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HAMILTON'S FORCES OF NATURAL SELECTION AFTER FORTY YEARS

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In 1966, William D. Hamilton published a landmark paper in evolutionary biology: "The Moulding of Senescence by Natural Selection." It is now apparent that this article is as important as his better-known 1964 articles on kin selection. Not only did the 1966 article explain aging, it also supplied the basic scaling forces for natural selection over the entire life history. Like the Lorentz transformations of relativistic physics, Hamilton's Forces of Natural Selection provide an overarching framework for understanding the power of natural selection at early ages, the existence of aging, the timing of aging, the cessation of aging, and the timing of the cessation of aging. His twin Forces show that natural selection shapes survival and fecundity in different ways, so their evolution can be somewhat distinct. Hamilton's Forces also define the context in which genetic variation is shaped. The Forces of Natural Selection are readily manipulable using experimental evolution, allowing the deceleration or acceleration of aging, and the shifting of the transition ages between development, aging, and late life. For these reasons, evolutionary research on the demographic features of life history should be referred to as "Hamiltonian."

KEY WORDS: Aging, demography, experimental evolution, forces of natural selection, late life, senescence, William D. Hamilton.

In 1966, William D. Hamilton published "The Moulding of Senescence by Natural Selection" in *Journal of Theoretical Biology.* At the time, the paper was hardly noticed. Forty years later, as of this writing, it is clear that this paper was another milestone in Hamilton's miraculous decade of the 1960s. His best-known articles from this period are his two 1964 articles on kin selection (Hamilton 1964a,b) and his 1967 article on evolutionary strategies of sex-ratio manipulation. In those three articles, he laid foundations for contemporary research in behavioral ecology and cognate fields, including research on inclusive fitness and frequency-dependent strategies. These three publications are among the most heavily cited in the evolutionary literature, broadly construed. Here we will argue that Hamilton's 1966 article is at least as important as those three articles.

Hamilton was an avid disciple of R.A. Fisher (see the marginalia of Hamilton's 1996 volume), whose 1930 book *The Genetical Theory of Natural Selection* contained elliptical remarks on the parallels between age-specific reproductive value and age-specific survival probabilities, particularly the parallel between the decline of reproductive value and the decline of age-specific survival probability with increasing age. Haldane (1941), Medawar (1946, 1952), and Williams (1957) took up the same theme, although, like Fisher, none supplied a useful formal analysis. It was Medawar, especially in his 1952 publication, who popularized the term "force of natural selection." But there was no quantitatively explicit and cogent analysis of this evolutionary concept before Hamilton's 1966 analysis.

Like his other 1960s publications, Hamilton's 1966 analysis of the forces of natural selection contains obscure wording and inelegant mathematical notation. But he finally made the verbal hints and circumlocutions of his predecessors mathematically explicit. Hamilton's assumption, taken from Fisher, was that the

Malthusian parameter defines Darwinian fitness. He derived the first partial derivative for the proportional effect on fitness of age-specific changes in survival probability. This effect is given by $s(x)/T$, where T is a measure of generation length and

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

where 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. Ultimately, 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 1; 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

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

An interesting difference between these scaling functions is that the force of natural selection acting on survival only decreases with age *after the onset of reproduction*, whereas the force of natural selection acting on fecundity can increase or decrease before the onset of reproduction (Charlesworth 1994). When plotted against age, these functions have the general form exemplified in Figure 1.

From these equations and some numerical calculations, Hamilton (1966) argued that Fisher's (1930) reproductive value is not a valid explanation of the existence of aging, if aging is defined as an endogenous decline in adult life-history characters, which seems to have been Hamilton's definition (see also Rose 1991). (Here we use the term "life history" to refer to the complete spectrum of age-specific survival probabilities and fecundities, whether these characters are components of fitness or not.) Thus, Hamilton gave examples of life histories that produce steadily increasing reproductive value, when Hamilton's *s(x)* function instead always declines. Hamilton's reasoning was that if we assume that falling age-specific survival probability is universal among adult somata, in the absence of exogenous mortality, his *s(x)* function provided a more plausible theoretical explanation for aging than Fisher's reproductive value.

More generally, Hamilton contended that his scaling functions would correctly predict the evolution of the rate of aging among populations that are subject to different demographic regimes. Hamilton used historical life tables from human American and Taiwanese populations to illustrate the impact of different demographic patterns on the evolution of aging. The Taiwanese life-table that he used exhibited higher rates of early reproduction and population growth compared with the American life-table, which Hamilton calculated would lead to a more rapid fall in his Forces of Natural Selection among the Taiwanese. However, he did not make this comparison to predict the future evolution of aging in these two human populations; the calculations were only illustrative.

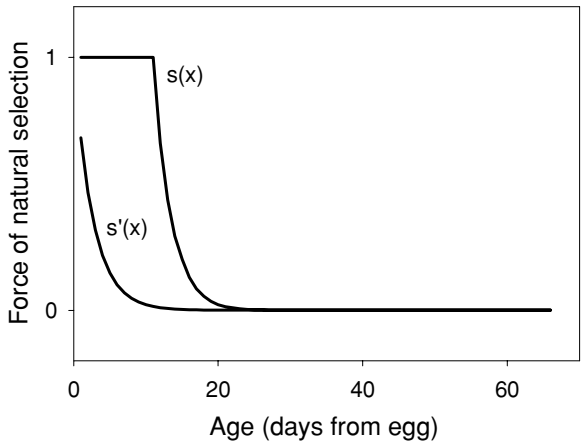

Figure 1. Hamilton's Forces of Natural Selection scaling functions with respect to somatic age: *s(x)* the scaling function for the force of natural selection acting on proportionally uniform changes in age-specific survival probability; and *s′(x)* the scaling function for the force of natural selection acting on changes in age-specific fecundity. Age-specific survival and fecundity values used to calculate these functions were derived from a cohort of 1111 female *Drosophila melanogaster* from population CO_1 of Rauser et al. (2006b).

