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Heterogeneity in Individual Mortality Risk and Its Importance for Evolutionary Studies of Senescence

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ABSTRACT: Mortality was simulated under the assumption of heterogeneity in individual age-specific mortality risk. Heterogeneity was modeled by assigning each individual its own Gompertz mortality function. Means and variances of the Gompertz intercept and slope parameters were based on published data for *Drosophila melanogaster*. Simulations of large cohorts reproduced mortality plateaus similar to those observed for actual cohorts of flies. Catastrophic late-age mortality was not observed except when heterogeneity was very low and rates of senescence were very high. A second set of simulations was designed to mimic experiments that have investigated age-specific patterns of genetic variance in mortality rates. Within-genotype heterogeneity in mortality risk resulted in a decline in genetic variance of mortality rates at old ages. That result suggests that the decline in genetic variance at old ages that has been observed in some experiments is an artifact of heterogeneity. Mortality rate plateaus, decrease in genetic variance of mortality rates at old ages, and absence of catastrophic late-age mortality all appear to contradict predictions of the evolutionary theory of senescence. Heterogeneity in mortality risk may explain those contradictions.

Keywords: senescence, evolution, mortality rate, frailty, Gompertz function, genetic variance.

Hamilton (1966) provided the quantitative foundation for the evolutionary theory of senescence. In an iteroparous, nonsenescent organism, the effects of changes in either mortality rate or reproductive success on lifetime fitness decline with increasing age once reproduction has begun. Hamilton's (1966), and later Charlesworth's (1980), analyses led to widespread acceptance of the idea that senescence is an essentially inescapable consequence of evolutionary forces. Theoretical analyses have led to additional predictions. First, after the onset of reproduction, mortality rates should increase with age (Charlesworth 1980, 1990). Second, there should be a total collapse in survival at sufficiently old ages. That result appears to be true whether senescence is due to mutation accumulation (Charlesworth 1990; Partridge and Barton 1993; Pletcher and Curtsinger 1998) or to antagonistic pleiotropy (Pletcher and Curtsinger 1998). Third, under mutation accumulation and possibly under antagonistic pleiotropy, additive genetic variance of mortality rates should increase with age (Rose and Charlesworth 1980; Charlesworth and Hughes 1996).

In contrast, very large-scale studies of medflies (Carey et al. 1992) and fruit flies (Curtsinger et al. 1992) demonstrated mortality rates that leveled off or, in some cases, declined at old ages. Level or declining mortality rates at old (postreproductive) ages were much <100%, contradicting the predicted collapse in survival. Both studies acknowledged that leveling off of age-specific mortality rates might be due to heterogeneity in individual mortality risk. For example, in a genetically heterogeneous cohort, genotypes with higher mortality risk will tend to die earlier, and the survivors will be those with lower death rates (Carey et al. 1992). While acknowledging the potential importance of heterogeneity in mortality risk (or "frailty"), both papers emphasized the challenge that their results posed for evolutionary theory and for conventional characterizations of senescence. For example, "if senescence is measured by the increase in age-specific mortality rates in a cohort, one is led to the unexpected conclusion that the oldest *Drosophila* of at least one genotype do not senesce" (Curtsinger et al. 1992, p. 463). Or, "our data are inconsistent with the concept that species can be characterized by their species-specific life spans as measured by … a pattern of age-specific mortality tending toward unity at the maximal age" (Carey et al. 1992, p. 460).

Several explanations have been offered for the "deceleration" of cohort mortality rates at advanced ages. These include declining density (Nusbaum et al. 1993), contamination of experimental cohorts by younger individuals (Brooks et al. 1994), and various forms of heterogeneity within cohorts (Kowald and Kirkwood 1993; Brooks et al.

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1994; Hughes and Charlesworth 1994). Additional experiments have been designed to exclude those explanations in particular instances. For example, even when density is maintained by replacing dead individuals with marked ones, leveling off is still observed (Khazaeli et al. 1996). Genetically, homogeneous (inbred) cohorts also demonstrate leveling off (Curtsinger et al. 1992; Fukui et al. 1993), thus excluding genetic variance in mortality rates within cohorts as a general explanation. Hughes and Charlesworth (1994) suggested that deceleration of mortality at old ages might be due to enhanced levels of individual variation in rates of senescence in inbred lines. Specifically, inbred genotypes are more sensitive to environmental causes of phenotypic variation. However, Fukui et al. (1996) observed mortality rate deceleration in genetically homogeneous cohorts that were also heterozygous, as well as in inbred cohorts. Thus, they simultaneously ruled out both genetic heterogeneity and increased environmental sensitivity of inbred individuals as general explanations for mortality rate deceleration. Many studies with flies have now demonstrated beyond any reasonable doubt that leveling off of cohort mortality rates at older ages is a "real" phenomenon that cannot be attributed to peculiarities of particular experiments. Furthermore, deceleration of mortality rates at old ages is not restricted to flies (Vaupel et al. 1998). Last, for flies, there appears to be a general tendency for mortality rates to level off within a fairly narrow range: 10%–30% mortality per day (see, e.g., Carey et al. 1992; Curtsinger et al. 1992; Khazaeli et al. 1995, 1996; Service et al. 1998).

Mueller and Rose (1996) attempted to show that mortality plateaus, produced by cessation of senescence at the individual level, are in fact consistent with both the mutation accumulation and antagonistic pleiotropy mechanisms for the evolution of senescence. Their simulations produced mortality plateaus under either mechanism. However, the Mueller and Rose models have been criticized strongly on the grounds that the mortality plateaus depended on particular, possibly unrealistic, assumptions (Pletcher and Curtsinger 1998), or that they were not run for sufficient time to reveal limiting states (Charlesworth and Partridge 1997; Wachter 1999). Furthermore, the plateau mortality rates in the Mueller and Rose (1996) simulations were much higher than those commonly observed for experimental organisms.

The theoretical expectation that additive genetic variance of mortality rates should increase with age also has not been confirmed by experiments. In *Drosophila melanogaster*, genetic variance of mortality rates appears to increase from early to intermediate ages and then to decrease at old ages (Promislow et al. 1996). Pletcher et al. (1998) found that mutational variance for mortality rates in female *D. melanogaster* was lower at later ages than at earlier ages. In males, mutational variance for mortality rates was greatest at intermediate ages.

