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Aging, fertility, and immortality

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Abstract

Evolutionary theory suggests that fecundity rates will plateau late in life in the same fashion as mortality rates. We demonstrate that late-life plateaus arise for fecundity in *Drosophila melanogaster*. The result qualitatively fits the evolutionary theory of late life based on the force of natural selection. But there are a number of alternative interpretations. Fecundity plateaus could be secondary consequences of mortality-rate plateaus. Female fecundity plateaus might arise from diminished male sexual function. Another alternative hypothesis is analogous to male sexual inadequacy: nutritional shortfalls. These may arise later in life because of a decline in female feeding or digestion. If some females have a life-long tendency to lay eggs at a faster rate, but die earlier, then aging for fecundity could arise from the progressive loss of the fast-layers, with the late-life plateau simply the laying patterns of individual females who were slow-layers throughout adult life. If this type of model is generally applicable to late life, then we should find that the females who survive to lay at a slow but steady rate in late life have a similar laying pattern in mid-life.
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1. Introduction

1.1. The end of aging?

Late-life plateaus in age-specific mortality rates have been found in *Drosophila* and a number of other organisms, including medflies, wasps, nematodes, yeast, and humans (Charlesworth and Partridge, 1997; Vaupel et al., 1998). At present there is no widely accepted explanation for these late-life mortality-rate plateaus. When late-life mortality-rate plateaus were first discovered (Carey et al., 1992; Curtsinger et al., 1992), they seemed to challenge then current theories of aging (vide Finch, 1990; Rose, 1991; Brooks et al., 1994). The plateauing of cohort mortality rates late in life suggested that, in an infinite population, some organisms could theoretically live forever. This finding challenged our fundamental understanding of aging.

1.2. Theories that explain the end of aging

Since the discovery of late-life mortality-rate plateaus, two types of theory have been proposed to explain their existence: evolutionary and demographic. One evolutionary theory for late-life mortality is based on *optimality*, assuming trade-offs between survival and reproduction (Abrams and Ludwig, 1995; reviewed in Charlesworth and Partridge, 1997). Such models sometimes produce late-life mortality-rate plateaus, and sometimes do not, depending on the model parameters. The kinds of parameters involved in these models are almost always unknown, making such theory difficult to test.

Another evolutionary theory for late-life mortality is based on *the force of natural selection*, using the fact that the force of natural selection plateaus at or near zero at late ages (Rose and Mueller, 2000). Research on the evolution of aging has shown that mortality rates earlier in life follow the force of natural selection; that is, as the force of natural selection decreases, mortality rates increase (Rose, 1991). Intuitively, then, mortality rates late in life should similarly follow the force of natural selection and plateau when the force of natural selection plateaus. They always do so in our explicit simulations (Mueller and Rose, 1996; but see Pletcher and Curtsinger, 1998 for caveats).

In the study of Mueller and Rose (1996), we were primarily interested in determining if simple models of natural selection could produce late-life mortality-rate plateaus. While the models we developed are just a few

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of many that might be considered appropriate, they serve as a counter-example to any general claim that natural selection cannot produce such patterns. Our results were obtained through computer simulations. These simulations were based on a sequence of substitutions, without any possibility of polymorphism. Other theoretical work has since shown that our basic results can be obtained even when this assumption is relaxed (Charlesworth, 2001). Our simulations show that, at very late ages, mortality patterns are roughly level, and there is no association between age and rate of mortality. Thus we suggest that leveling off of mortality rates late in life is the pattern that is to be expected evolutionarily.

By contrast, the demographic theories explain late-life mortality plateaus using life-long heterogeneity. That is, individuals that are less robust *throughout life* are expected to die off at earlier ages, compared to individuals that are more robust throughout life. This leaves individuals with life-long superiority in robustness (Fig. 1A) preponderant among those that reach extremely late ages. These individuals then cause a slowing in mortality rates at late ages because the less robust individuals (Fig. 1B and C) are no longer around to affect mortality rates (Vaupel et al., 1979; Vaupel, 1988, 1990). It should be noted that this effect only works when robustness levels are consistent throughout an organism's life. If there is no correlation between robustness at different ages, late-life mortality levels will not be affected by this mechanism. But when such demographic heterogeneity in life-long robustness is extremely pronounced, late-life plateaus could indeed arise from this mechanism (Kowald and Kirkwood, 1993).