Hamilton also discussed the population genetics of the evolution of aging, although his treatment was verbal and intuitive, without a mathematically explicit population genetic analysis.

Although there were few published signs that Hamilton's 1966 article was noticed in the remaining years of that decade, starting in 1970 research predicated on Hamilton's results began to spread. The first results were theoretical, primarily a series of articles by Brian Charlesworth and his colleagues (e.g., Charlesworth and Williamson 1975). Experimental publications based on Hamilton's Forces of Natural Selection also appeared, particularly research on *Drosophila melanogaster* (e.g., Rose and Charlesworth 1980).

In the remaining sections of this article, we take up the twists and turns by which Hamilton's 1966 findings have redefined evolutionary research on life history, including such topics as the evolution of aging and the possibility of a late life after the cessation of aging. We treat the radiating impact of Hamilton's paper on both evolutionary theory and evolutionary experimentation. We discuss quantitative theory first, then research on standing genetic variation, followed by experimental evolution. We include an

historical perspective on the parallels between Hamilton's Forces of Natural Selection and Einstein's Theories of Relativity.

Age-Structured Population Genetics Theory

HAMILTON'S SCALING OF THE FORCES OF NATURAL SELECTION IN THE POPULATION GENETICS THEORY OF AGING

A key aspect of Hamilton's 1966 analysis was the assumption that fitness is equivalent to the Malthusian parameter in age-structured populations. It is an important point in the history of evolutionary theory that the use of the Malthusian parameter as fitness in evolutionary theory was not just an ex cathedra assumption of R. A. Fisher in his 1930 book, *The Genetical Theory of Natural Selection.* Both Haldane (1927) and Norton (1928) developed mathematically sophisticated treatments of selection in age-structured populations, providing conditions under which the Malthusian parameter effectively equals Darwinian fitness, such as weak selection or random mating.

Charlesworth (e.g., 1970, 1980, 1994) extended and clarified the earlier work of Norton and Haldane, covering cases with sex differences, nonrandom mating, density-dependent effects, and environmental fluctuation. Although he found instances where the Malthusian parameter no longer predicts the course of natural selection accurately in age-structured populations, it remains the case that the effect of an allele on the Malthusian parameter is the best general guide to its likely evolutionary fate. Therefore, Hamilton's (1966) analysis supplies a first-order characterization of the effectiveness of natural selection acting on age-specific survival and fecundity.

More explicit analyses of the population genetics of aging illustrated the merits of Hamilton's original analysis of the evolution of aging, even though these analyses often incorporated population genetic details that were not present in Hamilton's original 1966 publication. It was necessary to do this because Hamilton (1966) did not present explicit population-genetic models, only general-purpose verbal scenarios for possible evolutionary-genetic patterns.

Charlesworth and Williamson (1975) showed that the likelihood that a mutant allele with beneficial age-specific effects would successfully invade an age-structured population was numerically parallel to Hamilton's Forces of Natural Selection, showing the same age-dependent pattern. Notably, Fisher's reproductive value does not show this quantitative parallel, supporting Hamilton's (1966) original criticism of the use of reproductive value to explain the evolution of aging. Charlesworth (1980, 1990, 2001) also supplied analyses of the equilibrium value of a deleterious recurrent mutation with effects confined to specific age classes. In these analyses, the terms that give the age dependence of these equilibrium values are Hamilton's $s(x)$ and $s'(x)$ functions.

Similarly, in Rose's (1985) analysis of antagonistic pleiotropy with overlapping generations, it was shown that alleles with multiple pleiotropic effects on age-specific survival and fecundity characters have first-order effects on the Malthusian parameter that were weighted by these same s functions. The scaling of these genetic effects by Hamilton's s functions explicitly shows that it is more likely that alleles that have beneficial effects on early life-history characters will be strongly favored, even when those alleles have deleterious effects on later life-history characters, as Medawar (1952) and Williams (1957) had conjectured. Rose (1985) also showed that recessive deleterious effects would foster the maintenance of genetic polymorphism when alleles affect multiple life-history characters pleiotropically, with antagonistic "trade-offs" between life-history characters in at least some cases. This result implies that, if there are alleles with antagonistic pleiotropy between life-history characters that cause aging, some of these alleles might remain polymorphic due to balancing selection, resulting in negative genetic correlations between early and later life-history characters, like early fecundity and adult longevity.

