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Fisher, Medawar, Hamilton and the Evolution of Aging

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THE idea that senescent decline in the performance of biological systems must have an evolutionary basis traces back almost to the beginnings of evolutionary biology (Rose 1991, Chap. 1), although Darwin does not seem to have discussed the problem. At first sight, the nearly universal existence of senescence in species of multicellular organisms is paradoxical, given that natural selection supposedly causes the evolution of increased, not decreased, fitness. As discussed by Comfort (1979), many biologists have, therefore, taken the view that senescence reflects an inevitable process of damage accumulation with age, and indeed an analog of senescence can be seen in complex machines such as cars (Gavrilov and Gavrilova 1991). But unicellular organisms, such as bacteria, which propagate simply by binary fission, and the germ lines of multicellular organisms, have been able to propagate themselves without senescence over billions of years, showing that biological systems are capable of ongoing repair and maintenance and so can avoid senescence at the cellular level. Senescence cannot, therefore, just be an unavoidable cumulative result of damage. The large amount of variation among different species in their rates of senescence also clearly indicates that aging is subject to variation and selection (Comfort 1979; Finch 1990; Rose 1991; Wachter and Finch 1997). This conclusion is backed up by the existence of both quantitative genetic variation and major gene mutations affecting the rate of aging (Finch 1990; Rose 1991; Wachter and Finch 1997).

Modern evolutionary theory has demonstrated that, in species with a clearcut distinction between parent and offspring, senescence is a virtually inevitable result of the fact that genes that affect survival or fecundity only early in life have a greater selective impact than genes whose effects are manifest only late in life. The purpose of this *Perspectives* article is to trace the history of this idea, with especial emphasis on William Hamilton's (1966) classic paper and its influence on subsequent work. This was motivated by Hamilton's untimely death earlier this year and the fact that his work on the evolution of senescence has probably received less attention than his other seminal contributions to evolutionary theory.

Within modern evolutionary genetics, the first discussion of the evolution of senescence was that of Fisher (1930), in the context of his famous concepts of the "Malthusian parameter" and "reproductive value." Fisher considered a sexually reproducing, age-structured population reproducing in continuous time, with a probability of survival to age x of $l(x)$, and a rate of production $m(x)$ of offspring of the same sex as their parent at age x. He pointed out that such a population reaches an asymptotic exponential rate of population increase, r, which is given by the (single) real root of the equation

$$\int_0^\infty e^{-rx} l(x)\, m(x)\, dx = 1. \qquad (1)$$

Fisher called r the Malthusian parameter of the population, in reference to Malthus's preoccupation with the supposedly inevitable exponential increase in numbers of the human species. Although not mentioned by Fisher, this result traces back to the work of Euler (1760) and Sharpe and Lotka (1911). r is now commonly referred to as the "intrinsic rate of increase" of the populations, and Equation 1 is often called the Euler-Lotka equation.

Fisher drew attention to the quantity defined by the relation

$$v(x) = \frac{e^{rx}}{l(x)} \int_x^\infty e^{-ry} l(y)\, m(y)\, dy. \qquad (2)$$

This is the reproductive value of individuals of age x and measures their contribution to the future ancestry of a population growing at rate r, normalized to a value of unity at the time of conception. Fisher (1930) stated (p. 27), "The direct action of Natural Selection must be proportional to this contribution." He showed a curve of

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reproductive value for Australian women, which rises with advancing age during childhood, reaches a maximum around 19, and then declines steadily, reaching zero at close to 50, when most women have reached menopause. He commented (p. 29),

> It is probably not without significance in this connexion that the death rate in Man takes a course generally inverse to the curve of the reproductive value. The minimum of the death rate curve is at twelve, certainly not far from the primitive maximum of the reproductive value; it rises more steeply for infants, and less steeply for the elderly than the curve of reproductive value falls, points which qualitatively we should anticipate, if the incidence of natural death had been to a large extent moulded by the effects of differential survival.