Demographic heterogeneity models also require extreme differences in robustness throughout life to explain mortality-rate plateaus. Demographic heterogeneity this extreme has yet to be shown experimentally. However, a theoretical analysis of the Carey et al. (1992) mortality data for medflies
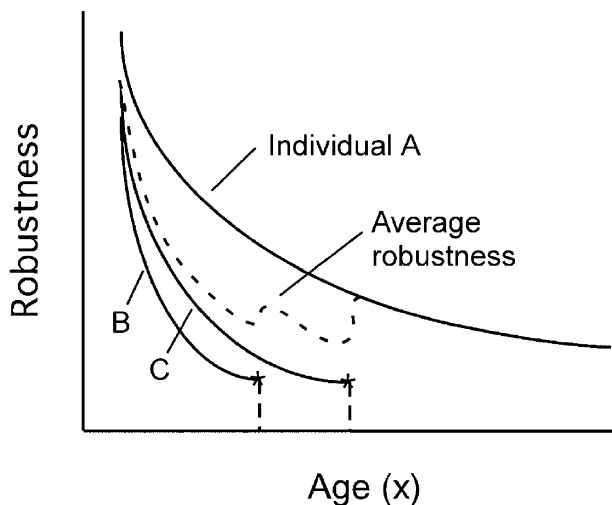

Fig. 1. The effect of individuals with various levels of robustness on the average robustness of a cohort. Robust individual A is present at extremely late ages because the less robust individuals, B and C, have already died.

demonstrated that their data could be fitted post hoc to a cohort demographic heterogeneity model (Kowald and Kirkwood, 1993), using hypothetical high levels of life-long heterogeneity.

There is little experimental evidence in favor of demographic heterogeneity as an explanation for late-life mortality-rate plateaus. Brooks et al. (1994) found that mortality rates in an isogenic population of the nematode *Caenorhabditis elegans* showed a less distinct plateau than in a genetically heterogeneous population. However, Vaupel et al. (1994) quickly pointed out that the isogenic line studied by Brooks et al. was grown at a higher temperature and a higher food concentration than the heterogeneous line, complicating the interpretation of the mortality patterns. In addition, comparisons of isogenic with heterogeneous populations of *D. melanogaster* do not consistently show effects of varying heterogeneity levels (Curtsinger et al., 1992; Fukui et al., 1996). Khazaeli et al. (1998) found that environmentally induced demographic heterogeneity among individual flies is not a primary factor in determining late-life mortality rates. Lastly, Drapeau et al. (2000) found no differences in late-life mortality between cohorts of flies having markedly different levels of early robustness. Collectively, these results are evidence against the demographic heterogeneity theory for late-life mortality.

1.3. Extension of the evolutionary theory for late-life, based on the force of natural selection, to fecundity

Evolutionary theory predicts that the *force of natural selection acting on fecundity* also declines with age, like the force of natural selection acting on mortality, until it hits zero at the last age of survival in the habitat in which the population evolves (Hamilton, 1966). The force of natural selection acting on age-specific fecundity scales according to $s'(x) = e^{-rx} l_x$, where, x is the age of a genetic effect on fecundity, r is the Malthusian parameter for the population, and l_x is survivorship to age x (Fig. 2). After the last age at which individuals survive in the population's evolutionary history (say d, which is not the last age of cohort survival under protected conditions) $s'(x)$ converges on zero, remaining there forever after. Therefore, fecundity rates should plateau at very late ages, as mortality rates do, starting at some age x greater than d.

