REVIEW ARTICLE

Evolution of ageing since Darwin

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Abstract

In the late 19th century, the evolutionary approach to the problem of ageing was initiated by August Weismann, who argued that natural selection was more important for ageing than any physiological mechanism. In the mid-twentieth century, J. B. S. Haldane, P. B. Medawar and G. C. Williams informally argued that the force of natural selection falls with adult age. In 1966, W. D. Hamilton published formal equations that showed mathematically that two 'forces of natural selection' do indeed decline with age, though his analysis was not genetically explicit. Brian Charlesworth then developed the required mathematical population genetics for the evolution of ageing in the 1970's. In the 1980's, experiments using *Drosophila* showed that the rate of ageing evolves as predicted by Hamilton's 'forces of natural selection'. The discovery of the cessation of ageing late in life in the 1990's was followed by its explanation in terms of evolutionary theory based on Hamilton's forces. Recently, it has been shown that the cessation of ageing can also be manipulated experimentally using Hamilton's 'forces of natural selection'. Despite the success of evolutionary research on ageing, mainstream gerontological research has largely ignored both this work and the opportunity that it provides for effective intervention in ageing.

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Introduction

Evolutionary biology provides the only cogent, formally developed, and experimentally corroborated theory for biological ageing. There are a variety of hypotheses about the mechanistic physiology of ageing, hypotheses that are characteristically ill-defined, taxonomically specific, or experimentally unsupported. Arking (2006) supplies a review of this corpus of scientific work. This is not to say that molecular or cell biologists have not documented the features of ageing at the physiological level. Their problem is its ultimate explanation. In this respect, they are remarkably confused at the present time (e.g. Shostak 2006), and they have been so for some time (e.g., Bidder 1932; Comfort 1956, 1964, 1979). Fortunately, their difficulties are not our present concern.

In this essay, we supply a brisk run through the highlights of evolutionary research on the biology of ageing. One of us have already provided an entire book on this topic (Rose 1991), and we are now working on an update in light of the research of the last 17 years. Thus, we do not suppose that we have adequately documented the years of painstaking and ingenious research contributed by evolutionary biologists working on ageing. Instead, we have deliberately focussed on important achievements and key scientific figures in what we regard as one of the great successes of evolutionary biology since the life of Charles Darwin. To guide the reader through this abbreviated history, we head each section with the range of dates of key publications and before 1980, the key person(s) whose research advanced our understanding of the evolution of ageing.

1881–1892: Weismann proposes that ageing is a product of evolution

In the latter part of the 19th century, German-language biologists were leading proponents of Darwin's theory of evolution by natural selection. Ernst Haeckel is the most famous of Darwin's German followers, but in many respects August Weismann (1834–1914) was a more important evolutionary theorist. In particular, the term 'neo-Darwinism' was originally used to refer to Weismann's version of Darwinism, a

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version in which Darwin's intermittent reliance on the inheritance of acquired characters to supply new hereditary variants is explicitly foresworn. Weismann has long been famous within biological circles for cutting off the tails of mice generation after generation, with no effect on the growth of tails among any of the descendants of these mice, an elegant refutation of the inheritance of acquired characters.

In his lecture titled 'The duration of life' delivered in 1881, August Weismann was the first to publicly analyse causes of senescence in terms of evolution by natural selection. He rejected the historical assumption that an organism's longevity was somehow determined by its physiological 'construction', and proposed instead that longevity was programmed by "the needs of the species" (Weismann 1891, pp. 9). Weismann's pioneering ideas about the evolution of ageing, in this lecture and other essays, were published together in German (Weismann 1892a) and in English translation (Weismann 1889, 1891, 1892b). In these collected works, Weismann articulates several original theories regarding the ultimate causes of ageing and of death. These theories have been historically criticized as illogical and inconsistent with a thorough understanding of natural selection. However, they contain elements that have played a role in modern interpretations of the evolutionary biology of ageing.