These ideas greatly influenced Medawar (1946, 1952) when he was formulating the first explicit model of the evolution of aging. Medawar took it for granted that Fisher's reproductive value measures the relative effectiveness of selection at age x. Given this premise, a hypothetical mutant gene that increases survival over a small time interval at an age when reproductive value is high would thus have a higher net effect on fitness than a gene acting at an age when reproductive value is low. Since reproductive value declines over much of adult life, this leads to the expectation that selection will be more effective in improving performance early in adult life than late in life. He pointed out that this means that deleterious alleles with effects restricted to late stages of life would equilibrate at higher frequencies at mutation-selection balance than alleles that act earlier, the process now referred to as the "mutation-accumulation" theory of aging (Rose 1991, Chap. 4). Late-acting deleterious mutations are, of course, familiar to medical geneticists. Haldane (1941, pp. 192–194) had previously suggested that there would be selection for modifiers that postpone the age of onset of the effects of such mutations, and Medawar laid considerable stress on this possibility. However, the relevant selection pressure is of the order of the mutation rate to the trait in question, and so postponement is unlikely to be a major factor in the evolution of senescence (Charlesworth 1994, p. 200).

Medawar also pointed out that alleles with positive effects on performance early in life, but with negative effects because of physiological trade-offs later on, are more likely to be established by selection than alleles with the opposite pattern. This idea was more fully developed by Williams (1957) and is now known as the "antagonistic pleiotropy" theory of aging (Rose 1991, Chap. 4). Both of these mechanisms could cause an initially nonsenescent life history, in which mortality rates are independent of age, to evolve gradually to a state in which death rates increase with age, the commonly used demographic criterion for senescence (Comfort 1979; Finch 1990). The relative importance of mutation accumulation *vs.* antagonistic pleiotropy in the evolution of aging is still an unsettled issue (Rose 1991; Wachter and Finch 1997).

Hamilton (1966) noted that it is fallacious to use reproductive value as a measure of the effectiveness of selection as a function of age, and that a different measure should be used. He started with the Fisherian assumption that r is an appropriate measure of net fitness, so that a mutant gene whose effect on survival or reproductive succcess increases the value of r over that for the current population will be favored by selection. He noted that it is possible to make explicit calculations of the effects on r of small changes in survival or fecundity at a given age, by the method of implicit partial differentiation of Equation 1. In the context of Fisher's continuous-time model, if the integral of the fecundity rate between ages x and $x + \delta x$ is changed by a small amount $\delta m(x)$, the associated change in r as δx approaches zero is given by

$$\delta r \approx \frac{\delta m(x)\, e^{-rx} l(x)}{T}, \tag{3}$$

where T is a measure of the generation time of the population, given by

$$T = \int_0^\infty x e^{-rx} l(x)\, m(x)\, dx. \tag{4}$$

A similar treatment can be applied to the age-specific mortality rate, defined as

$$\mu(x) = -\frac{d \ln\, l(x)}{dx}. \tag{5}$$

The change in r associated with a small change, $\delta\mu(x)$, in the integral of the mortality rate between ages x and $x + \delta x$ is given by

$$\delta r \approx -\frac{\delta\mu(x) \int_x^\infty e^{-ry} l(y)\, m(y)\, dy}{T}. \tag{6}$$

Neither of these formulae corresponds to reproductive value, as given by Equation 2, and they have rather different implications for the relation between the age of effect of a gene and its impact on fitness. If the population is stationary in size or growing, as must be the case in the long term if it is not doomed to extinction, Equation 3 implies that, all else being equal, there is always a greater selective premium on early rather than late reproduction, since $l(x)$ declines with age. This is not predicted from the reproductive value curve, which increases during infancy, and it reflects the fact that a gene whose effect on fecundity occurs late in life may be removed by death of its carrier before this effect is expressed.

