*Evolution*, 57(7), 2003, pp. 1478–1488

# ANTAGONISTIC PLEIOTROPY, MORTALITY SOURCE INTERACTIONS, AND THE EVOLUTIONARY THEORY OF SENESCENCE

PAUL D. WILLIAMS[1] AND TROY DAY[2]
[1]*Department of Zoology, University of Toronto, 25 Harbord Street, Toronto, Ontario M5S 3G5, Canada*
*E-mail: paulw@zoo.utoronto.ca*
[2]*Departments of Mathematics and Biology, Jeffery Hall, Queen's University, Kingston, Ontario K7L 3N6, Canada*
*E-mail: tday@mast.queensu.ca*

*Abstract.*—Most theoretical work on the evolution of senescence has assumed that all individuals within a population are equally susceptible to extrinsic sources of mortality. An influential qualitative prediction based on this assumption is Williams's hypothesis, which states that more rapid senescence is expected to evolve when the magnitude of such extrinsic mortality sources is increased. Much evidence suggests, however, that for many groups of organisms externally imposed mortality risk is a function of an organism's internal condition and hence susceptibility to such hazards. Here we use a model of antagonistic pleiotropy to investigate the consequences that such interactions (between environmental hazard and internal condition) can have for Williams's hypothesis. As with some previous theory examining noninteractive extrinsic mortality sources, we find that an increase in interactive extrinsic sources of mortality makes it less likely that an individual will survive from birth to any given age, weakening selection against physiological deterioration at all ages and thus favoring more rapid senescence. However, an increase in interactive mortality sources also typically strengthens selection against physiological deterioration at any age, given an individual has survived to that age, because it reduces the fitness of poor-condition individuals more than good-condition individuals. These opposing effects are not felt equally at all ages, with the latter predominating at early ages. The combined effects can therefore result in the novel prediction that an increase in interactive extrinsic mortality sources can select for slower senescent deterioration early in life but more rapid deterioration late in life.

*Key words.*—Antagonistic pleiotropy, evolution, extrinsic hazard, interactions, senescence.

Received October 11, 2002. Accepted January 2, 2003.

Senescence has been defined as a persistent decline in the somatic function of an organism with increasing chronological age, leading to decreased survival probability and/or fecundity (Abrams 1991; Rose 1991; Partridge and Barton 1993, 1996). Evolutionary theories of senescence are predicated on the premise that, even in the absence of decreases in age-specific fitness components due to intrinsic deterioration, the force of selection on any trait declines as the age of expression of that trait increases. This occurs because the probability of survival to any given age decreases as that age increases due to externally imposed mortality factors such as accidents, predation, or parasitism (Medawar 1952; Williams 1957; Hamilton 1966; Charlesworth 1994). A number of mechanisms that could account for senescence have been proposed, with both the antagonistic pleiotropy and the mutation accumulation hypotheses receiving considerable attention. Empirical studies have generated evidence for both theories (pleiotropy: Rose and Charlesworth 1980, 1981; Walker et al. 2000; mutation accumulation: Mueller 1987; Charlesworth and Hughes 1996; Pletcher et al. 1998), although pleiotropy appears to be more strongly supported at present (Partridge 2001).

A putative implication of evolutionary models of senescence is the often-quoted Williams's hypothesis (after the pioneering work of G. C. Williams) in which higher extrinsic (environmentally imposed) mortality rates are predicted to result in the evolution of higher rates of intrinsic, or senescent, mortality (Williams 1957; Edney and Gill 1968; Promislow 1991; Rose 1991; Stearns 1992). A number of studies have sought to confirm the validity of evolutionary theories of aging by testing this prediction through selection experiments (Stearns et al. 2000) and intraspecific/sister species comparative studies (Austad 1993; Tatar et al. 1997; Dudycha and Tessier 1999), as well as by appealing to patterns of longevity in broad, cross-taxa contrasts (Austad and Fisher 1991; Promislow 1991; Keller and Genoud 1997; Ricklefs 1998). Most of these studies report results that conform to this prediction, although a recent investigation with field crickets (Gray and Cade 2000) failed to generate any supportive data. Another recent study, with mice stocks from island and mainland populations (Miller et al. 2002), produced results that run counter to those of Austad's (1993) from his work with island and mainland opossums, while some preliminary work with guppy populations from high- and low-predation-risk environments by Reznick et al. (2001) may also prove to be an important counterexample.