The necessity of death is a major theme in '*The duration of life*'. Weismann best illustrated his idea of the futility of immortality by supposing that an individual of a species could be immortal (Weismann 1891, pp. 23–24). He explains that if such an individual was not killed by accident, it would nevertheless experience injuries over time. The inability to heal such injuries perfectly would result in older organisms being less fit than younger ones. Older individuals would be taking up resources better saved for the young of the species, thus creating a selective advantage for death at old ages. His assumption that organisms cannot heal perfectly forever creates a circular argument that Medawar (1952) later criticized. While Weismann proposed limits to somatic cell replication as a mechanism for this inability to heal, he never provided a functional explanation for why this might be true.

The second edition of the English translation of '*The duration of life*' was published with a footnote from the editor that includes some of A. R. Wallace's notes written between 1865–1870. Evidently, prior to Weismann's lecture, Wallace had independently formulated the idea that 'when one or more individuals have provided a sufficient number of successors they themselves, as consumers of nourishment in a constantly increasing degree, are an injury to those successors...natural selection therefore weeds them out'.

In his essays '*Life and death*', and '*On heredity*', Weismann suggested that once a selective advantage for death has been established, there would be no barrier to selection for any advantageous characteristics that might trade-off against immortality. Possibly, the forgoing of immortality might have made more resources available to reproductive cells. At that point, he considered the loss of immortality as an example of a process he called "panmixia". The central tenet of Weismann's panmixia theory is that characters useless to an organism escape the action of natural selection and therefore eventually disappear. Thus, immortality was 'lost' in the same way that 'a species which has retired into dark caverns must necessarily come to gradually possess less developed powers of vision' (Weismann 1891, pp. 299; see Kirkwood and Cremer (1982) for their detailed description of this 'non-selective' argument).

Weismann himself may have abandoned his 'adaptive' views of ageing by the end of his life (Kirkwood and Cremer 1982). In any case, his panmixia theory was a startling anticipation of modern thinking about the evolution of ageing, and deserves particular mention in this review. We will conclude this section with the following quotation, which eerily foreshadows classic experiments on the evolution of ageing that would take place nearly 100 years later:

"In answering the question as to the means by which the lengthening or shortening of life is brought about, our first appeal must be to the process of natural selection. Duration of life, like every other characteristic of an organism, is subject to individual fluctuations. From our experience with the human species we know that long life is hereditary. As soon as the long-lived individuals in a species obtain some advantage in the struggle for existence, they will gradually become dominant, and those with the shortest lives will be exterminated" (Weismann 1891, pp. 20).

1941: Haldane's intuition of the declining force of natural selection

The modern solution to the mystery of ageing first popped into the mind of John Burdon Sanderson (JBS) Haldane (1892–1964), one of the great figures of British science between World Wars I and II, a long-serving editor of this journal, and later a major figure in the development of biology in the newly-independent India. As a scientist, Haldane is best known for his work on the problem of predicting the genetic progress of selection using mathematical models, an approach that he would help make fundamental to biological theory, along with R. A. Fisher and Sewall Wright. Using this type of theory, he would tackle many of the basic problems of evolution, as summarized in his 1932 book '*The causes of evolution*'.

Haldane published the key insight into the evolution of ageing in one of his popular science works, '*New paths in genetics*', from 1941. The critical clue to the cause of ageing for Haldane was the human genetic disease then known as Huntington's Chorea, now called Huntington's disease. This disorder is caused by a single gene: having only one copy of the Huntington's disease allele is enough to give rise to the disease in all who live long enough (we now know that the locus involved is *lamin A*).

The medical symptoms of Huntington's are first subtle, a small loss of coordination, a weaving walk. But neurological

difficulties progress. Walking and other basic tasks become difficult, as movement is very hard to control for the Huntington's patient. Mental faculties are impaired. The personality deteriorates, and sufferers may become highly aggressive. Finally, the nervous system is unable to coordinate the most basic bodily functions, from continence to heart-beat, and death results. The whole progression may take more than a decade, but all victims die of the condition, if they do not kill themselves first.

Haldane was struck by the age at which victims of Huntington's first show symptoms, usually their thirties, or later. He argued that a disease this devastating could only occur because, in our ancestral conditions before agriculture and civilization, such a disease would have had no selective effect. Natural selection would have little 'force' at late ages, under natural conditions. Few people would have survived into their forties anyway, before the advent of civilization, and their late-life medical genetic problems simply would not have mattered to evolution by natural selection.

