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EVOLUTIONARY PATTERNS AMONG MEASURES OF AGING

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Abstract—Maximum lifespan has been one of the most common aging measures in comparative studies, while the Gompertz model has recently attracted both proponents and critics of its capacity to adequately describe the acceleration of mortality in the oldest age classes. The Gompertz demographic model describes age-dependent mortality rate acceleration and age-independent mortality using the parameters α and A, respectively. Evolutionary biologists have predominantly used average longevity in studies of aging. Little is known about the evolutionary relationships of these measures on the microevolutionary time scale. We have simultaneously compared Gompertz parameters, average longevity, and maximum longevity in 50 related populations of *Drosophila melanogaster*, many of which have been selected for postponed aging. Overall, these populations have differentiated significantly for the A and α parameter of the Gompertz equation, as well as average and maximum longevity. These indices of aging appear to measure the same genetic changes in aging. However, in some specific population comparisons, the relationships among these measures are more complex. In a second experiment, environmental manipulation of longevity had substantially different effects from genetic differentiation, with the A parameter accounting for changes in overall mortality. The adequacy of the maximum lifespan and the Gompertz equation as indices of aging in evolutionary studies is discussed.

Key Words: Gompertz equation, measures of aging, evolution of aging

INTRODUCTION

RECENT WORK in the evolutionary biology of aging has proceeded largely with the use of such characters as average lifespan and average late fertility (Rose, 1991). However, other studies of aging have been based on maximum lifespan (Comfort, 1979) or on fitted mortality models (e.g., Finch, 1990; Finch *et al.*, 1990; Carey *et al.*, 1992; Curtsinger *et al.*, 1992; Brooks *et al.*, 1994). Many of the latter studies have measured what they consider rates of aging using the α parameter of the Gompertz equation, where this equation gives the dependence of age-specific mortality on age as follows:

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$$m(x) = A \exp(\alpha x)$$

where $m(x)$ is the mortality rate at age x, A is the initial mortality rate, and α is the exponent term for the acceleration in mortality rate as a function of age. However, the rationales for both maximum lifespan and the Gompertz parameters as measures of aging are somewhat obscure. Maximum lifespan has the advantage that it is not as dependent on environmental vagaries (Comfort, 1979; Rose, 1991), but it is inherently sample size dependent. As for the Gompertz model and its variants, even their proponents remark that, "The Gompertz model is empirical and is not based on any principle or law" (Finch, 1990, p. 16).

This situation may be contrasted with that of the evolutionary theory of aging, which explains patterns of aging by deduction from genetic principles, but makes no use of the Gompertz model (Charlesworth, 1980; Rose, 1991). It may be asked whether maximum lifespan and Gompertz parameters have a heritable genetic basis and, thus, might be subject to selection. But even if they have heritable underpinnings, what would the pattern of selection be for these characters? It is impossible to make deductively derived predictions where these models are concerned, absent ad hoc assumptions connecting them to evolutionary theory (cf. Promislow, 1993). Another issue is whether maximum lifespan and Gompertz parameters reflect similar or different underlying processes or determinants of aging, compared to characters like age-specific survival probability or fecundity. While all these characters may be related to one another algebraically, they are by no means identical. For example, in principle average longevity can be changed by manipulating A, or α, or both. Is there any need to consider the maximum longevity and Gompertz parameters separately? An additional issue is whether or not the demography of aging is essentially a fixed characteristic of each species, as argued by Fries (1980), and, therefore, impossible to change. More particularly, are average longevity, maximum longevity, and the parameters of the Gompertz equation unresponsive to selection or environmental manipulation? Given the effects of nutrition in modulating life histories (Stearns, 1992), one might expect such environmental intervention to influence the expression of these measures of aging. If these measures are responsive, does selection cause different patterns in their relationship than does environmental manipulation?