Because evolutionary theory predicts fecundity plateaus late in life, fecundity can also be used to study the evolution of late life. In fact, fecundity may be a better character than mortality to study the evolution of late life, because later fecundity is not necessarily conditioned on early fecundity, unlike mortality. With mortality, death at one age completely conditions the likelihood of survival at a later age. Or more simply, an individual that dies early is not around to die later. However, fecundity at one age does not similarly condition later fecundity with the same absolute necessity. For example, individuals that lay eggs early are not absolutely
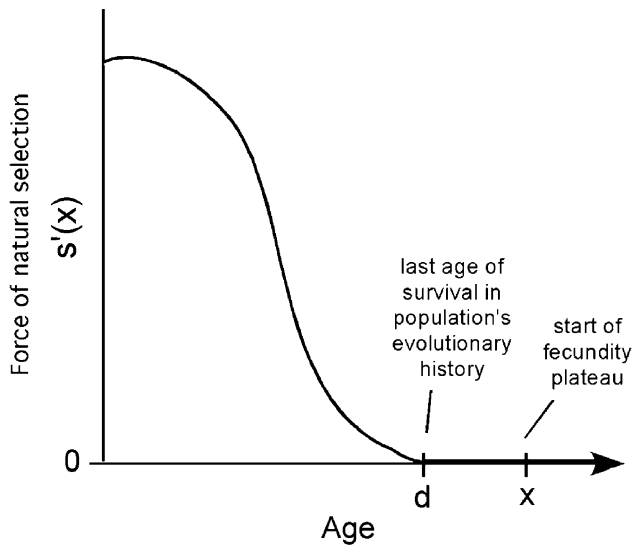
Fig. 2. The force of natural selection acting on fecundity. The symbol *d* indicates the last age of survival in the population's evolutionary history. After *d* the force of natural selection plateaus, remaining at zero forever. The symbol *x* indicates the start of the fecundity plateau.

precluded from laying eggs late in life. In addition, the necessary effects of early mortality on later mortality are a major problem for evolutionary theories of late-life mortality. This is because it is almost inevitable that life-long heterogeneity in robustness will produce some measure of slowing in later mortality, even if it may not be so extreme as to generate mortality-rate plateaus in late life (Fig. 1).

Late-life fecundity's freedom from these demographic heterogeneity effects (leaving aside the question of whether or not such demographic heterogeneity is sufficient to explain late-life mortality plateaus) makes it superior to the study of late-life mortality with respect to late-life evolution.

2. Materials and methods

2.1. Late-life plateaus for fecundity?

To our knowledge, the existence of late-life plateaus for fecundity has never been experimentally established. Therefore, our goal was to test this *existence hypothesis* in *D. melanogaster*. We tested whether late-life fecundity plateaus exist by statistically testing whether fecundity models with late-life plateaus fit mid and late-life fecundity data significantly better than models without such plateaus. We used the statistical methods described below.

2.2. Culture and assay methods

All flies used in the experiment were raised as larvae in standard banana-molasses food at densities of between 50 and 80 eggs per 8-dram vial, with approximately 5 ml food.

Each assay started with 3200 females and as many males. During the assay, four females and four males were kept in each of the 8-dram vials containing charcoal food and 5 mg of yeast as a nutritional source. These are very benign, uncrowded conditions. All flies were kept in constant illumination at 25 °C. The flies were transferred and their eggs were counted daily. As mortality occurred, flies from different vials were combined to forestall age-dependent density effects (Graves and Mueller, 1993). The assay was conducted on flies that had undergone two generations of controlled density rearing.

The flies were taken from three replicated ACO populations studied by Chippindale et al. (1997). These are populations that develop rapidly and have a last age of reproduction of 9 days. Three assays, one for each population, were done in total.

2.3. Data analysis

We needed to decide on which objective criteria should be used to decide if there was a plateau late in life. With survival data we can use maximum likelihood methods for inferring plateaus in mortality rates at late age. However, there is no equivalent sampling model for female fecundity. Also, there is no generally accepted model that can be used to describe fecundity prior to the plateau. Accordingly we have sought methods that do not require us to assume anything about the shape of the female fecundity prior to a plateau other than it will decrease at some age just prior to a plateau.

To determine if there is a fecundity plateau and when that plateau starts, we use all ages with at least one observation. In the case of the ACO_1 population, day 48 was the last age used in the analysis (Fig. 3). We want to use a method that will not depend on how long the plateau is, because we will
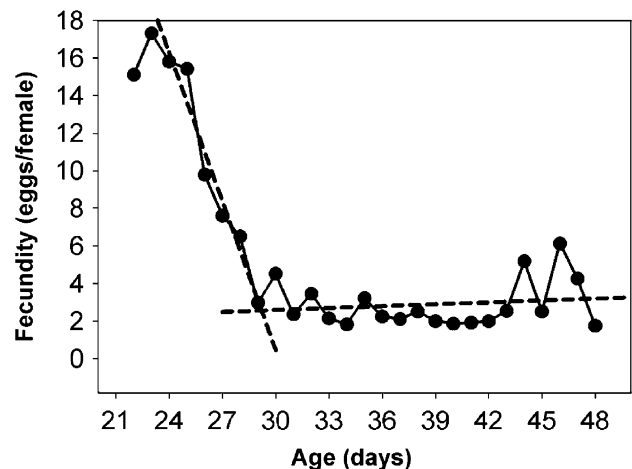