1946–1957: Medawar and Williams develop Haldane's idea

Since Haldane, being involved in military research, did not have time to pursue this idea of the force of natural selection in the 1940's, it was taken up by a younger British scientist, Peter Medawar (1915–1987). An outstanding writer of popular science, like Haldane, Medawar later received the Nobel Prize for his work on immunology, and head up the British National Institute for Medical Research. Medawar was the person who first published many of the key ideas that underlie the evolutionary analysis of ageing, publishing first an essay entitled '*Old age and natural death*' in 1946.

The sad thing about Medawar taking up this task was that he just did not have the mathematical skills required to do the job well. In his 1952 essay, '*An unsolved problem of biology*', Medawar would lay out the basic evolutionary problem of ageing and provide a verbal sketch of a solution. But his analysis was basically misleading, relying on a simile to the loss of test tubes in a laboratory. Even though Medawar reiterated Haldane's verbal formulation of a falling force of natural selection as the explanation of ageing, he signally failed to make the idea coherent or quantitatively useful.

Medawar is widely credited with the idea of "mutation accumulation," in which evolution allows alleles with deleterious effects only at later ages to accumulate by a combination of mutation pressure and genetic drift, unopposed by natural selection. However, he neither posed this hypothesis with particular clarity, nor did he argue for it as preeminent over the idea of genetic trade-offs, contrary to some erroneous discussions in the evolutionary literature.

A deprived child of the American Great Depression, George C. Williams (1926) was saved first by military service during World War II and then a GI Bill education. Emerging finally with a Ph.D. in the 1950's, he proceeded to tackle the deep problems of evolutionary biology. In 1957, he published a paper on the evolution of ageing that was more detailed and satisfying than anything that had come before it. Focussing specifically on the idea of trade-offs between fitness and later survival, he argued that natural selection would actively favour genes that had ageing as a side-effect, providing they had a beneficial effect during youth. Rose (1982) would later name this idea "antagonistic pleiotropy," the commonly used term for this mechanism in present-day scientific discourse.

Williams applied this idea of antagonistic pleiotropy to the evolution of ageing with great vigour and clarity. Though his reasoning was much like Medawar's, it should be noted, for the purpose of historical accuracy, that Williams developed his analysis before he ever read the prior publications of Haldane and Medawar; he only learned about them after submission to the journal *Evolution* of the manuscript that would later be published by him in 1957 (G. C. Williams, personal communication).

1966: Hamilton works out formulas for the 'forces of natural selection'

The late William Hamilton (1936–2000) is widely regarded as one of the geniuses of 20th century evolutionary biology. He redefined our understanding of the evolution of the social life of animal families, including the unusual colonies of bees, ants, wasps, and termites, with their queens and kings. But it could be argued that Hamilton's work on ageing was even better. Up until his 1966 paper on the evolution of ageing, the subject had remained a mish-mash of verbally formulated ideas, none of which had progressed very far from Haldane's original intuition, 25 years earlier. Hamilton formally defined the force of natural selection, showing exactly how and when it could be expected to lead to the evolution of ageing. While his mathematical analysis was not quite complete, Hamilton was the person who broke the scientific problem of ageing wide-open. Since 1966, working on the problem has been relatively easy, at least for evolutionary biologists.

Hamilton's greatest achievement was to show just what is going on as the force of natural selection falls with adult age. He derived the first partial derivative for the proportional effect on the Malthusian parameter of age-specific changes in survival probability, where he took the Malthusian parameter as the best measure of fitness for a population with overlapping generations. This effect is given by $s(x)/T$, where T is a measure of generation length and

$$s(x) = \sum_{y=x+1} e^{-ry} l(y) m(y). \qquad (1)$$

In this equation (1), r is the Malthusian parameter, or the growth rate of the population, associated with the specified $l(y)$ survivorship and $m(y)$ fecundity functions. The dummy variable y is used to sum up the net expected reproduction over all ages after age x. To give an intuitive rendering of

the mathematics, the $s(x)$ function represents the fitness impact of an individual's future reproduction. Note that, before the first age of reproduction, s is always equal to one; once reproduction has ended, s is equal to zero; and during the reproductive period, $s(x)$ progressively falls.