The analyses of Charlesworth, Rose, and their colleagues helped delineate the contrast between two possible genetic mechanisms for the evolution of aging: mutation accumulation and antagonistic pleiotropy (Rose 1991). The term "mutation accumulation" in theoretical population genetics refers to the evolutionary accumulation of deleterious effects when natural selection is weak. (It is not related to the concept of somatic mutation, a physiological aging process occurring within individual somata.) Instead it arises from the tendency of most mutations with phenotypic effects on fitness to be deleterious, coupled with the predominance of genetic drift in the determination of allele frequencies when natural selection is absent. The term "antagonistic pleiotropy" refers to alleles that have beneficial effects on some components of fitness and deleterious effects on other components of fitness. (Not all cases of pleiotropy need involve such antagonism. Morphological size characters often show "positive" pleiotropy, whereby alleles that increase the size of one limb, for example, also tend to increase the size of other body parts.) Either or both of these population genetic mechanisms can lead to the evolution of aging. Although they are logical alternatives, both mutation-selection balance and antagonistic pleiotropy can lead to the maintenance of genetic polymorphism for life-history characters and can result in the evolution of aging within a single species. Thus, these population-genetic mechanisms are not empirically incompatible.

Feedback between the evolution of aging and the force of natural selection is conceivable *providing* senescence plays a large role in the pattern of mortality in a population. Under such

conditions, if more reproductive opportunities are available later in life, the force of natural selection should strengthen, leading to the evolution of still slower rates of aging and still more opportunities for later reproduction. This may have been the case with the evolution of human aging. As our intelligence and tool use increased, we may have forestalled diverse sources of early adult deaths or injury. This may then in turn have led natural selection to strengthen in force at later ages, leading to still more increases in human life span. However, most species have death rates in the wild that are determined by factors that are not so readily circumvented by additional adaptation, leaving doubt about the frequency with which this type of "positive feedback" scenario is achieved.

The generality of Hamilton's predictions concerning aging has been questioned recently (Vaupel et al. 2004; Baudisch 2005). Vaupel et al. develop optimization models that predict negligible or negative senescence among clonal organisms. Although these models are interesting for life-history theory, Vaupel et al. motivate their importance by reference to clonally reproducing organisms for which the Hamiltonian theories would not apply (see below also).

THE TERMINAL PLATEAUS OF HAMILTON'S FORCES OF NATURAL SELECTION

In 1992, Carey et al. and Curtsinger et al. published experimental data from large dipteran populations demonstrating that age-specific rates of mortality stop increasing at late ages and so "plateau." Several studies have corroborated these findings in a variety of organisms, including humans (Vaupel et al. 1998). Thus aging, as defined here and by Hamilton, essentially ceases at late ages in some species. At first some thought that this contradicted the predictions of Hamilton's force of natural selection theory with respect to the evolution of aging, because it was assumed that Hamilton's analysis implied that age-specific rates of mortality had to continually increase, producing a definite "limit" to life span (e.g., Curtsinger et al. 1992). On this interpretation, the cessation of aging amounted to a refutation of Hamilton's (1966) analysis. Some thus abandoned Hamilton's theory, and explained these plateaus in mortality instead using the hypothesis of lifelong heterogeneity for individual robustness (Vaupel et al. 1979; Vaupel 1988, 1990; Pletcher and Curtsinger 2000). Such nonevolutionary theories of mortality plateaus have an extensive history. Most make references to the Gompertz mortality model which posits that instantaneous age-specific mortality rates, $u(x)$, are an exponentially increasing function of age, $A\exp(\alpha x)$. In a large population mortality plateaus can be produced theoretically if mortality rates conform to a Gompertz model and individuals vary in their lifelong age-independent mortality rate (A) or their lifelong age-dependent mortality rate (α) (Beard 1959; Vaupel et al. 1979; Pletcher and Curtsinger 2000). This lifelong variation may be genetic or environmental in origin. These theories are called lifelong heterogeneity models because the differences in A and α should be sustained from the start of adult life to its end.

Mortality plateaus were observed in highly inbred lines ($F > 0.99$) of fruit flies (Fukui et al. 1993). For lifelong heterogeneity to be a viable theory then the lifelong variation that it assumes must arise from the environment. As a practical matter it is not possible to eliminate all environmental variation. However, in carefully controlled laboratory experiments Khazaeli et al. (1998) found that environmentally induced heterogeneity is not a primary factor determining late-life mortality rates.

It is known that several types of environmental manipulations do affect longevity by decreasing the age-independent parameter of the Gompertz equation (Nusbaum et al. 1996; Joshi et al. 1996). However, as pointed out by Mueller et al. (2003), the magnitude of variation required in A to produce mortality-rate plateaus in late life is much greater than has been observed in these experiments. There are to date no well-documented environmental factors that affect α of the Gompertz model. Nevertheless, fitting Gompertz models to data from large cohort mortality studies, to indirectly estimate the variation in α required to produce plateaus, yielded best-fit models that were substantially in conflict with the late-life mortality patterns of those same cohorts (Mueller et al. 2003). That is, it is difficult even to "force" lifelong heterogeneity models to fit the data obtained from some cohorts.

The latest version of the heterogeneity model (Weitz and Fraser 2001) supposes that random variation over time will continuously vary the Gompertz parameters. To our knowledge there has been no empirical research on the assumptions or predictions of this particular form of the heterogeneity model. However, though these nonevolutionary theories have received little experimental support (Khazaeli et al. 1998; Mueller et al. 2003; Rauser et al. 2005), the decade from 1992 to 2001 constituted a low point for Hamilton's (1966) analysis of life-history evolution.