In this article, I will argue that, for *D. melanogaster* at least, observed mortality dynamics can be explained easily and robustly by models that have realistic amounts of phenotypic variation in mortality risk and in which all individuals have exponentially increasing probability of mortality. Second, I will argue that the apparent reduction in genetic variance of mortality rates at old ages is a consequence of nongenetic variation in mortality risk. Third, I will argue that for organisms that undergo gradual senescence, heterogeneity leads to the conclusion that catastrophic old-age (postreproductive) mortality can probably never be observed. In my argument, leveling off of cohort mortality rates does not require leveling off of individual mortality risk. An alternative explanation is that cohort mortality rate plateaus are due to cessation (or slowing down) of mortality senescence at the individual level. I am not the first to construct strictly senescent heterogeneity models that produce decelerating old-age cohort mortality rates (Vaupel and Yashin 1985*b*; Kowald and Kirkwood 1993; Vaupel and Carey 1993). However, my analysis is more general, it is informed with more recent empirical data, and the implications of heterogeneity for evaluating the evolutionary theory of senescence are more fully developed.

Background and Methods

Mortality Rate Functions

The Gompertz hazard function (eq. [1]) is commonly used to describe age-specific mortality rates in populations and experimental cohorts:

$$\mu(x) = Ae^{bx}, \tag{1}$$

where $\mu(x)$ is the instantaneous mortality rate at age x; A is the initial mortality rate, sometimes referred to as the age-independent mortality rate; and b is the age-dependent mortality rate. If $b > 0$, the mortality rate increases indefinitely and exponentially with age. Thus, b is also called the "senescence parameter." The Gompertz function has the virtue of simplicity: it has only two parameters, and $\ln(\mu(x))$ is a linear function of x (with intercept $\ln(A)$ and slope b). Because it is commonly presented in logarithmic form, A and b are also known as the "intercept" and "slope parameters," a convention that I will follow. The Gompertz function provides a fairly good fit for mortality rate data in a wide range of organisms (Finch 1990). However, it does not describe deceleration of mortality rates at old ages.

The Gompertz hazard function implicitly assumes that

all individuals in a cohort or population have the same mortality risk, an assumption that is biologically implausible. Vaupel and his collaborators have developed a class of mortality models that incorporate heterogeneity in individual mortality risk, or frailty (see, e.g., Vaupel et al. 1979; Vaupel and Yashin 1985*a*). A "frailty" model based on the Gompertz hazard function is

$$m_i(x) = z_i A e^{bx}, \tag{2}$$

where $m_i(x)$ is the mortality "rate" of individual i at age x and z_i is the frailty of individual i. An individual with a frailty of 2, for example, has twice the hazard at any given time as an individual with a frailty of 1. If it is assumed that mean frailty at birth is 1, and that frailty is γ-distributed with variance σ_z^2, then there is a relatively simple expression for the cohort mortality rate at age x:

$$\bar{\mu}(x) = \frac{Ae^{bx}}{1 + \sigma_z^2 A(e^{bx} - 1)/b}, \tag{3}$$

where $\bar{\mu}(x)$ is the "weighted average of the death rates of the individuals who comprise the population" at age x (Vaupel and Yashin 1985*a*, p. 184). If $\sigma_z^2 = 0$, equation (3) reduces to equation (1). If σ_z^2, $b > 0$, then $\bar{\mu}(x)$ increases exponentially at younger ages but eventually approaches an asymptote equal to b/σ_z^2. Equation (3), therefore, provides a mathematical function that is in broad qualitative agreement with observed age-specific mortality rates in experimental cohorts of flies. It is important to note that equation (3) differs from equation (1) only by the incorporation of a particular form of individual phenotypic variation in mortality risk. I refer to equation (3) as the γ-Gompertz mortality function (Service et al. 1998), but it has also been termed the "logistic model" (e.g., Promislow et al. 1996). The three parameters of equation (3) can be estimated for experimental cohorts by maximum likelihood, and equation (3) generally provides a better fit for fly mortality data than does equation (1) (Fukui et al. 1993, 1996; Promislow et al. 1996; Service et al. 1998). Despite the fact that the γ-Gompertz model is explicitly based on the concept of individual heterogeneity in mortality risk and despite the fact that it provides a clear mathematical demonstration of the power of heterogeneity to cause cohort mortality rates to level off, the role of individual heterogeneity in accounting for mortality rate deceleration has been consistently underemphasized. For example, σ_z^2 has been described as the "deceleration" parameter (Fukui et al. 1996; Promislow et al. 1996) without any reference to its original meaning of variance in individual frailty (Vaupel et al. 1979).

In this study, mortality was simulated by assuming that each individual in a cohort had its own Gompertz hazard function:

$$m_i(x) = A_i e^{b_i x}. \tag{4}$$

The means and variances of A_i and b_i at the birth of a cohort were $\bar{A}$ and $\bar{b}$ and σ_A^2 and σ_b^2. The variables A_i and b_i were lognormally distributed, ensuring that their values were >0. Thus, all individuals had exponentially increasing risk of mortality. I will refer to A_i and b_i as the intercept and slope "parameters" of individuals, although strictly speaking they are variables. (Note that if b_i is constant, then eq. [4] is equivalent to the γ-Gompertz model because A_i in eq. [4] can be replaced by $z_i A$ in eq. [2].)

Equation (4) cannot be used directly for discrete-time simulations. The probability that individual i will die in the interval x to $x + 1$, given that it has survived to age x, is

$$q_i(x) = 1 - \frac{S_i(x + 1)}{S_i(x)}, \tag{5}$$

where $S_i(x)$ is the survivorship function—the probability that individual i at age 0 will live to age x. The Gompertz survivorship function is

$$S(x) = e^{[-A(e^{bx} - 1)/b]} \tag{6}$$

(Lee 1992), which is readily adapted to individual variation in parameter values.