Like mortality, the age-specific force of natural selection acting on fecundity has a scaling function:

$$s'(x) = e^{-rx} l(x). \quad (2)$$

When plotted against age, these functions have the general form shown in figure 1.

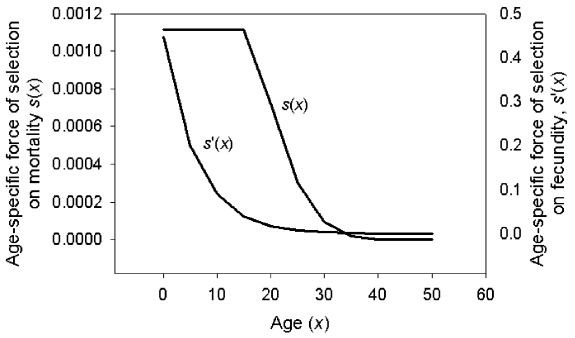

Figure 1. The strength of natural selection on age-specific mortality ($s(x)$) and fecundity ($s'(x)$). Life-tables from the U.S. population between 2000 and 2004 were used to construct these figures, based on five year age-classes.

1970–1980: Charlesworth develops the theoretical population genetics of ageing

As crucial as Hamilton's derivation of explicit formulas for the forces of natural selection was, it still did not supply a completely worked-out theory. Minding the p's and q's of the theoretical population genetics of the evolution of ageing would be Brian Charlesworth's (1945) first major scientific contribution in a career that has had many highlights. His published work in this area began with a seminal paper on the use of the Malthusian parameter as a measure of fitness, a key assumption of Hamilton's (Charlesworth 1970). A series of papers in the 1970's culminated with a landmark 1980 book, *Evolution in age-structured populations*.

Over the course of the decade from 1970 to 1980, Charlesworth developed a mathematical analysis of sufficient power to render previous verbal suggestions and speculations mathematically explicit. Charlesworth showed that both mutation accumulation and antagonistic pleiotropy could lead to the evolution of ageing, thanks to the falling force of natural selection. Of particular note, in view of later confusion on this topic (e.g. Baudisch 2005, 2008), explicit population-genetic applications of Charlesworth's mathematical machinery to the evolution of ageing naturally recovers the terms of Hamilton's forces of natural selection in the equations that determine the evolution of alleles subject to either mutation accumulation (Charlesworth and Williamson 1975; Charlesworth 1980) or antagonistic pleiotropy (Rose 1985).

1980–1984: First deliberate laboratory evolution of slower ageing

Working as Brian Charlesworth's graduate student at the University of Sussex in the 1970's, Michael R. Rose (1955) realized that delaying the first age of reproduction could lead to the evolution of postponed or slowed ageing, if enough generations of such delayed reproduction were sustained (Rose 2005). By the end of 1977, a small *Drosophila* experiment of this kind was initiated by Rose without informing Charlesworth, and the expected result was obtained in 1979, first publication of this result came in 1980 (Rose and Charlesworth 1980).

This experiment was repeated with better replication by both Rose and Luckinbill during the early 1980's, culminating in simultaneous publications in the journal *Evolution* in 1984. There have been many corroborations of this result since, both in other *Drosophila* populations (e.g., Partridge and Fowler 1992; Deckert-Cruz *et al*. 2004) and in other animal species, even mice (e.g. Nagai *et al*. 1995). An example of results of this kind is given in figure 2. In any case, by 1984 the theoretical development of the evolutionary theory of ageing and its experimental corroboration were well in hand. Additional work is ongoing on the two key population genetic mechanisms for the evolution of ageing, antagonistic pleiotropy and mutation accumulation, a recent review of this work being that of Rose *et al*. (2007). Both mechanisms appear to be involved, as these two mechanistic hypotheses are not mutually exclusive, although the evidence in favour of antagonistic pleiotropy as a genetic mechanism for the evolution of ageing has generally been clearer than that for mutation accumulation.