Fig. 3. The circles are mean fecundity values obtained for 400 random females from an initial cohort of 3200 ACO_1 females. The plateau in this population appears to begin around day 29. The dashed lines represent the best-fit lines of the two-stage fecundity model.
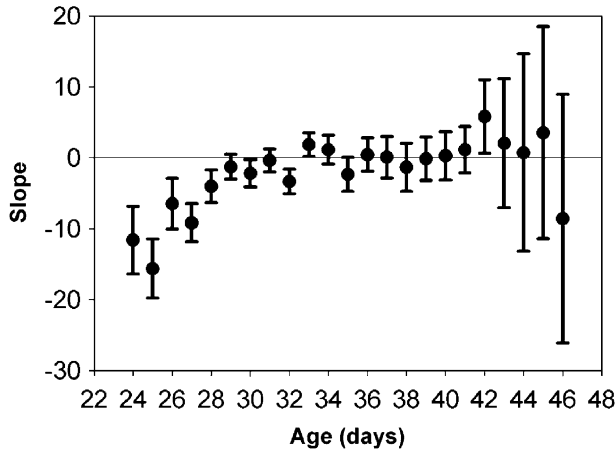
Fig. 4. Each point shows the estimated slope for 3 days of ACO_1 fecundity data starting at the age indicated on the x-axis. The bars are 95% confidence intervals. Since the first two significant negative slopes occur at ages 28 and 27 we place the break day at 29 days.

ultimately be comparing the particular age at which plateaus start, or what we call the 'break day,' between populations that may have very different break days and plateau lengths. The break day is determined such that rates of change in fecundity just prior to the break day are fit to a downward sloping line, while fecundity rates after and including the break day are fit to a regression line. This two-stage linear model is analogous to the two-stage models that we fit to mortality data (Drapeau et al., 2000).

The break day was first determined by computing slopes, along with the 95% CI, over running 3- and 4-day intervals, starting from the last observation and moving back in age, to determine which size interval would most accurately give us the break day. Thus, for the ACO_1 population we first estimated the slope over 3-day intervals using the observations at ages 46–48, the second slope would be based on ages 45–47, etc. (Fig. 3). When estimating the slope over 4-day intervals we used observations at days 45–48, 44–47, etc. The break day was determined to be the day just before, moving earlier in time, we observed two intervals in a row with significantly negative slopes. We have not found any important differences between 3 and 4-day intervals in our analyses, so we have settled on the 3-day interval (the 2-day interval gave unstable results).

Once the break day was determined, we fit the data 5 days prior to and all data after and including the break day to

their respective best-fit lines. We then determined the slopes for those lines in the two-stage model and calculated the 95% CI. Lastly, we tested whether the slope of those lines after and including the break day, or the plateau slopes, were significantly different from a slope of 0.

3. Results

3.1. A plateau for late-life fecundity

Both the 3- and 4-day analyses supported a break day at age 29 days for the ACO_1 population (Fig. 4; 4-day analysis not shown). The break day for the ACO_2 population was determined to be at age 37 days and age 30 days for the ACO_3 population (Table 1).

Fig. 5 shows the mid and late-life fecundity for all three ACO populations assayed, along with the average fecundity for the three populations. Slopes of the best fit lines were determined for each of the ACO populations for the fecundity data 5 days prior to the break days and then for the fecundity data after and including the break day. The slope of the best fit line for the fecundity data 5 days prior to the break day in the ACO_1 population was -2.6398 (95% CI (-4.0664, -1.2132)), -1.3256 (95% CI (-1.4181, -1.2330)) for the ACO_2 population and -0.4030 (95% CI (-2.6652, 1.8592)) for the ACO_3 population. We only used fecundity data for the 5 days immediately before the break day because, although mid-life fecundity declines, there is no standard model for mid-life fecundity like there is for mortality. Slope of the best fit line for the plateau, or the fecundity data including and after the break day, in the ACO_1 population was 0.0337 (95% CI (-0.0682, 0.1357)), -0.1447 (95% CI (-0.3260, 0.0366)) for the ACO_2 population and -0.0122 (95% CI (-0.0424, 0.0180)) in the ACO_3 population (Table 1). The late-life fecundity slopes in the three ACO populations were not found to be significantly different from zero ($p > 0.50$).