Parameter Estimates

Drosophila mortality data are most commonly fit to the Gompertz or γ-Gompertz hazard functions. When daily *Drosophila* mortality data are fit to equation (3), estimates of A range between 3.4×10^{-5} and 6.5×10^{-2}, with a representative value of about 5×10^{-4} (Fukui et al. 1993, 1996; Promislow et al. 1996; Service et al. 1998). Estimates of b range between 0.032 and 0.318, with a mean of about 0.150. Fukui et al. (1996) estimated A and b for approximately 25 *Drosophila* lines that were isogenic for chromosome 2. Their published data may be used to estimate several important parameters. For example, among-line variance in estimates of b can be taken as a rough estimate of the total genetic variance in Gompertz slope due to chromosome 2. Estimates of additive genetic variance of b due to second chromosome variation are also available (Promislow et al. 1996). Hughes and Charlesworth (1994) provide estimates of genetic and environmental variances of Gompertz parameters for third-chromosome lines of *D. melanogaster*. Estimates of genetic variance are notoriously imprecise. However, these data allow rough esti-

mation of the genetic and phenotypic variances and coefficients of variation of the Gompertz intercept and slope parameters, A_i and b_i in equation (4). The coefficients of genetic variation (CV_A or CV_G) for the slope parameter are remarkably similar in all three studies (table 1). For the intercept parameter, A, the data of Fukui et al. (1996) lead to much higher estimates of CV_P than do the data of either Promislow et al. (1996) or Hughes and Charlesworth (1994). However, the discrepancy is probably a scale effect. The estimates by Promislow et al. (1996) and by Hughes and Charlesworth (1994) are for $\ln(A)$, whereas Fukui et al. (1996) provide estimates for A. To illustrate, if $\ln(A)$ is normally distributed with $\bar{X} = -8.0$ and CV = 0.20, then the mean and coefficient of variation of A are approximately 1.1×10^{-3} and 2.5, respectively, on a linear scale.

The estimated coefficients of genetic variation (CV_A or CV_G) in table 1 are for single chromosomes only. If the intercept and slope parameters of individual hazard functions are assumed to be typical quantitative characters, then multiple loci affecting those traits may be distributed throughout the genome. Loci influencing life span in *D. melanogaster* have been localized to all three major chromosomes, although the relative importance of each chromosome is not consistent across studies (Luckinbill et al. 1988; Nuzhdin et al. 1997). Based on map length, chromosomes 2 and 3 each account for 35%–40% of the *D. melanogaster* genome. My estimates of total phenotypic coefficients of variation (CV_P) for the intercept and slope parameters assume that each chromosome contributes to the total genetic variation in proportion to its length. If available, I used published estimates of environmental variation for the Gompertz parameters (Hughes and Charlesworth 1994). Otherwise, I assumed that the environmental variances of the parameters were equal to their genetic variances. Those may be conservative underestimates of environmental variance because they are equivalent to assuming a heritability of 50%. In general, heritabilities of life-history traits in *D. melanogaster* are <50% (Roff and Mousseau 1987; Service 2000). Environmental influences on life span or age-specific mortality rates in *D. melanogaster* include density (Khazaeli et al. 1995), mating frequency, mating status, and egg-laying rate (Partridge and Farquhar 1981; Partridge et al. 1986, 1987; Service 1989; Trevitt and Partridge 1991; Chapman et al. 1995).

A striking feature of published data is the strong positive correlation between estimates of the slope parameter, b, and variance in frailty, σ_z^2. For example, from the data in Fukui et al. (1996), the product-moment correlation coefficient across isogenic lines was $r = 0.61$ for males ($N = 23$), and $r = 0.63$ for females ($N = 25$). From Promislow et al. (1996), the additive genetic correlation between b and σ_z^2 (again estimated from second-chromosome lines) was 0.75 for males and 0.95 for females (Shaw et al. 1999). From Service et al. (1998), $r = 0.98$ across nine outbred populations (sexes combined). From the same data sets, correlations between the intercept parameter, A, and σ_z^2 were consistently negative but significantly so ($P < .05$) only for males in the study by Fukui et al. (1996).

Large-Cohort Simulations

In order to have relatively accurate estimates of mortality rates at old ages, cohorts of 1 million individuals were simulated. Several combinations of means and variances were simulated for each parameter. For simplicity, only one of the parameters of the mortality model was allowed to vary in a given simulation. Simulations proceeded one individual at a time. Starting at age $x = 0$, $q_i(x)$ was calculated using that individual's mortality function. The value of the function $q_i(x)$ was compared to a uniformly distributed pseudorandom number between 0 and 1. If the random number was less than or equal to $q_i(x)$, the individual was "killed." If not, the procedure was repeated for subsequent age classes until the individual "died." Because these simulations use parameter estimates from daily *Drosophila* mortality, x is in units of days. Pseudorandom numbers were obtained using the CombLS2 generator (Tezuka 1995). The basic output from each simulation was the number of individuals dying in each age interval, x to $x + 1$. The cohort mortality probability in each age interval $q(x)$, without subscript, was the number of deaths in the interval x to $x + 1$ divided by the number of individuals alive at age x. A typical pattern was for $q(x)$ to increase initially and then level off. The beginning of the mortality plateau was arbitrarily defined as the first age (after the initial increase) for which $q(x + 1)$ was $< q(x)$. The "height" of the plateau was the mean value of $q(x)$ for all x from the age class immediately preceding the start of the plateau until (but not including) the first age with no deaths. If there was no old-age class without any deaths, the last age class, for which $q(x)$ is necessarily 1.0, was excluded from the calculation. The mean age of death was also calculated.

For the large-cohort simulations, results are given in terms of $q(x)$, the probability of dying in the interval x to $x + 1$, given that an individual has lived to age x. In other studies, mortality data are sometimes shown as the instantaneous mortality rate, $\mu(x)$, where $\mu(x)$ is approximated as $-\ln(N_{x+1}/N_x)$ and N_x is the number of individuals surviving to age x (Promislow et al. 1996). Because it is a probability, $q(x)$ has an upper bound of 1, and there must necessarily be convergence of mortality trajectories at the upper bound when the last individual in a cohort dies. The function $\mu(x)$ is an instantaneous rate and can increase indefinitely. In practice, however, when the last individual in a cohort dies the approximation for $\mu(x)$ is undefined. Practically speaking, there is little difference

Table 1: Estimates of variance components and coefficients of variation for Gompertz intercept and slope parameters

Component/ coefficient	Intercept/ chromosome			Slope/ chromosome		
	2[a]	2[b]	3[c]	2[a]	2[b]	3[c]
V_A (or V_G)	4.61×10^{-7}	*.766*	…	8.36×10^{-4}	*2.10* × *10*$^{-3}$	…
V_D	…	…	*NS*	…	…	*NS*
V_E	1.15×10^{-6}	…	…	2.09×10^{-3}	5.25×10^{-3}	…
V_P	2.31×10^{-6}	…	…	4.18×10^{-3}	1.05×10^{-2}	…
CV_A	.884	.102	*NS*	.216	.238	*.203*
CV_E	1.397	.151	*.270*	.342	.376	*.210*
CV_P	1.976	.228	.270	.484	.532	.384

Note: Published values in italics; calculated values in standard-face type. For all three studies, genetic variances and coefficients of variation are for one chromosome. Environmental and phenotypic variances and CVs are "total." Estimates of total phenotypic variance assume $V_D = 0$, that the studied chromosome contributes 40% of total genetic variance, and that $V_E = V_G$ unless separate estimates of V_E (or CV_E) are provided in the cited studies.