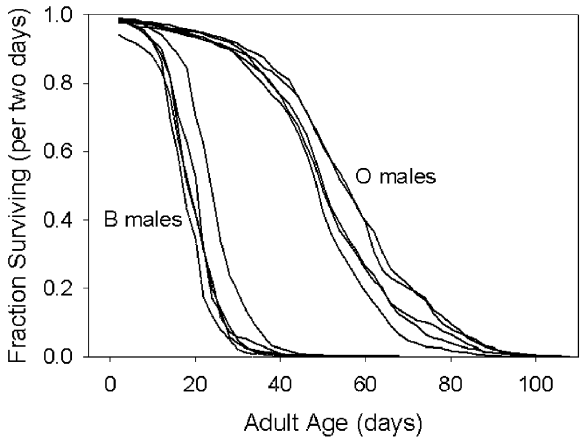

Figure 2. The fraction of surviving adults as a function of age in males from two *Drosophila* populations (replotted from Rose *et al*. (2002)). The five independent replicates of the B (early reproducing) and O (late reproducing) populations are shown.

Of greater interest to scientists outside of evolutionary biology, *Drosophila* populations that have been made to evolve slowed ageing in the laboratory have in turn been a fruitful system for mechanistic work on the genetic and physiological mechanisms for the evolution of ageing. The work on this topic by the Rose laboratory is compiled in Rose *et al.* (2004), along with comments on similar research by others.

1992–2001: Discovery of late life and its subsequent evolutionary explanation

Until the early 1990s, both mainstream gerontologists and evolutionary biologists agreed that, even under ideal conditions, ageing should continue accelerating until all members of a cohort die off (Comfort 1979; Rose 1991). European human mortality data that showed a deceleration of mortality rates at advanced ages (Greenwood and Irwin 1939; Gavrilov and Gavrilova 1991) was usually dismissed as the consequence of better health care for the elderly or historically variable causes of death, such as war and pandemics.

In 1992, two studies using dipteran species yielded a surprising and significant finding: mortality rates in medflies (*Ceratitis*) and fruit flies (*Drosophila*) plateaued at late ages (Carey *et al.* 1992; Curtsinger *et al.* 1992), suggesting that demographic ageing slowed or stopped at these very late ages. An example of experimental results of this kind is shown in figure 3. The existence of true plateaus in mortality rates was widely questioned at first, one line of criticism being that densities were not kept constant in some of these experiments (Graves and Mueller 1993; Nusbaum *et al.* 1993). But, although density may have been a factor in the original observations (Carey *et al.* 1992; Curtsinger *et al.* 1992; Brooks *et al.* 1994), changes in density were explicitly ruled out as the sole explanation for decelerating mortality in both *Ceratitis* (Carey *et al.* 1995) and *Drosophila* (Khazaeli *et al.* 1996).

Since 1992, mortality rate deceleration and mortality rate plateaus have been found in a variety of organisms, including yeasts, nematodes, wasps and humans, suggesting that late-age mortality deceleration occurs generally among ageing organisms (Carey 2003; Fukui *et al.* 1993; Tatar *et al.* 1993; Brooks *et al.* 1994; Kannisto *et al.* 1994; reviewed in Charlesworth and Partridge 1997; Vaupel *et al.* 1998). The period in which mortality rates stop increasing exponentially is now sometimes called 'late life'.

The evolutionary explanation of late life is based on a more refined understanding of how Hamilton's forces of natural selection impact evolution after the last age at which organisms have remained alive in the evolutionary history of a population. This analysis shows that the period of exponentially increasing mortality rates is expected to come to an end, under the following conditions. Hamilton's forces of natural selection plateau on zero for all ages after both survival and reproduction ceased in the evolutionary history of a population. Thus, natural selection does not discriminate among genetic effects that act at very late ages because these genetic effects have had no impact on fitness during the evolutionary history of a population. Even in organisms that reproduce at all ages, the force of natural selection is eventually overwhelmed by drift in late life, a result that was obtained in explicit numerical simulations by Mueller and Rose (1996). An example of the kind of results that Mueller and Rose obtained is shown in figure 4. Other analytical solutions of this kind have been supplied by Charlesworth (2001).

