely accidental, accumulation of damage to cells common to all organisms; aging is instead an evolutionarily derived condition, dependent entirely on the pattern of the force of natural selection. In this sense, evolution can readily achieve biological "immortality," meaning an absence of the accelerating mortality rates that are customarily defined as aging.

Evolutionary Theory for Late Life Mortality and Fecundity Plateaus

In 1966 Hamilton derived the result that the force of natural selection acting on mortality is given by $s(x)/T$, where x is chronological age and T is a measure of generation length. The function s at age x is given by

$$s(x) = \sum_{y=x+1} e^{-ry} l(y) m(y) \quad (2)$$

where r is the Malthusian parameter, or the growth rate of the population, associated with the specified $l(y)$ survivorship and $m(y)$ fecundity functions. The dummy variable y is used to sum up the net expected reproduction over all ages after age x. The $s(x)$ function represents the fitness impact of an individual's future reproduction, after age x. Before the first age of reproduction s is always equal to one, once reproduction has ended s is equal to zero, and during the reproductive period $s(x)$ progressively falls. A detailed review of how Hamilton's forces of natural selection shape survival and fecundity patterns is given by Rose *et al.* [59].

The $s(x)$ function has been used since Hamilton [54] to explain and to manipulate the evolution of aging [e.g. 55, 60]. In addition, equation (2) has been used as a crude explanation of equation (1) [5]; exponentially increasing mortality rates during aging are easily generated from first principles using Hamilton's force of natural selection [vid. 61]. However, this same analysis also shows that the period of exponentially increasing mortality rates comes to an end.

In equation (2), s is equal to zero for all ages after reproduction has ceased. This plateau in the force of natural selection on zero implies that natural selection will no longer discriminate among genetic effects that act at very late ages because these genetic effects have had no impact on fitness during the evolutionary history of a population. While mutations and genetic drift increase the frequency of deleterious genes with more or less the same magnitude at all ages, the force of natural selection declines with age and stabilizes at a low level in late life. Therefore, even in organisms that reproduce at all ages, the force of natural selection is eventually overwhelmed by drift in late life (Fig. **6**), a result obtained in explicit numerical simulations by Mueller and Rose [61]. Other analytical solutions of this kind have been supplied by Charlesworth [62]. However, using formal analysis Wachter [63] has suggested that the plateaus found in the numerical simulations of Mueller and Rose [61] are only transient states under their assumed mutation model. Thus there is some theoretical work that remains to be done in order to place the Hamiltonian explanation of late life on a firm foundation.

Since there is no selection for post-reproductive longevity in organisms that do not contribute to the fitness of their offspring or relatives [5, 53, 54], mortality levels may be expected to reach 100% when natural selection plateaus on zero. An important elaboration of evolutionary theory has recently been contributed by Lee [64], who strikingly combines Hamilton's theory for the Forces of Natural Selection with Hamilton's inclusive fitness formulation of kin

selection. However, we will not be discussing this work further in this article, beyond pointing out that it is highly relevant for the evolution of aging in species like humans, in which parental care can continue for a decade or more. It is indeed possible that late-life plateaus will be at the zero-survival levels in some species [cf. 40]. However, when there are enough alleles that have age independent beneficial effects it is also possible to have positive-valued average survival and fecundity values during late life [vid. 62]. In such cases, any age-independent genetic benefits will be favored by natural selection acting at early ages and will have positive pleiotropic benefits at all later ages; an idea that has been called "protagonistic pleiotropy" [65, 66].