But Hamilton's equations had been misinterpreted. Implicit within Hamilton's (1966) original theory is an evolutionary explanation of the plateaus shown by late-life mortality rates (Carey et al. 1992; Curtsinger et al. 1992) and late-life fecundity (Rauser et al. 2003; Mueller et al. 2007). These predictions are sufficiently simple that they can be developed intuitively, although we have also used formal modeling (Mueller and Rose 1996; Rauser et al. 2006a). Notice that s and s' are equal to zero for all ages after reproduction and survival cease in the evolutionary history of a population. As shown in Figure 1, these s functions fall toward plateaus that stretch outward to indefinitely late ages. They do not continue to fall. Therefore, the late-life plateaus in age-specific mortality and fecundity observed under benign laboratory conditions might be explained by the asymptotic plateaus in the Forces of Natural

Selection, because natural selection cannot distinguish between fitness differences in survival at different ages after Hamilton's *s* functions plateau at zero. If the phenomenon of aging arises from the fall of Hamilton's *s* functions, and not just from these functions falling to low values, then it is intuitive to suppose that late-life plateaus might simply result from the plateauing of the *s* functions in late life. That is, the observed later plateaus among life-history characters might be explicable in terms of the later plateauing in the forces of natural selection.

Explicit theoretical analysis backs up this intuition. In our theoretical work on these problems (Mueller and Rose 1996; Rauser et al. 2006a), *s* never falls to zero exactly because we assume reproduction is possible at all adult ages. Plateaus nevertheless evolve. There is a simple theoretical explanation for this. At advanced ages, even though *s* is continuing to decline exponentially, the strength of selection is so weak that as an evolutionary force it is weaker than random genetic drift. Therefore we see the deterioration of both survival and fecundity due to either antagonistic pleiotropy or mutation accumulation for the first part of adulthood, but since genetic effects at very advanced ages are equivalent with respect to their effects on fitness no differentiation between ages is expected to evolve. Our simulations numerically demonstrate that late-life mortality plateaus can evolve as a consequence of natural selection in age-structured populations alone, without any special suppositions. In addition to demonstrating leveling of mortality rates at late ages, these models also produce an exponential increase in mortality rates at earlier ages, the pattern that is merely assumed by Gompertzian demographic models (this is discussed further below).

However, some criticized this theory on the grounds that mortality rates should rise to 100% during late life because of selection's inability to eliminate deleterious mutations at later ages (Pletcher and Curtsinger 1998; Wachter 1999). Charlesworth (2001) resolved this problem by showing, for a simple model of mutation accumulation, that age-independent beneficial effects can forestall the evolution of 100% mortality during late life.

Rauser et al. (2006a) supplied a numerical study of the evolution of late-life fecundity using age-structured population genetics, showing that the late-life plateau in $s'(x)$ tends to generate a late-life plateau for fecundity. Thus explicit calculations of the population genetics of late-life evolution end up supporting the application of Hamilton's original equations to the explanation of late life, even though no population geneticist realized the implications of these equations for late life before 1990. Whatever else they might be, late-life plateaus for mortality and fecundity are not anomalies for Hamiltonian theory. They are instead corollaries, corollaries that were not at first apparent, but were nonetheless inherent to Hamiltonian theory.

Experimental Genetics of Life History

It is a notable feature of Hamilton's (1966) analysis that it leads to predictions that are experimentally testable. Although evolutionary theories are sometimes good at explaining the existence of a phenomenon, it is often difficult to evaluate such theories using experiments that differentially test clear a priori predictions. This is not true of Hamilton's (1966) results. There are clear, general, a priori corollaries of his theory that have been tested experimentally. But mistakes have been made as to which of these corollaries are associated with particular population genetic hypotheses, as we will now explain.

EFFECT OF ADULT AGE ON GENETIC VARIANCES

One important finding of mutation-accumulation models of the evolution of aging was that weakening natural selection should lead to higher equilibrium frequencies of deleterious mutations at later adult ages. This makes sense because the equilibrium allele frequencies of deleterious mutants in mutation-selection balance models are inversely proportional to the strength of selection. This finding led Charlesworth (e.g., 1980) to the conclusion that increased additive genetic variance for life-history characters, like age-specific survival probability and fecundity, should arise as a result of mutation accumulation, a prediction open to experimental test.

Three theoretical problems with this prediction are worth noting. First, this prediction assumes a uniform pattern of mutational effects with respect to age, an assumption that is neither self-evident nor ineluctable. Second, for some life-history parameters, the quantitative predictions for mutation-selection balance models are not simple; it is even possible for the frequency of age-specific deleterious mutations to decrease slightly during midlife, before rising rapidly at later adult ages (Baudisch 2005). Third, the prediction of an increased additive genetic variance for life-history characters is not unique to the mutation-accumulation mechanism for the evolution of aging. Antagonistic pleiotropy in conjunction with the weakening Forces of Natural Selection can also produce increased additive genetic variances with age, under some conditions (Charlesworth and Hughes 1996).

Despite these theoretical ambiguities, Charlesworth's original intuition led to a significant research effort to test the prediction that age-specific additive genetic variances for life-history characters should increase with age. Rose and Charlesworth (1980, 1981) published the results of the first such test: the additive genetic variance for daily fecundity in *D. melanogaster* did *not* increase with age in a sibling analysis. Since then, most subsequent analyses have inferred age-specific patterns of additive genetic variance using chromosomal extractions and artificially

constructed genotypes (Kosuda 1985; Hughes and Charlesworth 1994; Hughes 1995; Charlesworth and Hughes 1996; Promislow et al. 1996; Tatar et al. 1996; Shaw et al. 1999). The results of these studies are strikingly equivocal and inconsistent. Charlesworth's original expectations have not been born out. (We offer an explanation of this below, after discussing other quantitative genetics research on life history.)