Similarly, Equation 6 implies that selection is indifferent to the timing of gene effects on age-specific mortality during infancy and that its intensity always decreases with age during adulthood. Again, this is quite different from the pattern predicted by reproductive value; the

difference arises from the fact that reproductive value is conditioned on an individual having survived to age x and discounts the amount of population growth that occurs over a time period x, whereas Equation 6 measures the expected fitness effect of a change in mortality at age x for individuals censused at conception. Hamilton (1966) pointed out that these differences are nontrivial. For example, if fecundity increases exponentially with age during adulthood, reproductive value also increases exponentially, so that its use would lead to the conclusion that selection opposes senescence. In contrast, Equation 6 implies that there is always a selective premium on early survival, given the monotonic decrease in the magnitude of its right-hand side with age, although the rate of decline of the intensity of selection with age is greatly slowed if fecundity increases with age.

On the basis of these results, Hamilton proposed that the more rapid incorporation of favorable mutations with early effects on survival or fecundity than mutations with effects later in life would cause an initially nonsenescent life history to evolve in the direction of relatively high mortality rates and low fecundity late in life, without having to postulate any harmful mutations or tradeoff effects. This explanation for the evolution of senescence has not been widely accepted, since (as Hamilton himself noted) it does not seem capable of explaining the evidently pathological aspects of many aspects of aging (Rose 1991, pp. 70–71). Instead, most applications of Hamilton's formulae to the evolution of senescence have applied the same basic results to the mutation-accumulation and antagonistic pleiotropy theories (Charlesworth 1994, Chap. 5).

Hamilton also pointed out that the oversimplified model of changes to mortality or fecundity at just one age can easily be extended, by calculating the net change in r owing to small changes in vital statistics at a whole range of ages. Functional relations among fecundity and mortality rates, reflecting resource allocation or physiological constraints, can also be included in such calculations, although he himself did not do this. The inclusion of such constraints has led to the development of elaborate models of life-history evolution, which attempt to predict optimal patterns of age-specific reproduction, growth, and survival and to relate comparative data on life histories to the predictions of these models (*e.g.*, Stearns 1992; Charlesworth 1994, Chap. 5; McNamara and Houston 1996). Hamilton's (1966) method of calculating the sensitivity of r to age-specific changes in vital statistics, later applied to the equivalent matrix model of discrete-time populations (Demetrius 1969; Goodman 1971; Caswell 1989), is at the core of this enterprise. Somewhat ironically, reproductive value reappears in optimization models as a weighting function for the effect of a change in fecundity at a given age on mortality at that age (Schaffer 1974), and optimal life histories can be viewed as maximizing reproductive value at each age (Schaffer 1974; Charlesworth 1994, pp. 237–238).

Hamilton's analysis left one important gap, however. This concerns the validity of assuming that the Malthusian parameter r is indeed the correct measure of fitness for an age-structured population, in the sense that it accurately predicts the effect of selection on gene frequencies. No justification of this was provided by Fisher, who seems simply to have taken it for granted, as did most people who pioneered the theory of life-history evolution (*e.g.*, Lewontin 1965) and many distinguished theoretical population geneticists such as Kimura (*e.g.*, Kimura 1958), for whom continuous-time models offered technical convenience.

It is easy to define r for a particular genotype, as the solution to Equation 1 for a (hypothetical) population consisting entirely of individuals with the set of $l(x)$ and $m(x)$ values characteristic of the genotype in question; this is presumably what Fisher had in mind as the Malthusian parameter of a given genotype. It is also easy to see that, with competition among clonally reproducing genotypes, the genotype with the highest r will outcompete the rest, since this situation is simply equivalent to a set of populations growing at different rates. It is less easy to see how to model a sexually reproducing diploid population in which each parent produces a mixture of genotypes, especially as changes in genotype frequencies induced by selection must cause continual changes in age structure (Moran 1962, p. 90; Charlesworth 1970).

There is, thus, no obvious guarantee that the use of r as a fitness measure gives correct results. In fact, although Fisher characteristically made no reference to their work, Haldane (1927) and Norton (1928) had made great progress toward solving this problem. Haldane (1927) derived integral equations to represent the effects of selection on genotype frequencies in an age-structured population. He analyzed them by making the simplifying assumption that selection was weak and population growth was slow. Using some rather cumbersome algebra, he was able to obtain an approximate expression for the rate of change of gene frequency, in terms of the differences in lifetime expectations of offspring among genotypes. He returned to this problem at the end of his life (Haldane 1962).