[a] Fukui et al. (1996); γ-Gompertz hazard function; separate estimates for males and females are averaged.

[b] Promislow et al. (1966); γ-Gompertz hazard function; intercept parameter expressed as $\ln(A)$; separate estimates for males and females are averaged.

[c] Hughes and Charlesworth (1994); Gompertz hazard function; intercept parameter expressed as $\ln(A)$; data for males only.

between $q(x)$ and $\mu(x)$. The approximation for $\mu(x)$ is equal to $-\ln(1 - q(x))$, and $\mu(x) \approx q(x)$ when $q(x)$ is small. For example, when $q(x) = 0.25$, $\mu(x) = 0.29$; but when $q(x) = 0.5$, $\mu(x) = 0.69$. If a mortality plateau is observed for $q(x)$, then a plateau will also be observed if the same mortality data are plotted as $\mu(x)$, although the plateau will be somewhat higher in the latter case.

I have also chosen to plot $q(x)$ on a linear scale, rather than the logarithmic scale that is frequently used for $\mu(x)$. Theoretical analyses predict simply that mortality rates should increase with age. There is no special significance attached to log(mortality rate) other than the fact that the Gompertz hazard function is linearized by a logarithmic transformation, and the parameters of the function were formerly estimated by linear regression. Linear-scale plots are easier to interpret than logarithmic plots. For example, mortality rates may appear to decelerate (be concave downward) when plotted on a logarithmic scale, but not on a linear scale. However, deceleration on a linear scale also implies deceleration on a logarithmic scale. For convenience, shorthand descriptions of cohort mortality trajectories will be used throughout. "Accelerating" or exponential mortality rates are concave upward when plotted on a linear scale. "Decelerating" mortality rates are concave downward when plotted on a linear scale. "Declining" mortality rates have negative slope on a linear (or logarithmic) scale. "Leveling off" of mortality rates, or mortality rate "plateaus," occur when mortality rates appear to oscillate around a mean value for several consecutive age intervals.

Small-Cohort Simulations

Small-cohort simulations were done in order to see if the essential results of the experiment of Promislow et al. (1996) could be reproduced. That experiment examined age-specific mortality rates in 25 second-chromosome genotypes of *D. melanogaster*. Genetic variance for mortality rates (analyzed as $\log[\mu(x)]$) was low at young ages, increased at intermediate ages, and decreased at later ages. A reanalysis of the data has corroborated the original conclusion that variance of mortality rates declined at old ages (Shaw et al. 1999). Mortality data for each line were fit to the γ-Gompertz function (eq. [5]). Mean values of the parameters (averaged across sexes and genotypes) were $\ln(A) = -8.57$, $b = 0.193$, and $\sigma_z^2 = 0.768$ (σ_z^2 was called *s* by Promislow et al. 1996). Additive genetic variances for all three parameters were significantly >0 in both sexes, except for σ_z^2 in males. The additive genetic variance of V_A for $\ln(A)$ was 0.766 and V_A for b was 0.0021. Dominance variance was small compared to additive variance at all ages.

A simulation involved 24 lines (cohorts) with 1,250 individuals each (approximately the number of individuals per sex and chromosome line in Promislow et al. 1996). Simulations used Gompertz-like mortality (eq. [4]). I used the Promislow et al. (1996) estimates of mean values for $\ln(A)$ and b as the mean values for the simulations. For among-line variance of $\ln(A)$ and b, I used the Promislow et al. (1996) estimates of additive genetic variance for those parameters. In essence, among-line variance of mortality

rates in the simulations is equated with additive genetic variance in Promislow et al. (1996). Within-line (environmental) variances of $\ln(A)$ and b were assumed to be constant and equal to the among-line (genetic) variances of those parameters. Thus, environmental variances may be underestimated because the genetic variances are for a single chromosome. The variable A was assumed to be lognormally distributed among and within lines. In order to accurately simulate the mean and variance of b reported by Promislow et al. (1996), a γ distribution was used for that parameter.

For each line, mortality was simulated using the procedures described above. For comparison with Promislow et al. (1996), mortality rates were computed as $\mu(x)$ and then log transformed for analysis. I also analyzed untransformed mortality rates in order to investigate the effects of the logarithmic transformation. Because mortality rates behave erratically when very few individuals remain alive, $\mu(x)$ was not calculated for age classes in which there were 10 or fewer survivors at the beginning of the interval. After all 24 lines had been simulated, among-line variance of mortality rates was calculated. Among-line variance was determined only for ages at which there were survivors in all 24 lines. Therefore, age-specific trends in among-line variance cannot be due to the extinction of some lines and survival of others. Ten replicate simulations of 24 lines were performed. In order to determine the sensitivity of these simulations to the amount of within-line variance in hazard function parameters, an additional set of 10 simulations was done with the within-line variances of $\ln(A)$ and b reduced by one-half. Finally, as a control, 10 simulations were done with the within-line variances of $\ln(A)$ and b set to 0. The expectation for the control was that among-line variance in mortality rates would increase indefinitely at older ages because of variation in the slope parameter among lines.

Results

Large-Cohort Simulations

Results of the Gompertz-like simulations with cohorts of 1 million and variation for only the slope parameter are summarized in table 2 and figure 1. Decelerating mortality rates were produced in all cases and conspicuous mortality rate plateaus were produced in many cases. The largest coefficients of variation examined were about 0.5. Those always resulted in declining mortality rates at old ages (not necessarily shown in the figures, which are truncated at age 100 d) but also resulted in unrealistically long maximum life spans. For any given value of $\bar{b}$, the height of the mortality plateau was inversely correlated with σ_b^2. For a given CV, the height of the mortality plateau was positively correlated with $\bar{b}$. Over all nine parameter sets with variable slope and constant intercept, the mortality rate plateaus fell within the range 0.05–0.47 (one simulation did not produce a plateau). These parameter sets encompassed threefold variation in the mean of the slope parameter and 25-fold variation in the variance of the slope parameter for each value of the mean. Individual variation in the Gompertz intercept parameter also produced plateaus, and their heights fell in the range 0.26–0.51 (table 3; fig. 2). There was little obvious correlation between $\bar{A}$ and the height of the plateau. Larger CVs tended to result in lower plateaus. Considering the cohort sizes, maximum life spans were probably too low. The coefficients of variation in slope or intercept parameters sufficient to produce mortality plateaus ($CV(b) = 0.20$, fig. 1*B*; $CV(\ln(A)) = 0.09$, fig. 2*A*) are similar to those reported for genetic variation due to single chromosomes (table 1). Thus, the appearance of plateaus does not depend in any critical way on the assumptions that all chromosomes contribute to genetic variation in hazard function parameters or that environmental variance is equal to genetic variance.