HYBRID VIGOR EFFECTS

As the analysis of Charlesworth and Hughes (1996) shows, a better differential test of mutation accumulation is to test for pronounced dominance variance at later ages, which should also generate hybrid vigor among differentiated populations upon crossing. Intuitively, this can be seen as a natural effect of mutation-selection balance. It is a standard result in theoretical population genetics that dominant deleterious alleles are kept at lower equilibrium gene frequencies compared to recessive deleterious alleles, assuming that these alleles have deleterious effects of similar magnitude when they are homozygous. Thus, alleles that are at high frequencies specifically as a result of mutation-selection balance, rather than some other population genetic mechanism, should show a tendency to recessive deleterious gene action.

Mueller (1987) performed a test of hybrid vigor for later fecundity using small *D. melanogaster* populations cultured using young adults for many generations, populations in which relatively rapid genetic drift from small population sizes allowed the evolutionary accumulation of deleterious alleles specifically with effects at late ages. Mueller showed that these populations had pronounced hybrid vigor for fecundity at late ages, an age-specific pattern that fit the prediction of Charlesworth and Hughes (1996). But Mueller (1987) found that other fruit fly populations in which selection for later life-history characters was relatively stronger did not show the same hybrid vigor effect, presumably because a greater strength of selection at later ages forestalled mutation accumulation. In a separate study, Rose et al. (2002) found that crosses of other *D. melanogaster* populations with large effective population sizes failed to show hybrid vigor for age-specific mortality rates in both males and females.

TESTS OF ANTAGONISTIC PLEIOTROPY

Appropriate evidence for the occurrence of antagonistic pleiotropy includes the detection of negative genetic covariances or correlations between life-history characters as well as antagonistic indirect responses to selection, as already mentioned. The antagonistic pleiotropy mechanism does not require that all genetic covariances between life-history characters be negative, nor that all life-history characters respond antagonistically when other life-history characters are subjected to selection, nor that all allelic variation with such antagonisms remain segregating in particular populations. However, the occurrence of some cases with negative genetic covariance between characters and antagonistic indirect responses to selection is required.

Evidence for such patterns came early in genetic research on the quantitative genetics of life history. For example, Rose and Charlesworth (1981) found a negative genetic correlation between early fecundity and longevity in *D. melanogaster*.

But there are other cases in which such additive genetic correlations between life-history characters are overwhelmingly positive (e.g., Giesel et al. 1982; Murphy et al. 1983). These apparent anomalies have been explained in terms of inbreeding artifacts (e.g., Rose 1984a) and genotype-by-environment interaction (e.g., Service and Rose 1985).

Together the equivocal results from *both* tests of age dependence among genetic variances *and* tests of the signs of genetic correlations strongly suggest that using genetic variances or covariances in tests of the genetic mechanisms underlying the evolution of life-history characters is not a particularly good experimental strategy. Thirty years of experimental quantitative genetics have shown that the genetic variances and covariances of life-history characters are highly sensitive to population structure, selection history, and assay environment (Rose 1991; Leroi et al. 1994a,b; Rose et al. 2005a). There is almost always *some* genetic variation for life history in outbred populations, and there are sometimes negative genetic correlations between individual life-history characters, but there are few other patterns that hold up with much generality. This is not a criticism of Hamilton's (1966) theoretical analysis. Rather, it is a criticism of experiments that try to test evolutionary theories using quantitative genetic parameters. Whereas such parameters are useful in predicting the immediate outcome of artificial selection using populations maintained under the same conditions as those used to estimate these parameters, for life-history characters they do not show much empirical stability in the face of changes to environmental conditions, breeding pattern, or allele frequencies (Rose et al. 2005a).

LONGEVITY MUTANTS

An alternative experimental strategy that has been more fashionable lately is the study of mutant alleles that strongly increase longevity in model species like *D. melanogaster* and *Caenorhabditis elegans* (e.g., Kenyon 2005). It has been claimed that such mutants show general enhancement of functional characters. But this raises an evolutionary anomaly: such alleles should therefore have been favored by natural selection, making their de novo generation by laboratory mutagenesis puzzling. Such generally beneficial alleles surely should have already evolved to high frequencies in the prior history of the species.

More detailed scrutiny, however, has shown that such longevity mutants typically exhibit antagonistic pleiotropy with respect to early fecundity, metabolism, competitive ability, or survival under natural conditions (Van Voorhies et al. 2006),

explaining their rarity among natural populations. For example, the first long-lived *C. elegans* mutant, *age-1*, has reduced fitness when exposed to intermittent food levels (Walker et al. 2000). Another long-lived *C. elegans* mutant that has been extensively studied, *daf-2*, would be quickly replaced by wild-type worms if both genotypes were forced to compete for resources in a common environment (Jenkins et al. 2004). In addition to being outcompeted in tests of reproductive fitness, it also appears that *daf-2* mutants are less capable of withstanding stresses that they are likely to encounter in their natural habitat. Although *daf-2* mutants can live approximately twice as long as wild type when reared under relatively benign laboratory conditions, these mutants actually die sooner than wild-type worms when placed in conditions that more closely approximate their natural environment (Van Voorhies et al. 2006). These results make it apparent why such long-lived mutants are not found in wild populations: under natural conditions these mutants often have either reduced reproductive output or are less able to survive the stresses they would certainly encounter outside of laboratories.