The height of the plateau was 2.8746 eggs/day for the ACO_1 population, 1.6229 eggs/day for the ACO_2 population and 1.2671 eggs/day in the ACO_3 population (Table 1). The height of each plateau was determined by taking the average fecundity of all days after and including the break day.

Table 1
Break days, plateau heights and slopes of the best fit lines in the two-stage fecundity model for mid and late life in the three replicated ACO populations (early reproducing)

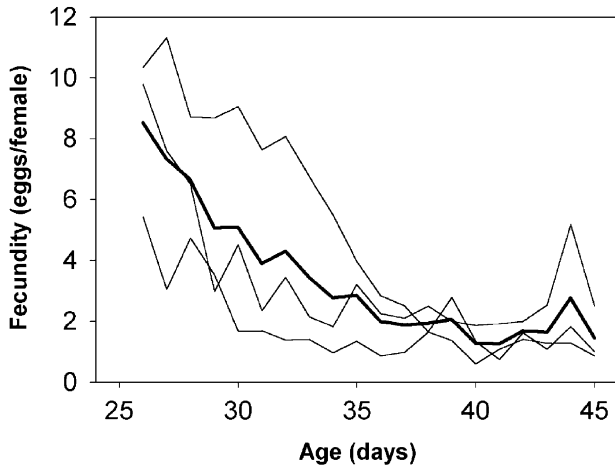| Population	Break day (age in days)	Slope prior to 'break day'	Plateau slope	Plateau slope 95% CI	Plateau height (eggs/day)
ACO 1	29	-2.6398	0.0337	-0.0682, 0.1357	2.8746
ACO 2	37	-1.3256	-0.1447	-0.3260, 0.0366	1.6229
ACO 3	30	-0.4030	-0.0122	-0.0424, 0.0180	1.2671
Mean		-1.4561	-0.0410		1.9215

Fig. 5. Mid- and late-life fecundity data for three replicated ACO (early reproducing) populations. The thick black line represents the average fecundity for all three populations.

3.2. Fitting functions to fecundity data

It is conceivable that the data for a particular line might be better fit to a declining exponential function, among other mathematical possibilities. However, there is no a priori reason for fitting any particular function to the fecundity data during mid-life. On the other hand, there is an a priori reason for testing a flat function to the fecundity data during late-life: the plateau in the force of natural selection.

4. Discussion

4.1. Possible artifacts

Late-life plateaus in age-specific fecundity apparently exist. The force of natural selection acting on age-specific fecundity supplies one ready explanation of these plateaus, but other explanations are conceivable.

Fecundity plateaus might be secondary consequences of mortality-rate plateaus. One mechanistic possibility is that a stabilization of the late-life soma is associated with the mortality-rate plateaus, and this stabilization in turn arrests further decline in fecundity. If the fecundity plateau is just a physiological side-effect of the mortality-rate plateau, the fecundity plateau should start either at the same time as the mortality-rate plateau, or shortly thereafter. We suspect that this is not the case here because our unpublished estimates of the onset of the mortality-rate plateau in ACO females is 42.8 days, later than the starting age of all three fecundity plateaus in the present data. On the other hand, these data were collected in a different experiment, raising the possibility that the present data came from cohorts that have earlier mortality-rate plateaus.

Female fecundity plateaus may arise from diminished male sexual function due to male aging. If diminished male sexual function reduces female reproduction, perhaps due to a lack of sperm, this could produce both a decline in female fecundity before the plateau and the plateau itself.

In the fecundity experiment described above, male and female cohorts were kept together throughout life. This resulted in a supply of older mates for older females, with no available young males for the older females to mate with, raising the prospect that older mates may have limited female fecundity. In practice, we are not concerned about this problem. We have already collected preliminary data (unshown) in order to ascertain whether the female response to young mates will be so great that the features of late-life fecundity would be delayed to very late ages. These preliminary data show that provision of young males later in the life of a female does cause an upward spike in her fecundity, on average, but fecundity quickly settles down after this initial response, subsequently exhibiting a late-life plateau.