Norton's (1928) paper is one of the most profound papers in both demography and population genetics. Harry Norton was a mathematician at Trinity College, Cambridge (UK), and a member of the Bloomsbury group of British intellectuals. *Eminent Victorians* was dedicated to him by Lytton Strachey. He is mentioned in Strachey's biography as the only person in the group who could hold his own with Bertrand Russell and John Maynard Keynes (Holroyd 1971). He had earlier anticipated Haldane's (1924) paper on the rate of change of gene frequency under selection, in a set of calculations published as an appendix to Punnett's (1915) book on

mimicry. Using integral equations similar to Haldane's, which Norton had derived independently in 1910 (Haldane 1927), he examined the asymptotic properties of a diploid, randomly mating population segregating for a single locus with two alleles. Under some simplifying assumptions, notably random mating with respect to age and genotype and no sex differences in vital statistics, the genotype with the highest r value will supplant the others if there is directional selection. With heterozygote advantage in r, a polymorphism is maintained; with heterozygote disadvantage, polymorphism is eliminated. He also showed that, with heterozygote advantage, the population ultimately approaches the neighborhood of a fixed gene frequency.

Later work, reviewed by Charlesworth (1994, Chaps. 3 and 4), has extended these pioneering analyses of age-structured populations. Sex differences in vital statistics, nonrandom mating, density-dependent modification of mortality and fecundity rates, and the effects of spatially and temporally fluctuating environments have all been included in the models. In the simplest case described above, when these complications can be neglected, we now know that the initial rate of increase of a nonrecessive rare mutant allele introduced into a large population is governed by its effect on the intrinsic rate of increase, even if its effect is arbitrarily large. In general, however, differences among genotypes in intrinsic rates of increase can be used only as approximate predictors of the rate of change of allele frequency under selection, although the approximation is very good if selection is weak.

Equilibrium frequencies of genotypes under the standard scenarios of population genetic models can, however, be calculated from equations that are of exactly the same form as those of the familiar discrete-generation models of deterministic population genetics (Crow and Kimura 1970), such that the Wrightian fitness weight for a genotype, w_i, is replaced by the expression

$$w_i = \int_0^\infty e^{-rx} l_i(x)\, m_i(x)\, dx, \qquad (7)$$

where r is the growth rate of the population as a whole, and $l_i(x)$ and $m_i(x)$ are the vital statistics for individuals of genotype i. If selection is weak, differences in the w_i among genotypes are approximately proportional to differences in the corresponding genotypic intrinsic rates, where the constant of proportionality is equal to the value of T for some standard genotype (Charlesworth 1994, p. 178).

It is interesting to note that the equilibrium gene frequency predicted from Equation 7 in the case of heterozygote advantage at a single locus with two alleles corresponds to the value that Norton (1928) showed is approached asymptotically. An exact analysis of Kimura's (1958) use of Malthusian parameters also enables Equation 7 to be recovered (Charlesworth 1970). Bill Hamilton would probably have regarded these results as minor technicalities, but it is satisfying that the assumptions that underly the use of r in explaining the evolution of senescence and life-history patterns can be made explicit and analyzed in population genetic terms.

Our understanding of the evolution of senescence is, at one level, very complete; we know that senescence is an evolutionary response to the diminishing effectiveness of selection with age and that this explains many aspects of the comparative biology of senescence (Williams 1957; Rose 1991; Charlesworth 1994; Ricklefs 1998). On the other hand, it is at present hard to be sure which of the two most likely important mechanisms by which this property of selection influences senescence (accumulation of late-acting deleterious mutations or fixation of mutations with favorable early effects and deleterious late effects) plays the more important role, especially as these are not mutually exclusive possibilities. If senescence does not take its toll, perhaps a future *Perspectives* by this author will provide an update on this problem.

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