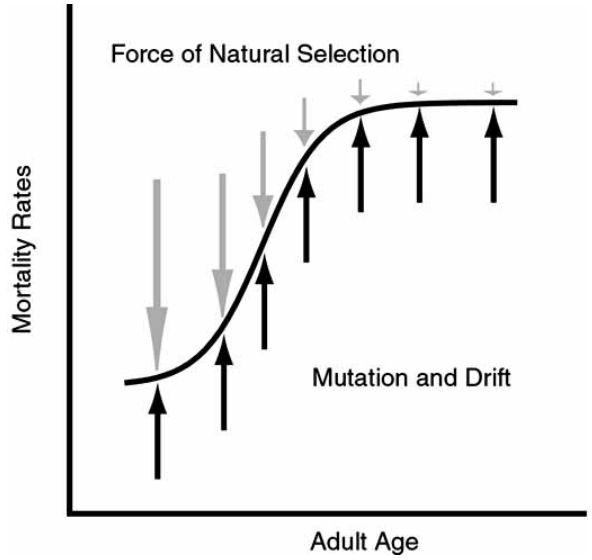

Fig. (6). Mutations and genetic drift increase the frequency of deleterious genes with more or less the same magnitude at all ages (black arrows pushing upwards on the mortality curve). Meanwhile, natural selection opposes these deleterious mutations (gray arrows pushing downwards on the mortality curve), keeping mortality rates low. The strength of natural selection decreases with the age of genetic effect, which weakens the force of natural selection. At very advanced ages, after the last age of reproduction in a population's evolutionary history, natural selection stabilizes at a low level. This leads to an end in the deterioration of the balance between selection and other evolutionary forces, and thus a plateau in mortality.

In evolutionary theories of late life based on the force of natural selection, aging can stop for individuals, when aging is defined in terms of age-specific components of fitness, as in Rose [5]. Thus evolutionary theory suggests that aging does indeed stop at the level of life-history characters. In some species, the cessation of aging can occur at fairly early ages, as shown in medflies by the results of Carey *et al.* [7].

Experimental Evaluation of Evolutionary Theories of Late Life

Predictions of the evolutionary theories of late life have been substantially corroborated in several studies. Mueller and Rose [61], using models of pleiotropy and mutation accumulation, based on the force of natural selection, predicted that late-life mortality plateaus should evolve according to the last age of reproduction in the evolutionary history of *D. melanogaster* populations. Rose *et al.* [67] tested this prediction in three independent experiments using 30 large cohorts of *D. melanogaster* that featured either a 55-day or an 18-day contrast in last ages of reproduction. They found a statistically significant difference in the day at which late life starts in these populations, when sample cohorts were handled simultaneously and in parallel (Fig. **7**). This difference is qualitatively in accord with the predictions of evolutionary theories of late life.

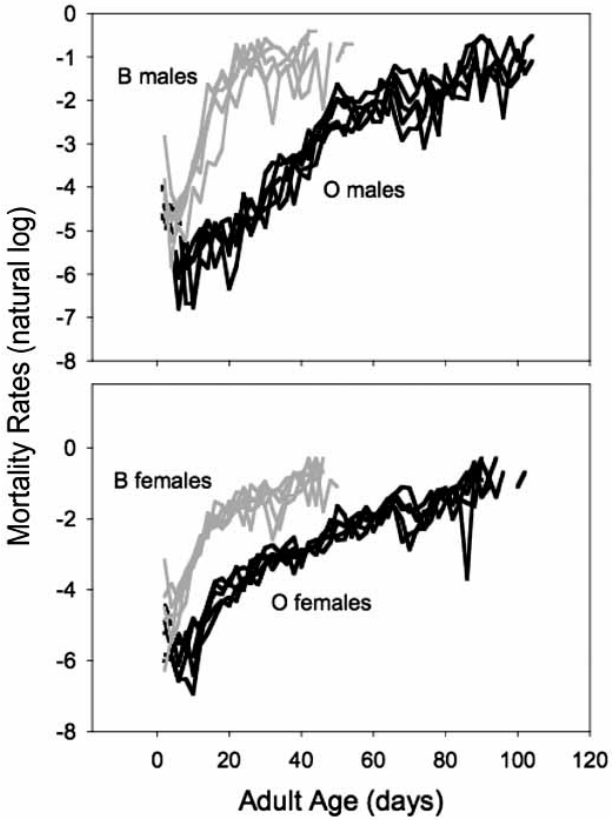

Fig. (7). Two-day mortality rates for 10 cohorts sampled from B and O populations. Short-lived B populations are shown as gray lines and long-lived O populations are shown as black lines. Occasional regions are missing because mortality rates of zero cannot be properly interpreted on a logarithmic scale (after Fig. (**5**), from Rose *et al.* 2002).