Another plausible alternative explanation to the force of natural selection is the hypothesis that a lack of nutrition might limit fecundity to some stable, low, level. Fecundity is well known to be highly responsive to nutrition in *Drosophila* (Chippindale et al., 1993). Nutritional shortfalls may arise later in life because of a decline in female feeding or digestion. However, data from the experiment of Chippindale et al. (1993) shows that fecundity levels fall to roughly stable, low levels in mid-life, around 40–50 days of age from egg, even with high nutrition. These earlier data are not adequate to define the late-life properties of fecundity with varying nutrition, but they do show that high and low nutrition groups end up with roughly similar fecundity levels at ages where we now observe the start of fecundity plateaus.

4.2. Heterogeneity models for fecundity plateaus

One of the problems with robustness theories in demography is that they depend on cryptic variables. Therefore, the life-long heterogeneity in robustness that could, in theory, generate mortality-rate plateaus late in life is extremely difficult to measure explicitly for the reasons discussed above (see also Rose and Mueller, 2000; Drapeau et al., 2000).

Fecundity, on the other hand, might exhibit heterogeneity sufficient to generate late-life fecundity plateaus. In addition, heterogeneity in fecundity, unlike heterogeneity in mortality, can be easily measured. Imagine a population that shows life-long heterogeneity in egg laying, parallel to the hypothetical life-long heterogeneity of robustness (Fig. 1). Some individuals lay many eggs quickly. Other individuals lay eggs at a low rate. Suppose further that individuals that lay quickly tend to 'burn out,' dying at earlier ages. Under these conditions, average mid-life fecundity should be high, but fall rapidly. In late life, only those individuals who have always laid at a slow rate would survive (see Fig. 6 for a cartoon). This scenario is similar to

Fig. 6. Outcome of heterogeneity experiment if life-long heterogeneity in egg-laying determines plateau patterns. Each line represents an individual female. Those females who have high fecundities in mid-life die before the fecundity plateau (*), while those that have low, relatively stable, mid-life fecundities continue to survive and 'produce' the fecundity plateau.

the heterogeneity theory of late-life mortality, with one additional hypothesis—the dying off of the fast egg-layers. There is considerable experimental evidence for the early death of rapid egg-layers in *Drosophila* (Maynard Smith, 1958; Rose and Charlesworth, 1980; Luckinbill et al., 1984; Rose, 1984).

The superiority of this fecundity heterogeneity theory comes from the fact that the variable which plays the causal role is not a cryptic robustness, but the observable variable of fecundity. If heterogeneity is the cause of the late-life fecundity plateau, then the females that survive and lay eggs during the plateau should be a distinct sub-group in mid-life, with measurably lower fecundities. Note that this heterogeneity in fecundity hypothesis closely parallels the conventional demographic heterogeneity models for mortality.

We predict that the total mid-life egg-laying of the group that survives to reach the fecundity plateau should be lower than those that do not survive to reach the plateau, if heterogeneity is itself the cause of the fecundity plateau. A particularly clear result in favor of heterogeneity theory would be if the fecundity trajectories of surviving plateau females were flat during mid-life, indicating that they were always 'on' the plateau. In effect, the plateau should be a product of the continued survival of females that always laid very few eggs, with the high mid-life fecundity pattern produced by females that do not survive to late life.

4.3. Using fecundity to understand late life

Age-specific fecundity apparently plateaus late in life, like age-specific mortality. This result conforms to evolutionary theory, though there are a number of other possible explanations, including life-long heterogeneity.

Mortality is a biological attribute ascertainable only at the time of death, a singular event in the life of an organism. Thus evolutionary, genetic, and demographic studies of mortality have to use the mortality trajectories of entire cohorts, considered as single entities (Curtsinger et al., 1992; Hughes and Charlesworth, 1994; Drapeau et al., 2000). This stringently limits the kinds of experiments that can be performed. The advantage of the fecundity plateau for research on late life is that the underlying physiology of fecundity is made manifest throughout adult life by the observable fecundity of adult females at each age. This allows, among other things, reasonably direct tests of theories that assume life-long robustness, as described above.

Acknowledgements

References

Abrams, P.A., Ludwig, D., 1995. Optimality theory Gompertz's Law, and the disposable-soma theory of senescence. Evolution 49, 1055–1066.

Brooks, A., Lithgow, G.J., Johnson, T.E., 1994. Genetic control of life span: age-specific mortality rate of a heterogeneous population of *Caenorhabditis elegans*. Science 263, 668.