In the present study, we attempt to address questions of this kind using a set of survival data collected from 50 *Drosophila melanogaster* populations that are closely related, but have, nonetheless, diverged considerably with respect to average lifespan. These data are analyzed for each population to obtain all the basic types of aging measures that have been of interest. Because these populations have been subjected to strong selection for some time, it is unlikely that their mortality schedules are changing rapidly, if at all. Consequently, these measures of aging are likely to be stable through time. We further analyze the data to compare patterns among populations for these indices. We find that there seem to be fundamental underlying survival changes that affect various measures in similar ways in analyses of all populations. However, in certain population comparisons, more complex patterns of association among these indices are apparent. We also find evidence for differences in the patterns of association among these measures of aging caused by selection and environmental manipulation.

Although the Gompertz equation has been in use for about 170 years (Gompertz, 1825), to our knowledge this is the first large-scale test of the Gompertz parameters against other commonly used indices of aging across many replicated, outbred populations of *Drosophila melanogaster*, all derived from a common ancestral population. In addition, this comparison was conducted using populations for which the genetic and physiological basis of aging is somewhat understood. Similarly, maximum lifespan has not been studied using replicated, outbred populations

within a species that are highly differentiated for average lifespan. By using many populations, derived from a single common ancestral population and displaying great ranges in longevity, we search for patterns in these indices of aging that have biological interpretation.

MATERIALS AND METHODS

Experimental populations

Each of these populations had been derived from a common ancestral stock, the IVs, which has been maintained in the laboratory since 1975 (Rose, 1984; Service *et al.*, 1985). The selection histories of these stocks are presented in Fig. 1. Each of these stocks are fivefold replicated and have been maintained at large populations sizes (at least 2000 flies/replicate population).

Demographically selected stocks, the Bs and Os, are derived directly from the IVs. The Bs are selected for early-life fertility, while the Os are selected for late-life fertility (Rose, 1984; Service *et al.*, 1985). The other stocks are selected for resistance to either starvation (SOs and their controls the COs, both derived from the Os, and the SBs and their controls the CBs, both derived from the Bs) or desiccation (Ds and their controls the Cs both derived from the Os) (Rose *et al.*, 1992). As controls for starvation-selected stocks, the CO and CB populations are