Table 2: Simulations of Gompertz-like mortality with individual variation for the slope parameter, b_i

		Plateau			Life span	
	CV	First age	q_p	N	$\bar{X}$	Maximum
$\bar{b} = 0.1$	.11	71	.250	29	47.7	104
	.18	83	.175	38	48.0	125
	.49	63	.047	165	50.5	365
$\bar{b} = 0.2$	.11	43	.465	13	27.3	58
	.20	48	.318	19	27.5	67
	.53	37	.077	119	29.2	263
$\bar{b} = 0.3$	.10	…	…	…	19.5	36
	.19	36	.365	14	19.7	52
	.52	31	.104	84	21.0	159

Note: The intercept parameter, A_i, was constant (5×10^{-4} in all cases). N = number of consecutive age classes used to calculate the plateau mortality rate, q_p.

All large-cohort simulations were repeated with γ-distributed hazard function parameters. Results (not shown) were very similar to those obtained with lognormally distributed parameters. A complete set of simulations was also carried out using the Weibull hazard function (Lee 1992), with parameters lognormally and γ distributed and constrained so that all individuals had exponentially increasing mortality rates. Mortality plateaus below 30% daily mortality probability were readily produced (results not shown).

Small-Cohort Simulations

Mortality rate curves for one simulation of 24 lines are depicted in figure 3*A*. The $\log(\mu(x))$ is plotted for com-

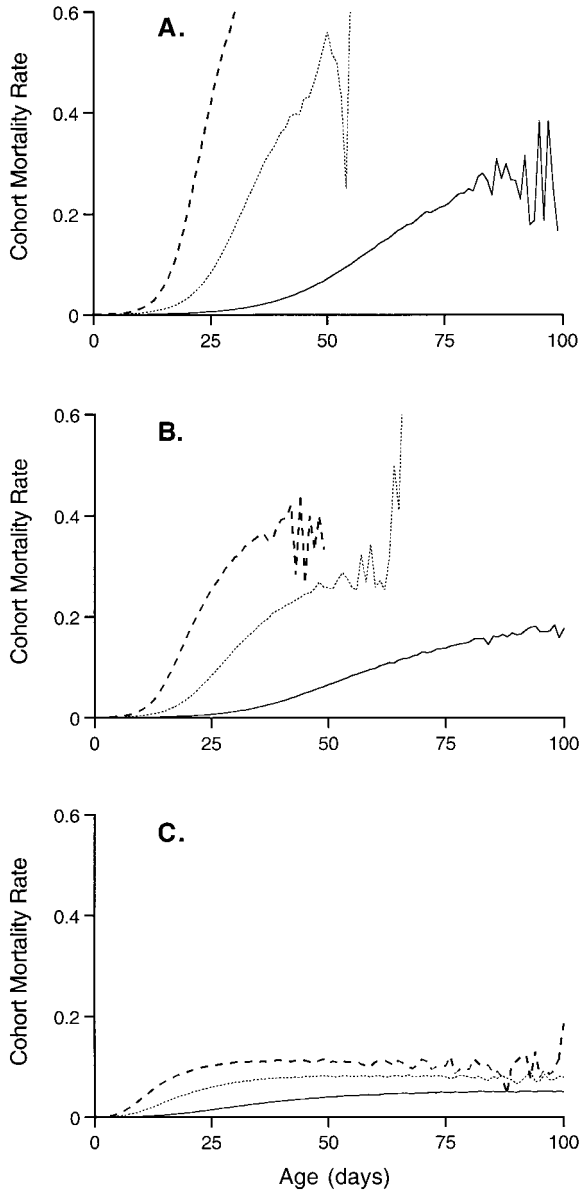

Figure 1: Gompertz-like simulations with individual variation in the slope parameter, b_i. *Solid lines*, $\bar{b} = 0.10$; *dotted lines*, $\bar{b} = 0.20$; *dashed lines*, $\bar{b} = 0.30$. *A*, Coefficient of variation approximately 0.10. *B*, CV ≈ 0.20. *C*, CV ≈ 0.50. Intercept parameter A_i was constant ($= 5 \times 10^{-4}$ in all cases). Cohort mortality rate calculated as $q(x)$, see text.

parison with figure 2 of Promislow et al. (1996). Deceleration of $\log(\mu(x))$ is apparent, as it was in Promislow et al. (1996). The age-specific pattern of among-line variance of $\log(\mu(x))$ is essentially the same as that reported by Promislow et al. (1996) for additive genetic variance (their fig. 1)—variance is small initially, increases to a maximum at intermediate ages, and then declines at older ages (fig. 3*B*). However, when $\mu(x)$ is analyzed (without the logarithmic transformation), among-line variance shows no tendency to decrease at older ages (fig. 3*C*). Those results indicate that conclusions about age-specific patterns of genetic variance for mortality rates may depend critically on the scale chosen for analysis of mortality rates. Promislow et al. (1996) used the logarithmic transformation in order to normalize their data and thus satisfy the requirements of their statistical analysis. However, it is not clear that $\log(\mu(x))$ is more biologically appropriate than $\mu(x)$.

For simulations in which the within-line variances of $\ln(A)$ and b were set to one-half the among-line variances of those parameters, the among-line variance of $\log(\mu(x))$ was again greatest at intermediate ages, but among-line variance of $\mu(x)$ oscillated irregularly after age 28 d and showed no tendency to decrease (results not shown). Those results indicate that rather modest amounts of within-line variation in frailty are sufficient to cause the among-line variance of $\log(\mu(x))$ to decline at older ages. For simulations in which the within-line variances of $\ln(A)$ and b were set to 0, among-line variance of both $\mu(x)$ and $\log(\mu(x))$ continued to increase though the oldest ages examined, as would be expected (results not shown).

