Explaining Fruit Fly Longevity

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Two recent reports have challenged the notion that death rates automatically increase with age. J. R. Carey et al. (1) studied a large, outbred population of the medfly, Ceratitis capitata, and report that mortality rate actually decreased in the older flies. J. W. Curtinsger et al. (2) examined smaller, inbred populations of Drosophila melanogaster and describe how mortality rate apparently leveled off at older ages. Although it has long been accepted that not all species undergo senescence (3), the idea that medflies and Drosophila might show constant or declining mortality at older ages was an unexpected and important result. Both these species might be expected to show progressive mortality rate increases with age.

We have examined the results of these reports and believe that there are important aspects of the interpretation of these data that have not received due attention. First, there is the problem of heterogeneity. Carey et al. point out that genetic heterogeneity at the level of the cohort might at least partly explain their finding, because in a mixed population the frail individuals die earlier, leaving the hardest to survive to the oldest ages. However, they do not explore this possibility further. We have calculated the theoretical survival curve of a population in which we assumed individuals varied in the rate parameter of a Gompertz mortality model (Fig. 1). We found that the population mortality rate declined in the same way the medfly rate declined even though in our model every individual fly has an exponentially increasing risk of dying (4).

Second, there is the problem of sample size. As noted by Carey et al. (1), a large sample size is essential to avoid large statistical fluctuations in mortality rate estimates for later ages. Even so, there comes an age for any sample when the population has dwindled to the last few survivors. In (2), the largest sample was only 5751 flies. The mortality rates plotted in (2) would not be inconsistent with a model of increasing mortality that allowed for this statistical variation. We therefore ran many simulations of populations of 5751 flies assuming a Gompertz mortality model (Fig. 2). As can be seen from our results, an apparent flattening of the mortality curve in old flies is consistent with chance.

The interpretations of Carey et al. and Curtinsger et al. now seem questionable. Where genetic heterogeneity exists as in (1), the mortality pattern for the population as a whole contains little information about the mortality pattern for individual genotypes. Heterogeneity can also be non-

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**Fig. 1.** Smoothed age-specific mortality rates (dots) taken from table 2 of (1). Age-specific mortality rates for a theoretical population comprising eight genotypes, each having a Gompertz mortality function (continuous curve) [see (4) for details].

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**Fig. 2.** Medians and interquartile ranges of age-specific mortality rates from 1000 random simulations of a population of 5751 flies, with the assumption of a Gompertz mortality function with intercept parameter 0.008 and slope parameter 0.09.
one in which there was the most pronounced fall in mortality with age. It is not stated whether groups were combined as the numbers of survivors declined. If not, the survivors would have enjoyed a progressive reduction in their crowding. In fact, if one examines figure 2 of (1), it may be seen that the impression of declining mortality derives mainly from this particular population. The impression is reinforced by Carey et al., plotting the data only up to day 100 (see their table 2). Between days 10 and 80, the mortality in their experiment 3 was markedly higher than in experiments 1 and 2, where crowding was less severe. Therefore, the possibility must be considered that experiment 3 shows mainly the effect of a transient stress caused by crowding.

In conclusion, we believe that both (1) and (2) are valuable studies that expose long-standing difficulties with simplistic paradigms of mortality and life-span. However, these studies themselves are open to question.

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REFERENCES AND NOTES

4. The intercept parameter of the Gompertz function was 0.001 in all cases. The slope parameters for the eight genotypes were 0.027, 0.077, 0.087, 0.114, 0.156, 0.182, 0.250, and 0.618 with initial population fractions 0.004, 0.017, 0.016, 0.262, 0.062, 0.244, 0.902, and 0.003, respectively. These values were estimated to minimize mean squared deviation with the use of the "downhill simplex method," as described in (5). Our choice of 8 for the number of genotypes was arbitrary, for illustrative purposes only, as was our assumption of a strict Gompertz mortality function.

The research of Carey et al. (1) has important implications for researchers in the fields of geriatrics and demography, as it attempts to address some of the fundamental suppositions behind theories of human life-span and biological survival. Their controlled study of 1.2 million medflies leads Carey et al. to question the assumption that species may be characterized by a species-specific life-span that is genetically determined. The results of this research are fascinating, but several points, on which Carey et al. largely base their conclusions, are open to question. These points are as follows. (i) The medflies in the study all died from old age; (ii) observations of mortality in the oldest old medflies showed evidence of a diminution in the risk of mortality over time; (iii) medflies provide a possible model for human mortality trends; and (iv) the Gompertz model is at present considered by demographers to constitute the best description of mortality rates.