These findings broadly support the importance of antagonistic pleiotropy in the age-specific action of natural selection, in that it appears to be difficult to find mutants with greatly increased longevity that do not suffer reductions in components of fitness. But they do not necessarily reveal the specific role of antagonistic pleiotropy in the evolution of life history in unmutagenized populations in nature. The spectrum of "longevity mutants" that have been created are not necessarily targeting the loci that have shaped the evolution of life-history characters among the species in which these mutants are obtained. For example, Maynard Smith's (1958) classic work on longer-lived *Drosophila ovariless* mutants involved sterile mutants that are unlikely to have played much role in the evolution of *Drosophila* life history.

LIFE-HISTORY GENETICS IS INHERENTLY DIFFICULT

Overall, the experimental genetics of life history have not proved of much help in testing Hamilton's original 1966 theory or the population genetic hypotheses that derive from it. We suggest that this problem is probably inherent to life-history characters. It *is* possible to study the quantitative genetics of "good" genetic characters, like pigmentation, profitably. Such characters are not influenced by large numbers of loci and are not affected as much by inbreeding depression or genotype-by-environment interactions. But life-history characters are demonstrably subject to all of these difficulties.

Experimental Evolution of Life History

Although the difficulty of using genetics to study life history from a Hamiltonian perspective might suggest that using experimental evolution to test Hamilton's theory would be even harder, it has not turned out that way. Surprisingly, experimental evolution has supplied striking evidence in support of Hamilton's (1966) analysis.

EVOLUTION OF AGING

The key to Hamiltonian research on the experimental evolution of aging lies in the pattern of the s and s' functions. Until $m(x)$ is greater than zero, $s(x)$, the Force of Natural Selection acting on age-specific survival probability, remains at its maximum value, as shown in Figure 1. Rose (as described in Rose 2005) realized in 1977 that Hamilton's (1966) results implied that aging could be postponed by natural selection simply by delaying the onset of reproduction in an evolving population in the laboratory, because this lifts the values of $s(x)$ farther into the adult period. Working as Charlesworth's doctoral student, he established a *D. melanogaster* population in which the onset of reproduction was delayed a few weeks experimentally by discarding all the eggs that females laid before the age of 28 days. This population then evolved an increased life span in about one year, as reported in Rose and Charlesworth (1980). Since then, this basic experimental evolution design has been emulated multiple times in experimental populations of *Drosophila* (e.g., Luckinbill et al. 1984; Rose 1984b; Partridge and Fowler 1992; Deckert-Cruz et al. 2004) and other species (e.g., Nagai et al. 1995). Figure 2 shows the typical kind of results. These delayed-breeding experiments

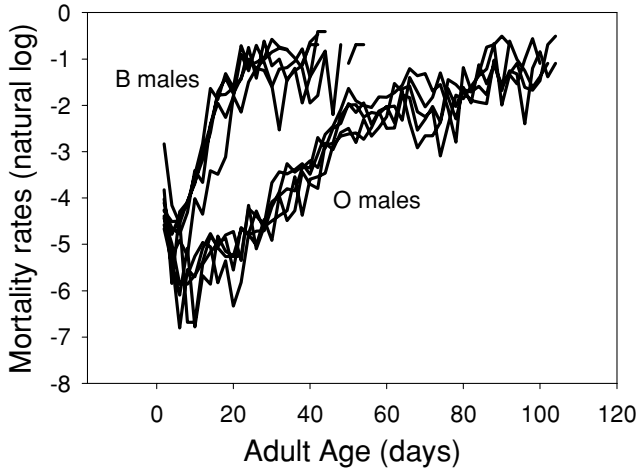

Figure 2. Age-specific adult male mortality rates in 10 *Drosophila melanogaster* populations cultured at 14 days of age (B) and 70 days of age (O) for more than 100 generations. All 10 populations were derived from one generation of a common ancestral population in 1980. The data show a slowing in the O rate of aging due to a delay in the age of onset of reproduction among O populations, *and* a later onset of mortality rate plateaus in the O populations due to a later last age of survival and reproduction in the evolutionary history of the O populations. Figure from Rose et al. (2002).

have consistently produced progressively slowed aging after 10 or more generations of natural selection with the onset of reproduction delayed, a clear experimental vindication of Hamilton's (1966) theoretical results.

Occasionally experiments carried out under uncertain conditions fail to corroborate Hamiltonian predictions. For example, Reznick et al. (2004) studied populations of guppies that had experienced high early mortality, which according to Hamiltonian theory ought to select for earlier onset of senescence, all other things being equal. Detailed measurements showed, however, that these populations do not senesce earlier than populations with low mortality, in ostensible contradiction to Hamilton's theory. However, these high mortality populations also develop more rapidly and have higher female fecundity at all ages, which has no obvious evolutionary interpretation in terms of demographic selection, suggesting that something other than demographic selection may be responsible for the genetically based differences in life history found by Reznick et al. This kind of ambiguity of interpretation is to be expected in data or populations collected from the wild.

Antagonistic pleiotropy has been inferred from reductions in early fecundity among longer-lived laboratory *D. melanogaster* populations that have been cultured exclusively using older flies (e.g., Rose and Charlesworth 1980; Luckinbill et al. 1984; Rose 1984b). However, such antagonistic responses vary somewhat in response to environmental conditions and genetic background, and are by no means easy to infer (Leroi et al. 1994a,b; Rose et al. 2005a).