Carey, J.R., Liedo, P., Orozco, D., Vaupel, J.W., 1992. Slowing of mortality rates at older ages in large med-fly cohorts. Science 258, 457–461.

Charlesworth, B., 2001. Patterns of age-specific means and genetic variances of mortality rates predicted by the mutation-accumulation theory of ageing. J. Theor. Biol. 210, 47–65.

Charlesworth, B., Partridge, L., 1997. Ageing: leveling of the grim reaper. Curr. Biol. 7, R440–R442.

Chippindale, A.K., Leroi, A.M., Kim, S.B., Rose, M.R., 1993. Phenotypic plasticity and selection in *Drosophila* life-history evolution. 1. Nutrition and the cost of reproduction. J. Evol. Biol. 6, 171–193.

Chippindale, A.K., Alipax, J.A., Chen, H.W., Rose, M.R., 1997. Experimental evolution of accelerated development in *Drosophila*. 1. Larval development speed and survival. Evolution 51, 1536–1551.

Curtsinger, J.W., Fukui, H.H., Townsend, D.R., Vaupel, J.W., 1992. Demography of genotypes: failure of the limited life span paradigm in *Drosophila melanogaster*. Science 25, 461–463.

Drapeau, M.D., Gass, E.K., Simison, M.D., Mueller, L.D., Rose, M.R., 2000. Testing the heterogeneity theory of late-life mortality plateaus by using cohorts of *Drosophila melanogaster*. Exp. Gerontol. 35, 71–84.

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

Fukui, H.H., Ackart, L., Curtsinger, J.W., 1996. Deceleration of age-specific mortality rates in chromosomal homozygotes and heterozygotes of *Drosophila melanogaster*. Exp. Gerontol. 31, 517–531.

Graves, J.L., Mueller, L.D., 1993. Population density effects on longevity. Genetica 91, 99–109.

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

Hughes, K.A., Charlesworth, B., 1994. A genetic-analysis of senescence in *Drosophila*. Nature 367, 64–66.

Khazaeli, A.A., Pletcher, S.D., Curtsinger, J.W., 1998. The fractionation experiment: reducing heterogeneity to investigate age-specific mortality in *Drosophila*. Mech. Ageing Dev. 105, 301–317.

Kowald, A., Kirkwood, T.B.L., 1993. Explaining fruit fly longevity. Science 260, 1664–1665.

Luckinbill, L.S., Arking, R., Clare, M.J., Cirocco, W.C., Buck, S.A., 1984. Selecction of delayed senescence in *Drosophila melanogaster*. Evolution 38, 996–1003.

Maynard Smith, J., 1958. The effects of temperature and of egg-laying on the longevity of *Drosophila subobscura*. J. Exp. Biol. 35, 832–842.

Mueller, L.D., Rose, M.R., 1996. Evolutionary theory predicts late-life mortality plateaus. Proc. Natl Acad. Sci. 93, 15249–15253.

Pletcher, S.D., Curtsinger, J.W., 1998. Mortality plateaus and the evolution of senescence: why are old-age mortality rates so slow? Evolution 52, 454–464.

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

Rose, M.R., 1991. Evolutionary Biology of Aging, Oxford University Press, Oxford.

Rose, M.R., Charlesworth, B., 1980. A test of evolutionary theories of senescence. Nature 287, 141–142.

Rose, M.R., Mueller, L.D., 2000. Ageing and immortality. Phil. Trans. R. Soc. Lond., Ser. B355, 1657–1662.

Vaupel, J.W., 1988. Inherited frailty and longevity. Demography 25, 277–287.

Vaupel, J.W., 1990. Relatives' risks: frailty models of life history data. Theor. Pop. Biol. 37, 220–234.

Vaupel, J.W., Manton, K.G., Stallard, E., 1979. The impact of heterogeneity in individual frailty on the dynamics of mortality. Demography 16, 439–454.

Vaupel, J.W., Johnson, T.E., Lithgow, G.J., 1994. Rates of mortality in populations of *Caenorhabditis elegans* (technical comment). Science 266, 826.

Vaupel, J.W., Carey, J.R., Christensen, K., Johnson, T.E., Yashin, A.I., Holm, N.V., Iachine, I.A., Kannisto, V., Khazaeli, A.A., Liedo, P., Longo, V.D., Zeng, Y., Manton, K.G., Curtsinger, J.W., 1998. Biodemographic trajectories of longevity. Science 280, 855–860.