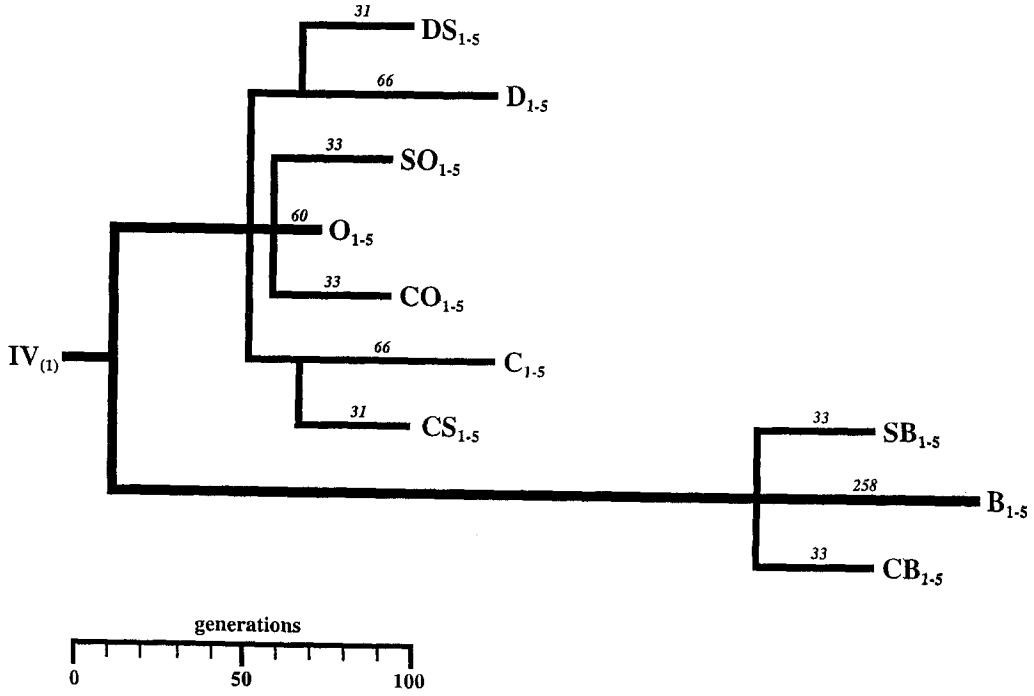

FIG. 1. Selection history of stocks employed in these studies. All stocks are ultimately derived from the unreplicated IV population of flies. All other stocks are fivefold replicated. Subscripts represent replicate numbers. Numbers above lines represent generations since derivation at the time of the longevity assays in this paper. The IV, B, O, CO, and CB populations are selected for demographic properties. All other populations are stress selected, either for starvation resistance (SO, SB, C, CS, DS) or desiccation resistance (D).

demographically selected. As controls for the Ds, the Cs are starvation selected, because the D selection protocol involves desiccation and starvation. DS and their CS controls were derived from the Ds and Cs, respectively, after the first 20 generations of selection on the latter groups of populations. Subsequently, DS and CS have both been starvation selected as in Rose *et al.* (1992). In the demographically selected stocks generation times vary from two weeks in the Bs to 10 weeks in the Os. For the stress-selected stocks typical generation times range from about 19 days in the Ds and Cs to about four weeks in the SO, CO, CS, and DS populations.

Experimental procedures

In 1990 we obtained data from mixed-sex cohorts of 86–114 *D. melanogaster* from each of the 50 replicates of the outbred populations discussed above. All flies were assayed in the same experiment except those in the nutritional manipulation assay (see below). Representative samples of flies from each replicate population were taken out of their normal selection treatment and handled identically for two generations to control for environment-specific effects. To control for density, rearing vials were standardized at 60–80 eggs. Longevity assays proceeded as in recent experiments from our laboratory (Rose *et al.*, 1992), adult flies being held uncrowded, in vials, until dead of natural causes. Longevity was measured by placing four male–female pairs in a 25 × 95 mm shell vial provisioned with standard molasses-banana medium. On average, 12 such vials were set up for each of the 50 populations. Flies were assayed for survival daily and transferred to new vials three times weekly. In addition to the assay of survival patterns among stocks, in a second experiment two selection treatment groups, B and O, were assayed at two levels of nutrition each: 1 mL and 10 mL of our standard yeast solution spread on the surface of the medium, as in Chippindale *et al.* (1993). In all other respects, these flies were handled identically to those of the first experiment. Although the exact nutritional content of the two yeast solutions is unknown, these solutions are known to differentially affect fecundity (Chippindale *et al.*, 1993), so we reasonably expect effects on survival schedules also.

Statistical methodology

The parameters of the Gompertz model were estimated by the maximum likelihood technique using the exact Gompertz model (Mueller *et al.*, 1995) directly on the survival data, without prior transformation. The rationale for this procedure is that it enabled us to fit the model without reorganizing the age classes. Earlier work has shown that this technique is superior to the typical least-squares linear regression approach used to estimate Gompertz parameters. The least-squares linear regression approach is biased and produces poorer estimates of the model parameters as a function of the duration of the age-intervals chosen and the number of individuals within the age classes (Mueller *et al.*, 1995).

The following analyses allowed us to investigate the relationships among indices of aging in these stocks. Analysis of variance (ANOVA) was performed on A, α, average longevity, and maximum longevity separately for each sex with stock type as the independent variable. Because each selection treatment type (e.g., B, O) has five independent replicates, there are five estimates of each aging measure for each selection treatment type. These provide the error estimates in the ANOVA. Paired or unpaired t-tests were used for specific comparisons between experimental populations and their controls. How populations were derived from ancestors determined whether paired or unpaired t-tests were employed in a particular case. All replicates of the B and O populations were derived from the same single ancestral population, so unpaired t-tests were used for comparison. All other populations were compared by paired t-tests because

each experimental treatment replicate and its like-numbered control replicate is derived from the same unique ancestral replicate population. Data from the second experiment was analyzed by ANOVA with stock type (B or O), yeast level, and sex as independent effects. This analysis was carried out to determine the influence of nutrition on each of the four indices of aging.