Some have questioned the validity of the experimental evolution strategy, based on the view that laboratory populations may not be an appropriate guide to evolution in nature (e.g., Promislow and Tatar 1998; Harshmann and Hoffmann 2000; Linnen et al. 2001). In particular, some assert that laboratory populations maintained with short, nonoverlapping generations evolve artificially shortened life spans, making the increased life span obtained with experimental evolution of doubtful importance (e.g., Linnen et al. 2001). However, as shown by Passananti et al. (2004) among others, it is apparent that aging readily evolves up or down in the laboratory in accordance with the first age of reproduction, as Hamiltonian theory predicts, regardless of prior histories of selection. In Hamiltonian research, life history is tuned primarily by the Forces of Natural Selection, so long as there is sufficient genetic variation (cf. Comfort 1953), regardless of whether the evolutionary process is "natural" or not (pace Stearns et al. 2000).

EXPERIMENTAL EVOLUTION OF LATE LIFE

Hamilton inferred that the Force of Natural Selection acting on survival, $s(x)$, has to decline throughout adult life until the last age of reproduction, after which the force of natural selection is zero for all remaining ages. Once the force of natural selection is zero at these late ages, selection is unable to distinguish fitness differences associated with changes in survival at different ages (Mueller and Rose 1996). Therefore, it is not surprising that explicit, numerical calculations of the outcome of evolution show that age-specific mortality rates do not continue to increase some time after reproduction has ceased. Hamilton's theory, then, neatly predicts that the timing of mortality-plateau onset should depend on the timing of the cessation of reproduction in a population's evolutionary history, which can be readily manipulated using experimental evolution.

Rose et al. (2002) explicitly tested this prediction in three independent sets of replicated comparisons using multiple *D. melanogaster* populations long selected for different last ages of reproduction. They found that the onset of late-age mortality-rate plateaus evolves as Hamilton's theory suggests, as shown in Figure 2. That is, the later the last age of reproduction in these populations, the later the onset of stable late-life mortality levels. This was the first experimental corroboration of any late-life theory.

Hamilton's results similarly imply the evolution of plateaus for late-life fecundity. According to Hamilton, the force of natural selection acting on fecundity, $s'(x)$, declines with age until the last age of survival in the population's evolutionary history. Rauser et al. (2003) intuited from this that late-age fecundity could mimic late-age survival patterns. That is, fecundity could stop decreasing and thus plateau at ages after which the force of natural selection declines to zero. In particular, the onset of plateaus in fecundity should evolve in accordance with the last age of survival in a population's evolutionary history. Computer simulations of life-history evolution support this theoretical inference (Rauser et al. 2006a). Rauser et al. (2003) experimentally established the existence of late-life plateaus in fecundity. It was then also demonstrated that fecundity plateaus evolve according to Hamilton's theory in two independent sets of replicated comparisons using multiple populations of *Drosophila* (Rauser et al. 2006b), with later onset of fecundity plateaus among populations with evolutionary histories having later last ages of survival.

EXPERIMENTAL EVOLUTION STRONGLY SUPPORTS HAMILTON'S THEORY

Unlike the problematic history of experimental genetic research, research using experimental evolution has generally supported Hamilton's (1966) analysis, particularly in well-replicated and controlled laboratory experiments. We are not aware of any laboratory evolution project that has allowed enough generations for evolution to act on a genetically variable population in which Hamiltonian demographic theory has not been corroborated.

More generally, we suggest that experimental evolution in the laboratory will often be a more useful research strategy for other evolutionary theories as well, as testing Hamilton's (1966) theory has been one of the most common uses of the technique.

Parallels between Hamilton and Einstein

The parallels between Hamilton in the 1960s and Einstein in the first decade of the 20th century are striking. Both were concerned with somewhat anomalous phenomena, some of which had long been noticed. The seeming anomaly of altruistic behavior in social insects was pointed out and addressed by Darwin in *The Origin of Species*, but it was not until Hamilton's (1964 a,b) papers that an appropriate formal analysis of kin selection began. Like Einstein's theoretical work, Hamilton's analysis of kin selection created a new set of theoretical problems for the mathematically adept to work on. But the formal intuition, the breakthrough to a new level of theoretical clarity, was entirely Hamilton's. In his work on kin selection, Hamilton gave biologists a better way to think about the problem of biological altruism.

But the parallels between Hamilton's (1966) Forces of Natural Selection and Einstein's Theories of Relativity are even better. Hamilton's Forces of Natural Selection are much like the Lorentz Transformations that Einstein derived in his Special Theory of Relativity. Formally speaking, Hamilton scaled the action of natural selection across the entire range of ages. Lorentz Transformations rescale space-time as speeds approach that of light. These kinematic transforms are not mere contrivances to make an adroit approximation. At low speeds these transforms collapse into the transformations of Galileo. Einstein derived them from a fundamentally new idea: that invariances underlie physical law, pervading diverse phenomena such as gravitation and electromagnetism. Einstein accordingly sought to integrate all these phenomena within a general mathematical framework, applicable to the full range of masses, velocities, etc.

Intuitive reasoning about the action of natural selection tends to be based on its consequences for early ages. Likewise, the early physical theories of motion, such as those of Newton, concerned low velocities and small masses, and used concepts like force, concepts that physics later abandoned in favor of Einsteinian symmetries and their consequent invariances. Both conventional Darwinian population genetics without age structure and Newtonian mechanics can be recovered as special cases of Hamiltonian population genetics with age structure and Einsteinian mechanics, respectively. To be specific, the special case of the Malthusian parameter with one juvenile age class and a single bout of adult reproduction exactly equals the product of viability and fecundity that determines fitness in typical discrete-generation theoretical population genetics.