Carey et al. state (1) that research using a cohort on a scale of millions cannot easily be achieved with other animal species. In France, however, approximately 55 million people are observed each year through the government registry office whose records have been exceptionally accurate since the 18th century (apart from a brief period after the French Revolution). The cohorts within the population vary in size from 750,000 to 850,000. The sample sizes are thus comparable to those in the study by Carey et al.

In order to compare human and fly life tables, we have reduced the human life-span to fly-scale. The two scales coincide nicely, with 1 year for a French male being equivalent to 2 days for a fly (Fig. 1). The age reached by a small percentage of survivors (close to 1%) is 48 days for the flies in experiment 3 (figure 2 of the report by Carey et al.) (1.22% survive this long) and, according to the French mortality tables from 1985 to 1987, 96 years for French males (1.15% survive this long) (Fig. 1). Survival for French males appears much more homogeneous despite the fact that they are in an uncontrolled environment. The fly survival curve, however, resembles the theoretical curve drawn to describe survival in prehistoric man (except for the low medfly infant mortality, which is not explained by Carey et al., and the survival curve for people in India between 1921 and 1930 from British death records (Fig. 1) (2)).

In the experiments of Carey et al. the medflies in cages apparently lived in conditions of severe overcrowding, and they showed subsequent over-mortality at an early age. The more protected medflies (in cups and cells) had mortality rates that approach a theoretical Gompertz curve and those demonstrated in experiments with other species such as the Drosophila (3). Furthermore, the apparent drop in mortality in the oldest old medflies is based on less than 1% of the original population, which, as Carey et al. point out in their introduction, can give rise to spurious calculations that result from instability at the end of the survival curve. Their conclusion that there may not be a biological species-specific limit to the life-span may be correct, but not for the reason given in their paper; that a drop in mortality rates could be observed when calculated for the tiny proportion of aged survivors.

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Response: Kowald and Kirkwood illustrate (in their figure 1) what we asserted (1, 2) and demonstrated (3)—that heterogeneity can explain observed fruit fly death rates. Their reference to the Drosophila sample (2) as "only" 5751 individuals is misleading; to our knowledge, this was the largest survivorship study ever executed with Drosophila, which has been a standard tool of experimental gerontology since the 1920s. Data on an additional 18,000 males and females from inbred lines in one of our laboratories (J.W.C.'s) have been analyzed and also show the pattern of leveling off at older ages. Kowald and Kirkwood (in their figure 2) illustrate that the error associated with estimated mortality rate increases as the cohort ages and decreases in numbers. This observation would apply to cohorts of any
Compositional Interpretations of Medfly Mortality

Death rates for a cohort of 1.2 million Mediterranean fruit flies (Ceratitis capitata) rose and then fell with age (Fig. 1) (1). If this pattern reflects age changes for individuals, biological theories of aging may have to be rethought (2). On the other hand, the age trajectory may be an artifact of the evolving structure of the population (3). Death changes the composition of a cohort by differentially removing the frail. It is possible that the age trajectory of mortality for medflies at any specific degree of frailty actually rises steadily with age.

We have closely fitted the observed medfly mortality pattern (1) with mixtures of increasing Gompertz (4) or Weibull (5) curves. Let $\lambda(x)$ denote the proportion of a cohort that survives to exact age $x$, where $\lambda(0) = 1$, and where the cohort is extinct or no longer observed at age $a$. Assume that the hazard of death at age $x$ for individuals with fixed frailty $z$ is given by $\mu(x, z)$. If $s(x, z)$ denotes the proportion of individuals with frailty $z$ who survive to exact age $x$, then

$$s(x, z) = e^{-\int_0^x \mu(z, x) dx}$$

Assume that frailty can be described by an $n$-point discrete distribution with probabilities $p(z)$. Then

$$s = sp$$

where $s$ is an $n$-element column vector, $s$ is an $n$-by-$n$ matrix, and $p$ is an $n$-element column vector.

If a hazard function $\mu$ and vectors $z$ and $p$ are specified, then estimated values of $s$ can be calculated, using a formula similar to Eq. 2, by letting $s$ be the matrix of elements $s(x, z)$ as defined by $\mu$ and by the values of $z$, as indicated in Eq. 1. An optimization algorithm can be used to estimate the vectors $z$ and $p$ that minimizes the discrepancy between the actual and estimated survivorship vectors.

To model the age-trajectory of medfly mortality, assume that

$$\mu(x, z) = \mu_0(z) x^{\beta}$$

where $\mu_0$ is the baseline hazard function. This proportional-hazards specification is widely used in survival analysis (6). More specifically, assume that the baseline hazard function in Eq. 3 is a Gompertz curve, where

$$\mu_0(x) = 0.003 e^{3x}$$

The proportion of the initial population of 1,203,646 flies that survived to day $x = 1$ to 121 defines the vector $s$. (Deaths were not