RESULTS

Table 1 shows the estimates of the means for A and α from the Gompertz equation, the average longevity, and the maximum longevity for each group of fivefold replicated populations, with the sexes separated. Table 2 summarizes the statistical analyses that we have performed on these data. Table 3 displays the estimates of the four measures of aging in each of the B and O replicate populations by sex.

TABLE 1. SUMMARY OF AGING MEASURES

Stock	A ($\times 10^4$)	*SE* ($\times 10^4$)	α	*SE*	*Average longevity*	*(SE)*	*Maximum longevity*	*(SE)*
				Males				
B	9.13	3.78	.123	.019	49.6	0.4	66.8	2.5
O	4.75	2.09	.059	.010	86.8	2.3	128.0	2.6
SB	26.90	5.12	.046	.007	60.9	1.4	109.4	4.8
CB	3.06	0.11	.110	.003	48.9	1.5	74.2	3.2
SO	5.07	0.17	.043	.002	94.3	3.7	137.6	2.3
CO	12.60	0.60	.058	.002	63.2	0.8	96.6	4.5
D	9.25	0.29	.060	.001	82.2	1.4	124.0	2.1
C	15.90	0.50	.047	.002	69.9	0.6	71.7	0.5
DS	11.90	1.10	.040	.007	85.9	4.8	130.4	1.6
CS	26.10	1.50	.041	.003	85.8	4.1	125.8	3.1
B low	27.80	1.28	.072	.006	43.4	1.1	68.2	5.2
B high	47.70	2.53	.080	.005	34.0	1.4	57.2	2.6
O low	8.73	0.30	.065	.003	63.0	1.7	91.0	2.5
O high	35.10	1.03	.046	.003	55.9	1.7	86.4	4.7
				Females				
B	18.06	7.66	.099	.013	41.0	1.8	63.4	5.9
O	20.43	6.78	.051	.006	74.3	1.6	116.4	4.6
SB	14.16	0.60	.061	.003	58.0	2.5	91.6	3.7
CB	4.21	0.46	.090	.005	45.8	2.0	68.4	4.8
SO	7.53	0.25	.047	.002	82.0	2.5	124.6	3.7
CO	17.30	0.92	.056	.002	58.6	0.7	90.4	4.0
D	17.40	2.04	.045	.005	66.0	2.5	110.2	5.3
C	17.43	1.68	.051	.005	62.6	2.0	103.4	4.5
DS	17.09	1.12	.036	.002	67.0	3.6	120.6	4.4
CS	19.07	1.10	.039	.003	72.7	6.9	115.2	3.9
B low	15.68	0.81	.102	.005	36.2	0.7	56.6	3.0
B high	53.78	9.74	.062	.016	29.1	1.1	51.2	4.9
O low	18.37	0.38	.058	.002	57.8	1.2	86.3	4.8
O high	31.32	1.50	.064	.003	44.5	1.5	73.4	1.5

Each of the 10 stocks employed in these studies is fivefold replicated. Each entry is the mean of the five replicates. SE represents the standard error of the mean. Measures of aging studied include A (day^{-1}) and α (day^{-1}) from the Gompertz model, average longevity (days), and maximum longevity (days). The B and O stocks were also measured in two nutritional environments, high yeast (=high) and low yeast (=low), in a second experiment.