The kind of predictions derived by Mueller and Rose [61] 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 sometime after the last age of survival in a population's evolutionary history. In two independent experiments, Rauser *et al.* [47] found late-life fecundity plateaus in several populations of *D. melanogaster*. More notably, they found statistically significant differences in the days at which late-life fecundity plateaued in populations with different last ages of reproduction in their recent evolutionary history. These results showed that late-life fecundity plateaus evolve according to the evolutionary theory for late life based on the force of natural selection.

Other laboratories have also performed experiments testing evolutionary theories for late life. For example, Reynolds *et al.* [68] used chromosomes extracted from isofemale lines of *D. melanogaster* to test the width of allelic effects on age-specificity. Their goal was to determine whether or not such allelic effects were too age-specific for Charlesworth's [62] explanation for the evolution of late-life plateaus with non-zero values of life-history characters. They found enough width of age-specificity to support Charlesworth's hypothesis, an encouraging result for the evolutionary approach.

Overall, a variety of experiments have cast doubt on lifelong heterogeneity theories while several experiments have corroborated the evolutionary theories of late life. An important implication of these results is that late life is not a mere sampling effect arising in subsidiary cohorts all of which undergo unremitting aging. Instead, 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. It appears possible for aging to stop, at sufficiently late ages, at least among some populations. Thus, there are three phases of life: development, aging, and late life. We now should be concerned not only with why and how aging happens, but also with why and how aging stops at late ages.

DOES AGING STOP PHYSIOLOGICALLY?

Almost everything that is currently known about late life concerns fitness characters such as age-specific mortality and age-specific fecundity. Fitness characters of individual organisms plateau at very late ages, so in some sense physiological aging must stop at the same old ages. But what happens to the constituent physiological mechanisms of such "plateaued" individuals remains an unanswered question. The functional physiological parameters that can be studied for changes in late-life must be those that are demonstrably related to adult survival, fecundity, or virility, since some physiological characters may have no effect on life-history characters. Currently, we have no intuitive understanding of the underlying machinery of late-life physiology. It is important to note, however, that our lack of understanding of late-life physiology is not due to some limitation on or impossibility of studying this phase of adult life. Using well-defined model systems, we could, in principle, follow age-specific physiology into the late-life period for an experimental cohort. We could then compare age-specific physiology during late life to age-specific physiology during aging. It seems that our lack of understanding of late-life physiology is largely due to the fact that late life is observable in laboratory populations of model organisms *only* when the starting population sizes are very large. Most studies of age-specific physiology do not extend into the late-life period because the sample sizes that can be obtained from cohorts of experimental populations are usually not large enough.

In 2000, Drapeau *et al.* [9] began an investigation of late-life physiology in *D. melanogaster* in which they specifically focused on physiological characters that have been shown to be mechanistically bound up with aging. Their results suggest that starvation resistance, defined as hours to death in moist conditions without food, plateau at late ages but that desiccation resistance, defined as hours to death in dry conditions without food, does not plateau. On the other hand, Nghiem *et al.* [69] found that desiccation resistance does seem to stop declining at very late ages, in ostensible contradiction to the findings of Drapeau *et al.* [9]. But the study of Nghiem *et al.* was not conducted in terms of a differentiation between aging and late-life phases of adulthood.

At this point, a discussion of how the start of the late-life period can be identified might be helpful. The age at which late life starts is sometimes called the "break-day," because it breaks adult life into the two periods of aging and late life. Estimating the break-day requires that experimenters collect mortality data on the population under study until very late ages. The recorded mortality data can then be fitted to a two-stage Gompertz equation using maximum likelihood techniques [67], as follows: d is set as the breakday or the age at which mortality rates become constant with age. Then, at ages x less than d, age-specific mortality rates are modeled by the continuous time Gompertz equation and set equal to $Ae^{\alpha x}$, where A is the age-independent rate of mortality and α is the age-dependent rate of mortality. For ages greater than d, mortality rates are assumed to equal a constant value A_2. A_2 is independent of age but differs from A. This two-stage Gompertz equation does not force a plateau onto the observed data, but allows for estimating the breakday if there is a plateau in the mortality data.