Discussion

Mortality Rate Plateaus

These simulations demonstrate that leveling off of cohort mortality rates at old ages is readily produced by heterogeneity in individual mortality risk, even though all individuals have exponentially increasing probability of mortality. That result is not dependent on any particular hazard function or on any particular distribution of the mortality rate parameters. Published estimates of variances in Gompertz hazard function parameters for *Drosophila melanogaster* reproduce cohort mortality trajectories that mimic trajectories of real cohorts. Mortality rate plateaus are produced by a wide range in the variances of mortality rate parameters (25-fold or more in some cases). A very broad range of means and variances for mortality parameters can produce mortality rate plateaus that fall in the region of 10%–30% daily mortality probability, the range commonly observed for *D. melanogaster*. In short, these simulations argue that leveling off of cohort mortality rates at old ages can be explained robustly and parsimoniously by heterogeneity in individual mortality risk. In contrast, Pletcher and Curtsinger (1998) suggested that heterogeneity is unlikely to be the explanation for mortality rate deceleration: either because unrealistic variance in mortality rate parameters is required or because deceleration is still observed even when great care is taken to reduce phenotypic variation.

Table 3: Simulations of Gompertz-like mortality with individual variation for the intercept parameter, A_i

			Plateau			Life span	
	CV(A)	CV(ln (A))	First age	q_p	N	$\overline{X}$	Maximum
$\overline{A} = 1 \times 10^{-4}$	.72	.07	69	.453	8	45.0	77
	1.34	.12	71	.369	17	45.0	88
	1.92	.18	72	.259	30	45.0	104
$\overline{A} = 5 \times 10^{-4}$	.67	.08	57	.512	8	34.3	65
	1.39	.14	61	.383	16	34.4	77
	2.23	.19	54	.275	33	34.4	89
$\overline{A} = 1 \times 10^{-3}$	.69	.09	51	.498	9	29.8	63
	1.53	.16	54	.339	21	29.9	77
	2.36	.20	65	.324	14	30.0	85

Note: The slope parameter, b_i, was constant (0.15 in all cases). See table 2 for explanation of table entries.

Heterogeneity causes cohort mortality trajectories to decelerate because the frailer individuals die earlier. As the cohort ages, it becomes increasingly composed of individuals with slower rates of senescence. Plateaus are produced when the deaths of frailer individuals balance the tendency for mortality rates to increase with age. For example, the individuals that enter some old-age class, x, will have a mean probability of mortality, $\bar{q}(x)$. On average, the frailer of those individuals will die in that age class. If the mean mortality probability of individuals entering the next age class, $\bar{q}(x+1)$, is equal to $\bar{q}(x)$, then a mortality plateau will result. It is even possible for cohort mortality rates to decline with age if heterogeneity is sufficiently great (fig. 1*C*).

The relatively small range of variation in plateau mortality rates (when obvious plateaus are produced) is probably a consequence of gradually increasing mortality risk and the fact that most individuals will die when their daily mortality risk is at an intermediate value. Once an individual's mortality probability reaches 30%–40% d^{-1}, it is unlikely to survive very long. If most of the survivors in each age class are individuals with lower mortality probability, then the cohort mortality rate, $q(x)$, will tend to be <30%–40%. Mortality rate plateaus are absent only when CVs of hazard function parameters are small and catastrophic mortality ($q(x) > 0.80$) appears to require both small CVs and high mean values of hazard function parameters (fig. 1*A*).

Age-Specific Patterns of Variance in Mortality Rates

The pattern of observed age-specific genetic variance of mortality rates obtained in these simulations is essentially the same as that reported by Promislow et al. (1996). For male *D. melanogaster*, mutational variance of mortality rates showed a similar age-specific pattern, but for females, mutational variance was relatively high at early and intermediate ages and then declined at older ages (Pletcher et al. 1998). The reduction in among-line variance of mortality rates at late ages in the simulations was due to within-line individual heterogeneity in hazard function parameters and the choice of a logarithmic scale for $\mu(x)$. In the absence of within-line heterogeneity, all individuals have the parameter values specified by their genotypic means, and among-line variance in mortality rates increases through the oldest ages examined because of the among-line variation in the slope parameter. The pattern of age-specific mutational variance in female mortality rates reported by Pletcher et al. (1998) could be produced if mutation accumulation lines varied only (or chiefly) in Gompertz intercept parameter (results not shown).

It is important to note that the observed decline in among-line variance of mortality rates at old ages in the small-cohort simulations was a consequence of individual heterogeneity within lines. If all individuals of a line have the same hazard function (specified by the mean for that line), no decline in among-line variance of mortality rates is observed. In effect, the nongenetic, within-line heterogeneity means that the individuals that survive to old ages are biased samples of their cohorts. They are the individuals with the lower rates of senescence and tend to resemble one another more closely across lines than do "average" individuals. The present simulations argue that the declines in variance of mortality rates observed by Promislow et al. (1996) and Pletcher et al. (1998) were an inescapable consequence of nongenetic heterogeneity in individual mortality risk and their decision to analyze log ($\mu(x)$). Within-genotype variation in mortality risk means that the "true" mortality rate of a genotype at old ages cannot be directly observed.

As noted above, when fly mortality data are fit to the γ-Gompertz hazard function, there is a strong positive