The most obvious conclusion is that these stocks are differentiated from each other with respect to all indices: *A*, α, average longevity, and maximum longevity, in both males and females (Table 2a). This differentiation indicates heritable genetic variation among stocks for these characters, because the stocks are derived from a common ancestor, the IVs. These results also corroborate the findings of Hughes and Charlesworth (1994), who detected heritable genetic variation in the IV stock. Selection on the fecundity schedules or on stress-resistance characters of these populations caused the indirect evolution of A, α, average longevity, and maximum longevity. While the evolutionary theory of aging predicts that changes in demographic selection will lead to changes in the pattern of aging within a population, the indirect

TABLE 2. SUMMARY OF STATISTICAL ANALYSES

	A	α	*Ave. longevity*	*Max. longevity*
(a) Univariate Analyses				
One-way ANOVA with stock as the independent variable				
		Males		
All Stocks	<0.026	<0.001	<0.001	<0.001
B vs. O	NS	0.018	<0.001	<0.001
		Females		
All Stocks	0.002	0.001	<0.001	<0.001
B vs. O	NS	0.011	<0.001	<0.001
t-Tests comparing pairs of experimental and control treatment groups				
		Males		
B-O	NS	0.03	<0.001	<0.001
C-D	<0.001	NS	0.002	<0.001
CB-SB	<0.01	0.0004	0.004	0.003
CO-SO	<0.0003	<0.004	0.001	0.002
CS-DS	NS	NS	NS	NS
O high-O low	<0.00002	0.01	0.004	NS
B high-B low	0.004	NS	0.009	NS
		Females		
B-O	NS	0.02	<0.001	<0.001
C-D	NS	NS	NS	NS
CB-SB	0.0002	<0.007	0.031	0.044
CO-SO	<0.0006	<0.03	<0.001	0.002
CS-DS	<0.001	NS	NS	NS
O high-O low	0.0007	NS	<0.001	NS
B high-B low	<0.02	NS	0.005	NS
	A	α	*Ave. longevity*	*Max. longevity*
(b) Multivariate Analysis				
Three-way ANOVA (stock yeast, sex) on B and O data from second experiment				
Stock	<0.001	<0.001	<0.001	<0.001
Yeast	<0.001	NS	<0.001	0.005
Sex	NS	0.006	<0.001	0.003

Each of the 10 stocks employed in these studies is fivefold replicated. The unit of observation is the estimated value for a replicate. Indices of aging studied are A (day^{-1}), and α (day^{-1}), from the Gompertz model, average longevity (days), and maximum longevity (days). Column entries are *p*-values unless otherwise indicated. The B and O stocks were also measured in two nutritional environments, high yeast (=high) and low yeast (=low), in a second experiment. All interactions NS except stock · yeast · sex for *A* ($p = 0.005$) and α ($p = 0.044$).

TABLE 3. B AND O DATA

Stock	*Sex*	A ($\times 10^4$)	α	*Average longevity*	*Maximum longevity*
B1	M	3.89	0.103	49.8	68
B2	M	7.29	0.094	48.0	71
B3	M	0.11	0.182	50.8	62
B4	M	1.25	0.081	49.8	73
B5	M	2.19	0.156	49.6	60
O1	M	1.05	0.041	85.0	129
O2	M	4.00	0.057	80.3	119
O3	M	8.55	0.040	88.0	133
O4	M	0.07	0.092	86.6	126
O5	M	0.59	0.064	94.3	133
B1	F	9.37	0.096	43.3	64
B2	F	18.7	0.112	34.1	49
B3	F	12.2	0.093	43.7	64
B4	F	3.07	0.137	42.2	56
B5	F	47.0	0.055	41.5	84
O1	F	31.6	0.060	71.4	120
O2	F	38.9	0.041	72.2	120
O3	F	20.7	0.036	74.6	123
O4	F	7.01	0.049	80.5	121
O5	F	3.91	0.066	73.0	98

Values of the Gompertz parameters A (day^{-1}) and α (day^{-1}), average longevity (days), and maximum longevity (days) for both sexes of each replicate of the B and O stocks from Experiment 1.

response of these measures to selection for stress-resistance characters is less straightforward. However, these indirect responses can be explained by the causal relationship between stress-resistance and longevity in these populations (Rose *et al.*, 1992). Moreover, the finding of indirect responses among measures of aging to selection on demography and stress-resistance immediately indicates that the idea of a fixed species-specific longevity is not universally valid, as perusal of Table 1 also suggests.

