ger analog (cAMP) or a transmitter (dopamine) to the whole slice to simulate L-LTP may allow study of the proteins and genes required for the induction and maintenance of L-LTP.

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26. We thank A. Barzilai for helpful instructions on the determination of cAMP concentrations and T. O'Dell and S. Siegelbaum for helpful comments on the manuscript. Supported in part by the Howard Hughes Medical Institute and by National Institute of General Medical Sciences grant GM32099.

2 December 1992; accepted 2 April 1993

TECHNICAL COMMENTS

Explaining Fruit Fly Longevity

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. Curtsinger *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 hardiest 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 medlfly 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 Curtsinger *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-genetic, so there may be implications for the results of (*2*). When sample sizes are small, as in (*2*), caution must be exercised in drawing conclusions. Some commentators on these reports have noted these problems, but also noted that Carey *et al.* (*1*) addressed the sample size issue, while Curtsinger *et al.* (*2*) addressed the heterogeneity issue. However, both problems need to be addressed together.

A third problem that received little comment in either report is the effect of age-related behavior changes on mortality risk. If old flies lead quieter lives (for example, crawling rather than flying), mortality may level off or even decline in spite of the fact that the animal gets progressively more frail. Data on age-related behavior changes are essential to complete the picture. Crowding is another factor. Carey *et al.* mention that flies in their large population (experiment 3 in their figure 2) were held in groups of 7200 and "subject to conditions that increase mortality risk—large cage size for flying, mating, some egg-laying, mechanical wear, and considerable stress due to crowding . . . ." This population was the

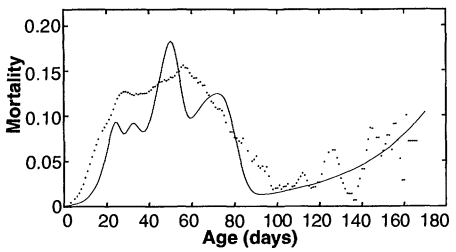

Fig. 1. Smoothed age-specific mortality rates (dots) taken from table 2 of (*1*). Age-specific mortality rates for a theoretical population comprising eight genotypes, each having a Gompertz mortality function (continuous curve) [see (*4*) for details].

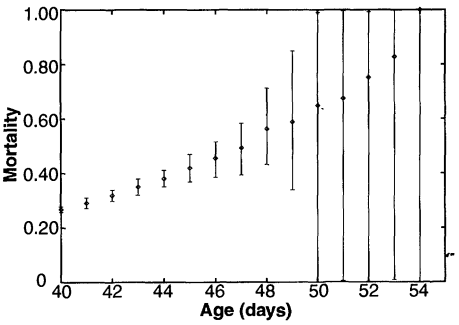

Fig. 2. Medians and interquartile ranges of age-specific mortality rates from 1000 random simulations of a population of 5751 flies, with the assumption of a Gompertz mortality function with intercept parameter 0.008 and slope parameter 0.09.

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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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, 0.392, 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 eight for the number of genotypes was arbitrary, for illustrative purposes only, as was our assumption of a strict Gompertz mortality function.
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2 April 1993; accepted 17 May 1993

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.

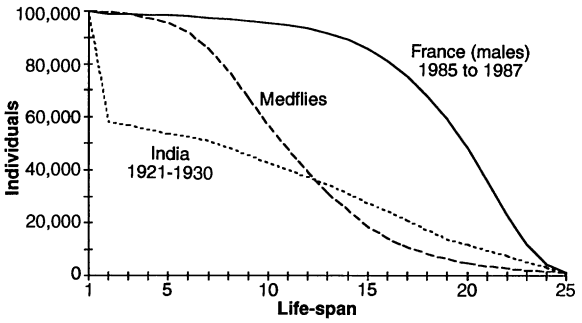

Fig. 1. Medflies and human survival curves on the same scale according to the age reached by the last surviving 1%. One interval on the *x*-axis equals 4 years for French males, 3.33 years for people in British India, and 2 days for medflies.