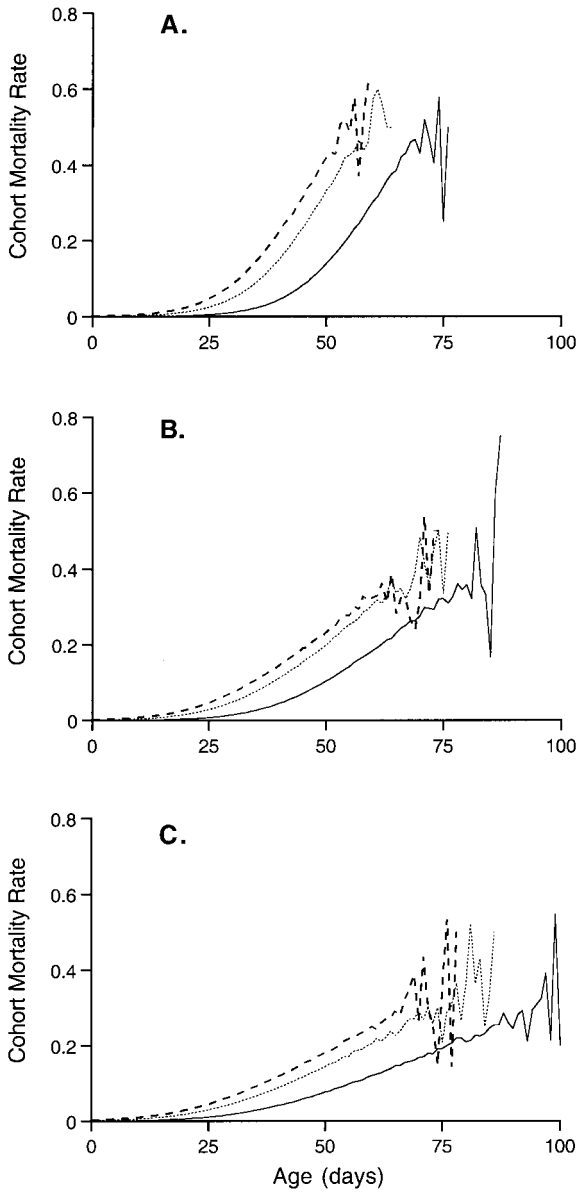

Figure 2: Gompertz-like simulations with individual variation in the intercept parameter, A_i. *Solid lines*, $\bar{A} = 1 \times 10^{-4}$; *dotted lines*, $\bar{A} = 5 \times 10^{-4}$; *dashed lines*, $\bar{A} = 1 \times 10^{-3}$. *A*, $CV(A) \approx 0.7$, $CV(\ln(A)) \approx 0.08$. *B*, $CV(A) \approx 1.4$, $CV(\ln(A)) \approx 0.14$. *C*, $CV(A) \approx 2.2$, $CV(\ln(A)) \approx 0.19$. Slope parameter b_i was constant (=0.15 in all cases). Cohort mortality rate calculated as $q(x)$, see text.

genetic correlation between the slope parameter, b, and variance in frailty, σ_z^2. Promislow et al. (1996) obtained such a correlation (Shaw et al. 1999) and a similar correlation was also observed among mutation accumulation lines (S. Pletcher, personal communication). Under the γ-Gompertz model, cohort mortality rates (expressed as $\bar{\mu}(x)$) approach an asymptote equal to b/σ_z^2. Therefore, a positive correlation between the two parameters among lines will tend to produce similar plateau mortality rates without the need of transforming mortality rates to a logarithmic scale. Thus, the old-age decline in among-line

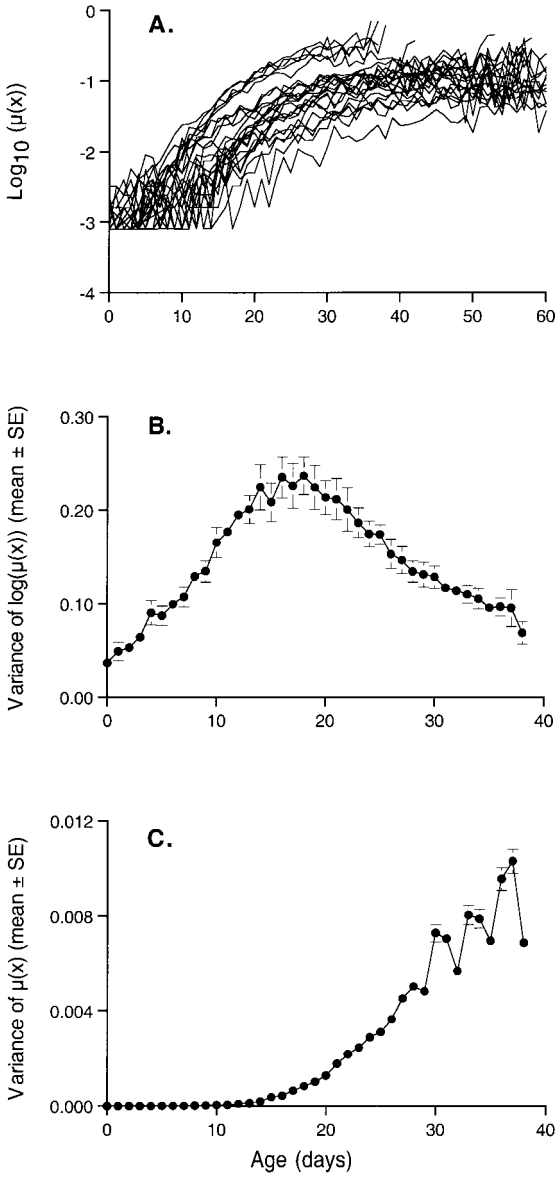

Figure 3: Simulations of 24 cohorts of 1,250 individuals each. Gompertz-like simulations with overall mean intercept parameter $\ln(A) = -8.57$ and overall mean slope parameter $b = 0.193$. Among- and within-line variance of $\ln(A)$ was 0.766, and among- and within-line variance of b was 0.0021; $\ln(A)$ normally distributed and b γ-distributed among and within lines. *A*, One replicate of 24 lines. *B*, Among line-variance of $\log_{10}(\mu(x))$ as a function of age, based on 10 replicate simulations. *C*, Same as *B* except mortality rate analyzed as $\mu(x)$.

variance of mortality rates observed in experiments may be due, at least partly, to the positive correlation between rates of senescence and heterogeneity in frailty and not solely to the choice of a logarithmic scale for analysis. However, it remains an open question whether σ_z^2 actually estimates variance in frailty, or whether it is simply a convenient parameter for producing mortality trajectories with plateaus.

Catastrophic Postreproductive Mortality

These simulations suggest that for species for which evolution has resulted in gradual senescence, catastrophic mortality will seldom, if ever, be observed. Cohort mortality rates approaching catastrophic levels are observed only when variation in hazard function parameters is very small and mortality probabilities increase very quickly, allowing a relatively large number of individuals to survive to ages at which their risk of mortality is very high. The simulations in this study assume that each individual has some underlying liability of mortality during each time interval and that the liability increases gradually with age. The underlying liability can in principle increase until it approaches 100%. However, even with cohorts of 1 million, few if any individuals will live to such ages. To do so would require surviving many earlier age intervals with lower, but substantial, liability. In fact, as I have already argued, most individuals are likely to die at ages at which they have relatively modest mortality risk, and the effect is to produce plateaus with values of $q(x)$ that are generally below 50%.