One of the most important specific comparisons of stocks is that of the B and O treatment groups (Table 3). These populations are well known for their contrasting aging patterns, from survival to physiology (Rose, 1984; Service *et al.*, 1985). Previously, it had not been shown that they were differentiated with respect to α. The present study now shows that they are differentiated in the manner expected, the short-lived Bs showing a faster acceleration of mortality rate with adult age than the long-lived Os (Table 1, Table 2a). It may also be noted that the B-O contrast has three indices of aging moving together, average longevity and maximum longevity increasing in Os as the acceleration of mortality rate, α, decreases. Although it is generally true that all measures differentiate across all stocks, concordant changes of α, average longevity, and maximum longevity are not evident in each comparison of selection treatment groups or nutritional treatments, as shown in Table 2 for the C-D, CS-DS, O high-O low, and B high-B low comparisons.

Moreover, in the nutritional experiments, B males and B and O females show variation in average longevity with no accompanying significant variation in maximum longevity or α (Table 2a). In addition, nutritional manipulation of longevity appears to affect the A parameter, with two- to threefold increases in A when a given population is reared on high yeast (Table 2b).

Environmental manipulation, as opposed to genetic differentiation, influences mortality schedules through the age-independent parameter, not the rate of aging (Table 2b). Only selection, as is the case with the SOs and SBs, has produced the fully concordant changes among all measures of aging.

DISCUSSION

The Gompertz equation is not based on any principle or law (Finch, 1990), and there has been controversy over the demographic theory it embodies (Carey *et al.*, 1993; Curtsinger *et al.*, 1993; but see Nusbaum *et al.*, 1993; Hughes and Charlesworth, 1994). Nevertheless, our results suggest that it can accurately summarize environmental and genetic alterations of longevity in a manner more or less consistent with other indices of aging. Thus, we have a general "postponed aging" syndrome, involving A, α, average longevity, and maximum longevity. However, not all stocks exhibit the full syndrome.

Johnson (1987, 1990) and colleagues observed differences in α, average longevity, and maximum longevity, but not A, among standard, recombinant-inbred, and mutant strains of *Caenorhabditis elegans.* This is a direct parallel to the B-O outcome, except that the differentiation of strains is not produced by selection. Finch (1990, see his Table 10.1, p. 508) surveyed studies of dietarily restricted rats and observed differences in both mortality rate doubling time (a statistic proportional to α) and maximum longevity. No consistent differences in the A parameter (called IMR) were evident. However, protocols differed among studies and no statistical analyses were conducted. In any case, the closest studies to our own (Johnson, 1987, 1990) produced analogous results, despite the use of inbred and mutant strains of *C. elegans* and our use of laboratory-selected outbred populations of *Drosophila.* Because of the analogous results between populations that differ in population genetic structure, we hypothesize that redundancy among these measures of aging has some credibility.

Here, we have shown that environmentally induced changes in aging largely affect A, the age-independent parameter of the Gompertz equation. Is it likely to be the case that environmental factors will normally alter A, as opposed to α, and, conversely, for genetic factors? Perhaps the dichotomy is one between environmental modulation of lifespan and genetic modulation of lifespan in which fitnesses are always reasonably high, the former changing A, the latter changing α. Testing this idea would require the assembly of a broad range of data, covering diverse genetic and environmental effects upon lifespan. On the other hand, because there is no profound theoretical basis for an association between genetic variation and the α parameter, or an association between environmental effects and the A parameter, any such study might prove largely vacuous.