Thus, when functional physiological parameters are measured at different ages for sample organisms in a cohort, these parameters can be plotted against age with the estimated

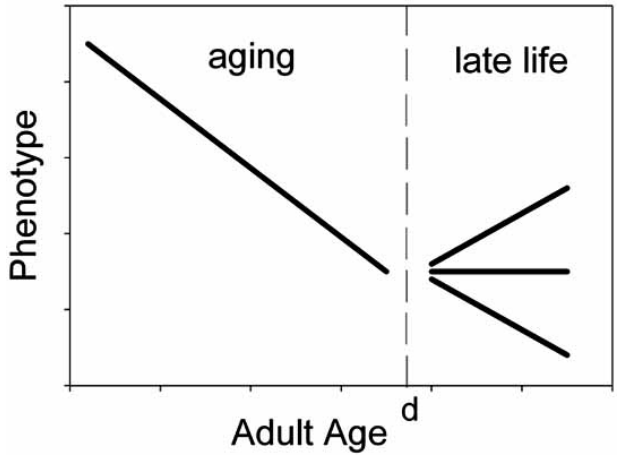

Fig. (8). Possible outcomes of late life physiology studies. Functional physiological parameters that are measured at different ages for sample organisms in a cohort can be plotted against age with the estimated mortality breakday (d) superimposed on the plot. If late life physiology is different from the physiology of aging, we should see a change in patterns of physiology between the two periods of adult life. In this figure the particular phenotype deteriorates during the aging period as may be expected from the pattern of increasing mortality rates during this period. In late life, the phenotype may stabilize, much like mortality and fecundity stabilize at late ages. The phenotype in late life could also continue to deteriorate, in which case it is conceivable that some other phenotype might improve during late life.

breakday superimposed on the plot, as illustrated in Fig. (**8**). If late life physiology is different from the physiology of aging, as is conceivable given the existence of late life, we should see a change in patterns of physiology between the two periods of adult life. In other words, if changes of mean value or second-order changes in the rate of change occur in a particular physiological parameter that is causally related to aging, such changes should occur near the breakday. For example, a particular phenotype might deteriorate with age during the aging period and then plateau in late life. Alternatively, the character might continue to get worse with age even during the late-life period, perhaps deteriorating at a more rapid rate during late life. If this is the case, another physiological character might possibly improve with age during late life and the effects of the two characters changing in opposite directions could balance.

At this point we can distinguish three broad alternative hypotheses for the physiology of late life. (i) The continued deterioration in all functional characters, which would suggest that there is something wrong about the evolutionary theory of late life discussed here. Our view is that the preliminary data already available suggests that this is not the universal pattern among such functional characters, but these data are too thin to this point to inspire much confidence. (ii) Convergence on a state of physiological "quiescence," in which functional characters generally stabilize, much as mortality and fecundity characters do. So far, there is the barest suggestion that this may in fact be the case. (iii) A complex scenario, like that discussed in the preceding paragraph, in which physiological characters vary with respect to their continued deterioration, stabilization, or even partial recovery. Deciding among these hypotheses poses a distinctly interesting challenge.

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. It is now clear that members of some species do indeed stop aging at very late ages, and there is an adequate evolutionary explanation for why this occurs. This previously unexpected situation poses exciting new problems for biological research. The cessation of aging can have significant implications for governments too, in terms of health and social costs, and also for actuaries who need to project future changes in life expectancy. The twentieth century has seen dramatic declines in human mortality rates at all ages, and there are now far more individuals living to very late ages than ever before [reviewed in 70]. In our fast-growing society it is conceivable that more and more people will live to experience a cessation in aging in their last years. Therefore, understanding late life is becoming greatly important to us all.

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