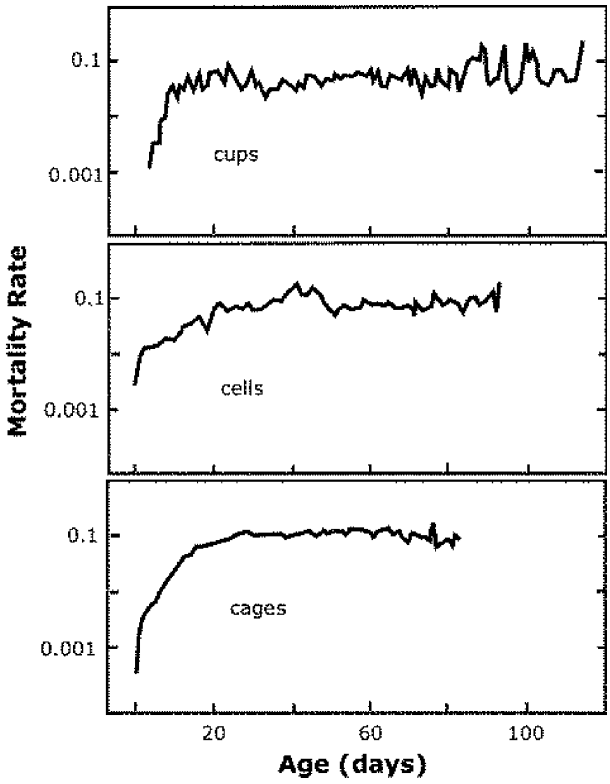

Figure 3. The log of mortality rate as a function of age in the Mediterranean fruit fly, *Ceratitis capitata* (replotted, after Carey *et al.* (1992)).

Since there is no selection for postreproductive longevity in organisms that do not contribute to the fitness of their offspring or relatives (Hamilton 1966; Rose 1991), mortality levels might be expected to reach 100% when natural selection plateaus on zero. In some species, late-life plateaus can indeed be at the 100% mortality level (see Pletcher and Curtsinger 1998). However, with enough alleles that have age-independent beneficial effects, it is also possible to have positive-valued average survival and fecundity values during late life (see Charlesworth 2001). In such cases, any age-independent genetic benefits will be favoured by natural selection acting at early ages, giving positive pleiotropic benefits for survival and reproduction at all later ages. This type of genetic mechanism has been called 'protagonistic pleiotropy' (de Grey 2007).

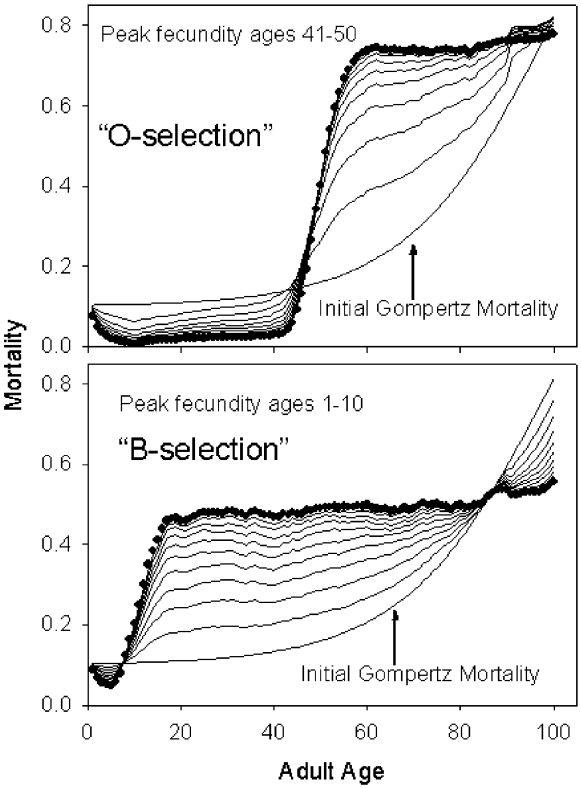

Figure 4. Simulated mortality rate evolution with antagonistic pleiotropic mutations. The starting populations each initially had a Gompertz pattern of mortality, but different ages of peak fecundity. The methods used were similar to those of Mueller and Rose (1996).