Despite the heritable genetic basis for and the empirical relationships among these four indices of aging in these 50 populations, we do not argue that the Gompertz model is the best or even necessarily a very good descriptor of aging in populations. There are reasons, grounded in first principles of age-specific population genetics theory and age-specific patterns of gene expression (Charlesworth, 1980), to expect that rates of aging may not continue to increase exponentially in the oldest age classes, as required by the model. In the evolutionary theory of aging, the force of selection falls with chronological age after reproductive maturity (Hamilton, 1966; Charlesworth, 1980; Rose, 1991). This fall may give rise to an accelerating increase in age-specific mortality rate, for a time. However, there is no mathematical necessity to any particular second-order form for the initial decline in the force of natural selection. The form will instead be determined by the age-specific mortality and fecundity schedules of the popu-

lation. A still more important point is that the fall in the force of natural selection eventually slows in rate, because that force cannot go below zero. It reaches zero, and then remains at that value thereafter. From that point on, if we assume complete age specificity in the evolution of life-history characters, the expectation is for a reduction in the upward acceleration of the age-specific mortality rate, all other things being equal. In other words, we expect a failure of the Gompertz model to fit at extremely late ages. This, of course, is the pattern that has been adduced by Gavrilov and Gavrilova (1991), Carey *et al.* (1992) and Curtsinger *et al.* (1992). Thus, the Gompertz model has little credibility as a generally appropriate model, if perfect age specificity of life-history evolution is assumed.

A considerable complication to this analysis is the question of pleiotropy between age classes. Any discussion that directly connects the force of natural selection to the shaping of age-specific fitness components assumes the effective absence of pleiotropy. But the theoretical (Charlesworth, 1980; Rose, 1985) and experimental (Rose, 1991) importance of pleiotropy in the evolution of aging is well established, even though it is not a universal phenomenon (Mueller, 1987; Service *et al.*, 1988). Therefore, the preceding argument is necessarily flawed. We cannot really make strong statements connecting the force of natural selection to demographic patterns, except for the broadest qualitative assertions that are embodied in the evolutionary theory of aging in general. Natural selection does not directly shape the timing of aging, even though it is the ultimate cause of that aging. Complex patterns of pleiotropy intervene. For example, the continued survival of some individuals in the laboratory, long after reproduction and, thus, long after force of natural selection has hit zero, indicates some kind of "pleiotropic echo," in which earlier adult adaptations for survival are keeping much older individuals alive. Thus, we cannot plausibly invoke the quantitative force of natural selection to guide the interpretation of life-history schedules, at least not exactly.

Finally, there is the purely practical question: should the Gompertz parameters or maximum lifespan be used in studies of the evolution of aging, given their redundancy? To this point, characters like average longevity and fertility have been used preferentially within evolutionary biology. They do not require fitting to a population's mortality pattern. They can be studied in terms of correlation between relatives and during artificial selection (cf. Falconer, 1981). Moreover, there are no profound theoretical motivations to use the maximum lifespan or the Gompertz parameters in evolutionary studies of aging, and, indeed, there are the theoretical and experimental problems with them discussed above. We conclude that the utility of studying these parameters is now an open question that requires further experimental investigation. This is not to question, for example, the utility of estimating life tables in studies of the evolutionary biology of aging, especially because the evolutionary theory of aging is an age-specific theory of survival and fertility. However, there may always be confusions generated by continuing attempts to explain demographic patterns in terms of ad hoc theory (Promislow, 1991, 1993), rather than the evolutionary theory developed for life history (e.g., Charlesworth, 1980).

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REFERENCES

BROOKS, A., LITHGOW, G.J., and JOHNSON, T.E. Mortality rates in a genetically heterogeneous population of *Caenorhabditis elegans. Science* **263,** 668–671, 1994.

CAREY, J.R., LIEDO, P., OROZCO, D., and VAUPEL, J.W. Slowing of mortality rates at older ages in large medfly cohorts. *Science* **258,** 457–461, 1992.

CHARLESWORTH, B. *Evolution in Age-Structured Populations,* Cambridge University Press, London, 1980.

CHIPPINDALE, A.K., LEROI, A. M., KIM, S.B., and ROSE, M.R. Phenotypic plasticity and selection in *Drosophila* life history evolution. I. Nutrition and the cost of reproduction. *J. Evolut. Biol.* **6,** 171–193, 1993.