But the actual "universes," evolutionary and physical, implied by the work of Hamilton and Einstein are qualitatively different from those of their predecessors, and logically more coherent. Thus Newton developed an ad hoc inverse-square Universal Law of Gravitation acting through space based on the falling off of light intensity from a source, even though he had no physical mechanism for gravitation. Einstein derived gravity as a secondary effect of space-time curvature in his General Theory of Relativity, so the underlying substrate of the Einsteinian universe was not space or time separately, but a wedded four-dimensional entity unknown to human intuition, space-time. Similarly, Gompertz and other demographers assumed ad hoc an exponential acceleration of age-specific mortality rates. In the calculations of Mueller and Rose (1996), Gompertzian patterns of survival during the first part of the reproductive period arise naturally as a result of Hamiltonian evolutionary mechanics. No ad hoc demographic model is required.

Far more important than the regeneration of earlier theoretical results and intuitions, the formal theories of Hamilton and Einstein also open up evolutionary and physical theory, respectively, in ways that allow us to go on to deal with counterintuitive phenomena.

Before Einstein, some had mused about whether a gravitating body could be so massive that even light could not escape it. In 1784 an English geologist, John Michell, used the Newtonian theory of gravity and the concept of escape velocity to compute how large a "dark star" needed to be so that light could not escape—about 500 times the radius of the Sun. But this estimate had no underlying vision behind it, and in the next two centuries, no one sought to prove that black holes existed. Einstein's work made black holes understandable, and indeed necessary, though even he did not at first see this consequence of his Theories of Relativity. Now black holes are commonly called "Einsteinian."

Likewise, we can now see that Hamilton's original derivation of the Forces of Natural Selection implied the existence of late-life plateaus for both mortality and fecundity, and thus the cessation of aging at very late ages, even though Hamilton had no such intuition in the 1960s. Naturally, his theory also supplies a structure within which we can study such phenomena as aging, late life, and biological immortality (Mueller and Rose 1996; Rose and Mueller 2000; Rose et al. 2005b). For these reasons, we refer to the study of life-history evolution in terms of Hamilton's Forces of Natural Selection as "Hamiltonian."

Adaptation and the Forces of Natural Selection

The explanation of aging and late life by Hamilton's Forces of Natural Selection is not their only value. Hamilton's Forces also offer a useful vantage point from which to understand adaptation itself, as both process and product of evolution. Pre-eminently, natural selection as a process is only effective over a brief initial window of somatic ages, as shown in Figure 1. Thus adaptation of somata, as both pattern and process, is expected only for those

attributes of the somata that *either* benefit all ages *or* benefit young somata specifically. Thus, given the evidence for age specificity of beneficial allelic effects disclosed by both the genetics and experimental evolution of life history, as summarized here, somatic adaptation should in general be viewed as a relatively age-limited feature of evolution. Whatever else evolution does, it does not produce somata that are perfect machines, not even machines that possess adaptations, that are durable over the life of a soma.

This may be contrasted with the adaptation of both germ lines and organisms that reproduce by fission, which is symmetrical with respect to any effect that selection can act upon. It is important to understand that this usage of the term "symmetry" distinguishes among different types of fissile reproduction. Fissile cells or organisms can in principle partition damaged components differentially to one of the two products of fission, effectively assigning it a "somatic" role. Thus the yeast species *Saccharomyces cerevisiae* is fissile, but the products of division are visibly not symmetrical, and the "mother" cell shows aging (Mortimer and Johnson 1959). The yeast species *Schizosaccharomyces pombe* was once thought to show symmetrical division and to be free of aging, but it is now known that its division is just more subtly asymmetrical, and it too undergoes aging (Barker and Walmsley 1999). Likewise, obviously asymmetrical division in bacterial species is known to produce aging (Ackerman et al. 2003), as does less obviously asymmetrical division in *Escherichia coli* (Stewart et al. 2005). Under such conditions of asymmetrical division, natural selection will undergo the diminishing force predicted by Hamilton's analysis, even with fissile reproduction.

Whether reproduction is sexual or asexual, with or without fission, evolution by natural selection will favor the indefinite propagation of the cells that sustain a lineage of organisms. This guarantees that germ lines will not show the diminution of function that characterizes all other living material, whether somatic tissue in multicellular organisms, asymmetrically disadvantaged products of fission, or indeed germ cells in older organisms that are not likely to reproduce.

In this sense, then, there are two broad domains of adaptation, one domain that determines the features of potentially immortal cell lineages and one that determines the features of cell lineages that are not potentially immortal. The accumulation of deleterious mutations, environmental accident, contagious disease, etcetera can undermine the propagation of potentially immortal germ-line cells, and thus cause the extinction of entire species. Yet natural selection will act at full force to sustain the survival of potentially immortal lineages. For this reason, each person reading this article is the product of lineages that have been sustained for hundreds of millions of years. But natural selection on somata will operate like Woody Allen's underachieving God, ensuring that the somatic life span of each of our readers will end on a vastly shorter time-scale than that of a mammalian species. Hamilton's (1966) Forces of Natural Selection are thus among the most significant equations in all of scientific theory.

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