2002–2006: First deliberate laboratory evolution of late life

Using models of pleiotropy and mutation accumulation under conditions with a falling force of natural selection, Rose *et al*. (2002) predicted that late-life mortality plateaus should evolve according to the last age of reproduction in the evolutionary history of *D. melanogaster* populations, if that timing of culture reproduction is sustained for enough generations. This prediction was tested in three independent experiments using 30 large cohorts of *D. melanogaster* that featured either a 55-day (B and O) or an 18-day (ACO and CO) contrast in last ages of reproduction (Rose *et al*. 2002). An example of the results obtained is shown in figure 5. In these studies, statistically significant differences were present as a function of the day at which late life started in short-lived population versus long-lived populations. This difference is qualitatively in accord with the predictions of evolutionary theories of late life.

The kind of predictions derived by Rose *et al*. (2002) for the evolution of late-life mortality rate plateaus can similarly be developed for late-life fecundity (Rauser *et al*. 2006a). In

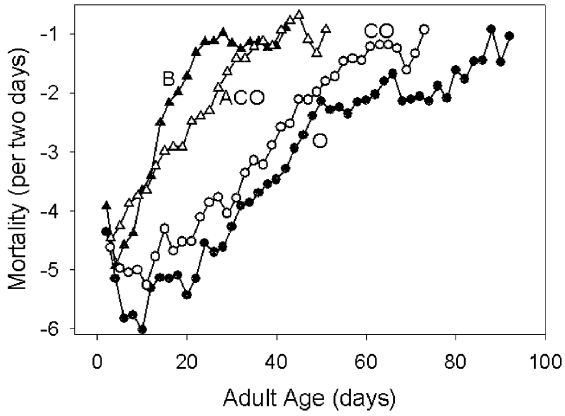

Figure 5. The mean age-specific natural log of mortality rates for males from the B, O, ACO, and CO populations.

particular, evolutionary theory suggests that fecundity should plateau sometime after the last age of survival in a population's evolutionary history. In several independent experiments, Rauser *et al*. (2003, 2006b) and Mueller *et al*. (2007) found late-life fecundity plateaus in populations of *D. melanogaster*. More notably, they found statistically significant differences in the days at which late-life fecundity plateaued in populations with different last ages of reproduction in their recent evolutionary history (figure 6; Rauser *et al*. 2006b). These results showed that late-life fecundity plateaus evolve according to the evolutionary theory for late life based on the force of natural selection.

Late life appears to be an evolutionarily distinct phase of life-history, evolving according to strictures very different from those that mould both early life and ageing. Thus, what has been called ageing research now needs to include late life, as well (Rose *et al*. 2005). The difficulty that this poses is that late life is observable only when experimental cohorts are very large and maintained for sufficiently long periods. Nonetheless, like the difficulty of studying physics under conditions for which the predictions of relativistic mechanics differ from those of classical mechanics, evolutionary research has shown that the fundamental scientific questions concerning the foundations of biological ageing are quite different from those that were at first supposed, even by evolutionary biologists. What we have elsewhere called 'Hamiltonian' research has thus led us into entirely revolutionary territory, in terms of our basic conception of what ageing is, and whether or not it stops on its own, among other issues (Rose *et al*. 2006).

Conclusion

We started by explicitly excluding nonevolutionary research on ageing from our purview. In concluding, however, we