COMFORT, A. *The Biology of Senescence,* 3rd ed., Churchill Livingstone, Edinburgh, 1979.

CURTSINGER, J.W., FUKUI, H.H., TOWNSEND, D.R., and VAUPEL, J.W. Demography of genotypes: Failure of the limited life-span paradigm in *Drosophila melanogaster. Science* **258,** 461–463, 1992.

FALCONER, D.S. *Introduction to Quantitative Genetics,* 2nd ed., Longman, London, 1981.

FINCH, C.E., PIKE, M.C., and WITTEN, M. Slow increases of the Gompertz mortality rate during aging in certain animals approximate that of humans. *Science* **249,** 902–905, 1990.

FINCH, C.E. *Longevity, Senescence, and the Genome,* University of Chicago Press, Chicago, 1990.

FRIES, J.F. Aging, natural death, and the compression of morbidity. *N. Eng. J. Med.* **303,** 130–135, 1980.

GAVRILOV, L.A. and GAVRILOVA, N.S. *The Biology of Life Span: A Quantitative Approach,* Harwood Academic Publishers, New York, 1991.

GOMPERTZ, B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philos. Trans. R. Soc. Lond. Series A* **115,** 513–585, 1825.

HAMILTON, W.D. The moulding of senescence by natural selection. *J. Theor. Biol.* **12,** 12–45, 1966.

HUGHES, K.A., and CHARLESWORTH, B. A genetic analysis of senescence in *Drosophila. Nature* **367,** 64–66, 1994.

JOHNSON, T.E. Aging can be genetically dissected into component processes using long-lived lines of *Caenorhabditis elegans. Proc. Natl. Acad. Sci. USA* **84,** 3777–3781, 1987.

JOHNSON, T.E. Age-1 mutants of *Caenorhabditis elegans* prolong life by modifying the Gompertz rate of aging. *Science* **249,** 908–912, 1990.

MUELLER, L.D. The evolution of accelerated senescence in laboratory populations of *Drosophila. Proc. Natl. Acad. Sci. USA* **84,** 1974–1977, 1987.

MUELLER, L.D., NUSBAUM, T.J., and ROSE, M.R. The Gompertz equation as a predictive tool in demography. *Exp. Gerontol.* **30,** 553–569, 1995.

NUSBAUM, T.J., GRAVES, J.L., MUELLER, L.D., and ROSE, M.R. Letter. *Science* **260,** 1567, 1993.

PROMISLOW, D.E.L. Senescence in natural populations of mammals: A comparative study. *Evolution* **45,** 1869–1877, 1991.

PROMISLOW, D.E.L. On size and survival: Progress and pitfalls in the allometry of lifespan. *J. Gerontol. Biol. Sci.* **48,** B115–B123, 1993.

ROSE, M.R. Laboratory evolution of postponed senescence in *Drosophila melanogaster. Evolution* **38,** 1004–1010, 1984.

ROSE, M.R. Life history evolution with antagonistic pleiotropy and overlapping generations. *Theor. Popul. Biol.* **28,** 342–358, 1985.

ROSE, M.R. *Evolutionary Biology of Aging,* Oxford University Press, New York, 1991.

ROSE, M.R., VU, L.N., PARK, S.U., and GRAVES, J.L., JR. Selection on stress resistance increases longevity in *Drosophila melanogaster. Exp. Gerontol.* **27,** 241–250, 1992.

SERVICE, P.M., HUTCHINSON, E.W., MAC KINLEY, M.D., and ROSE, M.R. Resistance to environmental stress in *Drosophila melanogster* selected for postponed senescence. *Physiol. Zool.* **58,** 380–389, 1985.

SERVICE, P.M., HUTCHINSON, E.W., and ROSE, M.R. Multiple genetic mechanisms for the evolution of senescence in *Drosophila melanogaster. Evolution* **42,** 708–716, 1988.

STEARNS, S.C. *Evolution of Life-Histories,* Oxford University Press, Oxford, 1992.