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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15 March 1993; accepted 12 May 1993

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

size. The issue is not whether the error is inflated at the tail of the survivorship distribution, but whether the Gompertz model fits actual observations better than alternative models of mortality. We found that a two-stage Gompertz model, with almost no increase in mortality rate at older ages, fits the observed data significantly better than a simple single-stage Gompertz model (*2*). Model fits were obtained by maximum likelihood methods, which take into account differential sample sizes as the cohort ages. The simulations by Kowald and Kirkwood provide no information that lead us to question the value of maximum likelihood fitting of alternative models to mortality data. We did not say that we were estimating morality curves for individuals; our research (*1–3*) discusses the role of heterogeneity in producing non-Gompertzian mortality for cohorts. Furthermore, it is a misrepresentation of these reports to suggest that one addresses the sample size problem and the other addresses the heterogeneity problem; both consider heterogeneity, and the *Drosophila* study (*2*) was sufficiently large to discriminate among alternative models of mortality.

Robine and Ritchie suggest that medfly survival appears similar to that of prehistoric man or of people in India from 1921 to 1930. This type of comparison between the survival schedules of a human and a nonhuman population does not shed light on the nature of mortality at older ages because survival curves are poorly suited for summarizing mortality patterns, as we stated in (*1*). Death rates for humans continue to increase at advanced ages; death rates for medflies and *Drosophila* level off or decline. Moreover, the medfly system was not designed to serve as a miniature *replica* for humans (or any other species), but rather was used as a model biological *system* for addressing fundamental questions about the nature of mortality at older ages.

Robine and Ritchie state that medflies in cups and cells (*1*) and *Drosophila* had death rates similar to the theoretical Gompertz curve. This is incorrect: the death rates leveled off at older ages (*1, 2*). Such leveling off is inconsistent with a species-specific life-span limit. Robine and Ritchie dismiss the drop in mortality at the extreme tail of the mortality curve as being based on "the tiny proportion of aged survivors." However, one of the main purposes of the medfly study was to examine the tail which, by definition, is some small fraction of the initial number. This "tiny proportion" consisted of over 2000 medflies contained in 156 cages (an average of 16 flies per cage for cages in which some medflies were still alive). That this number is a small proportion of the total starting number is irrelevant.

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20 April 1993; accepted 3 May 1993

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 $\bar{s}(x)$ denote the proportion of a cohort that survives to exact age x, where $\bar{s}(0) = 1$, and where the cohort is extinct or no longer observed at age ω. 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

$$s(x, z) = e^{-\int_0^x \mu(t,z)dt} \quad (1)$$

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

$$\bar{s} = sp \quad (2)$$

where $\bar{s}$ is an ω-element column vector, s is an n-by-ω matrix, and p is an n-element column vector.

If a hazard function μ and vectors z and p are specified, then estimated values of $\bar{s}$ can be calculated, using a formula similar to Eq. 2, by letting s be the matrix of elements $s(x, z)$ as defined by μ 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

$$\mu(x, z) = z\mu^0(x) \quad (3)$$

where μ^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

$$\mu^0(x) = 0.003e^{0.3x} \quad (4)$$

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

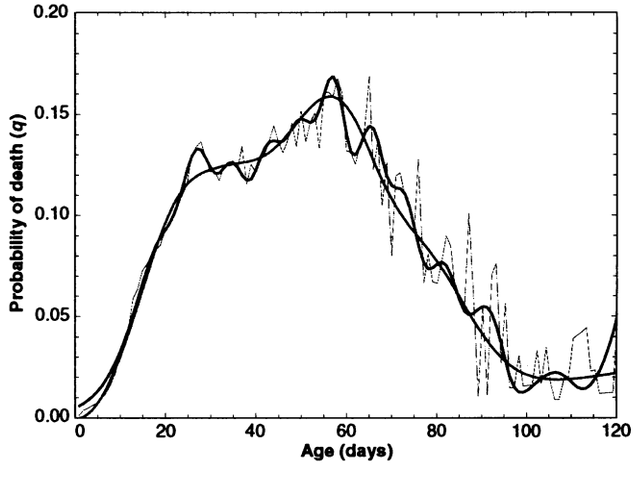

Fig. 1. Daily probability of death for a cohort of 1.2 million medflies. The thin line traces the observed trajectory of death rates. The red line was calculated with the use of the Gompertz model described in the text. The green line was calculated with the use of the Weibull model described in the text.