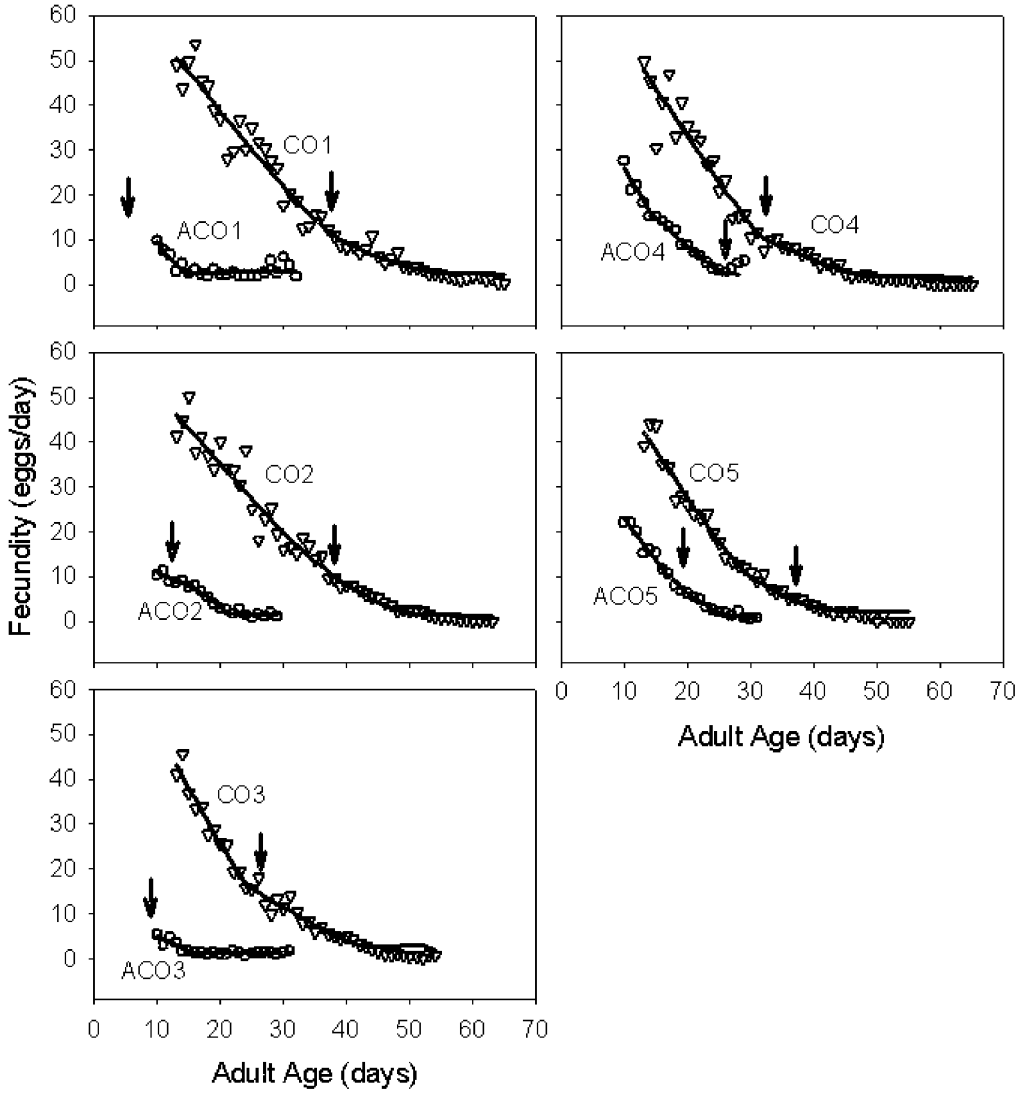

Figure 6. Age-specific fecundity for two populations of *D. melanogaster* subject to different demographic selection regimes. Mean fecundity for the early reproducing ACO (circles) and late reproducing CO (triangles) females are shown along with a fitted regression (solid line) based on the evolutionary heterogeneity model of female fecundity (Mueller *et al*. 2007). The estimated ages at which the fecundity plateaus begin are shown with arrows.

cannot resist the temptation to point out the contrast between the relative scientific standing of evolutionary biology and that of the rest of biology, where the explanation of ageing is concerned. The overwhelming preponderance of research on the biology of ageing has been performed without any detectable foundation in modern evolutionary biology. Leaving aside the intermittently bizarre assertions about evolution contained in publications concerning such research (e.g. Shostak 2006), this is an extensive research enterprise being conducted in apparently untroubled ignorance of the evolutionary machinery that is ultimately responsible for not only the existence of ageing, but also its rate, effects, and potential cessation.

Responsibility for this distressing state of affairs is difficult to allocate. Most biologists never acquire the mathematical training required to understand evolutionary theory. And as there are so few practicing evolutionary biologists in the world today, relative to the great mass of Ph.D.'s in biology as a whole, our attempts to enlighten our nonDarwinian colleagues are necessarily diluted in the vast oceans of 21st century biological publication. Yet, we also wonder if the prevailing culture of disinterest in profound scientific theory among the reductionist establishment of biomedical research does not also play a role?

Nevertheless, the evolutionary study of ageing has produced major scientific advances. These include: (i) a general and predictive theory of ageing, (ii) the first substantial and reproducible experimental postponement of ageing, and (iii) a theory of late life that has survived numerous experimental tests.

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