Two additional points can be made regarding the specific issue of extensive postreproductive survival. First, the evidence appears to come almost exclusively from studies of species in artificial environments (I include humans in this category). In such artificial environments, individuals may live to ages well beyond those attained in nature (or, in the case of humans, during relatively recent evolutionary history). Those are ages, therefore, that have not been subjected to selection against deleterious genetic effects. Consequently, the genetic load at those ages should be extremely high, as should mortality rates. There is a problem, however, and it arises directly from the fact that the environments in which extensive postreproductive survivorship is observed are not the environments in which those species have evolved. Those artificial environments have probably resulted in lower mortality rates at all ages. More individuals survive to postreproductive ages, and once they reach those ages, their mortality rates are lower than they otherwise would be. In other words, genetic effects on mortality rates are confounded with novel environmental effects. Extensive postreproductive survival in nature would be more problematic for the evolutionary theory of senescence. The extent of postreproductive survival in nature is poorly known (Finch 1990). Second, for species that undergo gradual senescence, it simply may be difficult for evolution to arrange for the immediate death of each individual once that individual (or at least the "average" individual) has ceased to reproduce. Catastrophic postreproductive mortality is observed for some taxa, such as annual plants and some species of salmon. In such species, it is reasonable to infer that evolution has resulted in a tight coupling between a single well-defined episode of reproduction and deterioration of the soma that then leads quickly to death. Such tight coupling between the cessation of reproduction and ensuing death might be much more difficult to achieve in an iteroparous organism.

Is Heterogeneity Sufficient?

Observed levels of genetic variance in rates of senescence are all that is required to produce late-age cohort mortality plateaus in outbred populations of *D. melanogaster*. Leveling off is also observed in genetically homogeneous cohorts. If leveling off in the latter cases is the result of heterogeneity, then the heterogeneity must be due to environmental causes. Assuming that environmental variance for individual hazard function parameters is similar in magnitude to genetic variance, mortality rate plateaus in genetically homogeneous cohorts may not pose any special problem. Also, heterogeneity in individual mortality risk appears to be sufficient to explain the reduction in genetic variance of mortality rates at old ages, particularly if mortality rates are log transformed or if genotypes with higher rates of senescence also have greater variance in frailty. These simulations suggest that alternative explanations for mortality plateaus are unnecessary. However, they do not prove that alternative explanations are not true. In practice, it may be extremely difficult to determine whether mortality plateaus are caused only by heterogeneity (with all individuals strictly senescent) or if there is also a contribution due to slowing or cessation of senescence at the individual level (e.g., Mueller and Rose 1996). Khazaeli et al. (1998) attempted to reduce heterogeneity by establishing cohorts of flies that had similar preadult development times ("fractionated" populations). Fractionation reduced the rate of mortality deceleration, as quantified by σ_z^2, in only one of six comparisons. That result may suggest that heterogeneity does not account for mortality rate deceleration in genetically homogeneous cohorts. However, it is also possible that the experimental treatment had little or no effect on environmental variance of mortality risk in adult flies (Khazaeli et al. 1998).

Is the Amount of Heterogeneity "Reasonable"?

The estimates of variances for hazard function parameters used in these simulations are based on published values for genetic variances in *D. melanogaster*. In addition, I have argued that the environmental variances of the parameters might be at least as large as the genetic variances, although that assumption is not critical to these analyses. Another approach to evaluating whether these simulations are reasonable is to examine the variation in the probability that a newborn individual will reach age x. For illustration, I use the simulation shown in figure 1*B* with $\bar{b} = 0.20$. If the values of b_i are arranged from lowest to highest, an individual at the fifth percentile of the distribution (from the bottom) has a slope parameter of $b_i = 0.1456$ and an individual at the 95th percentile has a slope parameter of $b_i = 0.2748$. The ratio of survivorship probabilities of fifth- and 95th-percentile individuals to various ages can be calculated from the Gompertz survivorship function (eq. [6]). For survival to the mean age of death in that simulation, 27.5 d, the ratio is about 27. It increases very quickly after that, reaching 775 by age 30.

That amount of variation in the probability of survival seems, at first glance, unusually high. However, the measure by which such variation should really be evaluated is fitness. In a stable population, a good measure of individual fitness is lifetime reproduction. For *D. melanogaster* females in typical laboratory culture, daily fecundity peaks at about 1 wk of adult age and declines rapidly thereafter so that 90% of lifetime fecundity may be realized by 2.5–3 wk (Partridge et al. 1986; Trevitt and Partridge 1991; Tatar et al. 1996). Using the example of the previous paragraph, the ratio of survivorship probabilities of fifth- to 95th-percentile individuals to 1, 2, and 3 wk is, respectively, 1.005, 1.06, and 1.67. Thus, the fitness differences implied by variation in the slope parameter may not be very large. Using estimates of daily fecundity for the first 3 wk taken from Tatar et al. (1996, their fig. 1), the expected reproductive success of fifth-percentile females is only about 3% greater than that of 95th-percentile females, assuming that they have similar age-specific fecundity schedules (calculations not shown). If genotypes with higher rates of senescence also have higher early fecundity (Tatar et al. 1996; Service et al. 1998), then fitness differences might be even less. A similar analysis was carried out for variation in the intercept parameter, A_i, using the simulation shown in figure 2*B*, with $\bar{A} = 0.0005$. The fitness difference between fifth- and 95th-percentile individuals was about 7%.

Conclusions

If the heterogeneity argument as developed in this article is essentially correct, then the predictions of theoretical analyses may not be directly observable. Phenotypic variation in mortality risk confounds our estimates of old-age mortality rates in a way that may be inescapable because the individuals that survive to old ages are not truly representative of their cohorts. Thus, "observations of the surviving population cannot be directly translated into conclusions about the behavior or characteristics of the individuals who made up the original population" (Vaupel and Yashin 1985*b*, p. 184). Within-genotype variance in mortality risk, for example, can probably never be eliminated from experiments. Therefore, it may not be possible to test by direct observation the prediction that additive genetic variance in mortality rates should increase with age. In effect, the "true" mortality rate of a genotype at old ages cannot be observed because the individuals that survive to old ages are a nonrandom sample of the genotype—the hardiest or least frail. Similar considerations might apply to the analysis of age-specific variance components of any phenotype that is correlated with survivorship, such as late-age fertility (Rose and Charlesworth 1980; Tatar et al. 1996; Service 2000). In fact, the cohort-level age-specific pattern of any phenotype that is correlated with an individual's hazard rate can be influenced by heterogeneity in mortality risk (Vaupel and Yashin 1985*b*). Last, I suggest that the failure of experiments to confirm theoretical predictions concerning age-specific mortality rates is not a consequence of fundamental flaws in the theoretical analysis of the evolution of senescence. Rather, the failure is due to unanticipated consequences of demographic heterogeneity on observed mortality rates.

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