One potential difficulty with many such tests, however, arises from an ambiguity in what is meant by ''extrinsic'' mortality. Following Partridge (1989), Abrams (1993) suggested age- and condition-independent as the most consistent operational definition of extrinsic, while also pointing out that sources of mortality generally thought of as extrinsic in empirical investigations, especially in comparative studies involving natural populations, are probably not condition-independent in this strict sense. That is, most of these sources are likely modified by a condition-dependent component, where individuals of poorer condition experience enhanced susceptibility relative to those in better condition. For example, studies of wolf-ungulate predator-prey ecology have consistently demonstrated a condition-dependent component to predation risk, with very old, very young, and debilitated members of the prey species being differentially vulnerable (Fuller and Keith 1980; Bjorge and Gunson 1989; Boyd et al. 1994; Mech et al. 1995). Age-related immunological com-

promises have also been empirically investigated in both wild and captive populations. While quantifying age-related differences in physiological response to infection with *Candida albicans,* Ashman et al. (1999) found that 64-week-old mice exhibit significantly greater levels of morbidity, as well as more rapid progression in a number of disease indicators, than a matched group of 6-week-olds. A recent study (Møller and de Lope 1999) of senescent changes in the barn swallow, *Hirundo rustica,* suggests the presence of age-related immunity decrements in birds as well. Here the authors found that, after an initial period of high parasite abundance during the first and second years of life, loads decreased in the third and fourth years and then increased to high levels at five years and older. Beyond the direct mortality effect of greater susceptibility to pathogens, higher parasite burdens might also impose additional costs through, for example, diminished foraging ability and/or increased risk of predation (Lafferty and Morris 1996; Bakker et al. 1997). Given the ubiquity of parasitism in natural populations, immunosenescence is likely an important component of condition-dependent mortality risk.

Abrams (1993) has previously suggested that reduced senescence should evolve whenever the expression of senescence greatly enhances an organism's susceptibility to environmentally imposed hazards, although he did not analyze the situation in any detail. In a similar vein, Finch (1990) pointed out that even relatively mild joint and/or bone deterioration might greatly increase a bird's probability of succumbing to environmental hazards and might help to explain the slow rate of senescence in many avian lineages (Finch 1990; Holmes and Austad 1995). Nevertheless, the potential importance of interactions between organismal condition and environmental hazard appears generally to have been underappreciated in most experimental studies of senescence evolution.

These ideas indicate that a more complete theory of senescence evolution needs to consider the consequences that changes in interactive types of environmental hazard can have for optimal senescence schedules. To address this issue, we develop a model of the antagonistic pleiotropy mechanism dealing explicitly with the greater susceptibility of senescent individuals to environmental hazards. We then use our results to reconsider Williams's hypothesis within this framework. In a theory that explicitly includes interactions, however, we need to be more circumspect about what is meant by an increase in extrinsic mortality rate. Mechanistically, it is more exact to speak of increases in some environmental hazard factor (predator density for example) and to then determine whether, and under what conditions, this produces a mortality effect. The quantification of such effects, however, is also made more problematic when interactions are considered. If an increase in mortality rate with age is due to a decline in physiological state that interacts with environmental hazard then, although senescence may be measurable (as declines in physiological functions) in a laboratory environment, mortality effects could be undetectable unless measurements are made under more stressful (natural) conditions (Roach 2001).

In developing the theory, expressions describing how the evolutionarily stable level of senescent deterioration changes in response to changes in the hazard level imposed by environmental sources will be obtained. In this paper, only the effects of single pleiotropic mutations that provide a fecundity benefit at one age at the cost of increased physiological deterioration beginning at some later age will be considered. Senescence patterns are likely shaped by the effects of numerous such pleiotropic mutations, and a more comprehensive investigation would have to include this consideration. Nevertheless, this simplest case provides the foundation for more general investigations.

## Interactions between Intrinsic State and Extrinsic Hazard

The modeling approach we follow is to begin with a fitness measure, $W$, which is a function of those demographic variables that determine an organism's life-history schedule, that is, $l(j)$, $m(j)$, $j = 1, \ldots, \infty$. Here $\infty$ is the maximum reproductive age class, $l(j)$ is the probability of survival from the onset of reproduction (age class 1) through age class $j$, and $m(j)$ is the average fecundity of an individual in age class $j$. Letting $\mu(k)$be the mortality rate at age class $k$, the probability of survival through age class $j$ can be written as

$$l(j) = \exp\left[-\sum_{k=1}^{j} \mu(k)\right]. \quad (1)$$

We model $\mu(k)$ to allow for mortality effects due to the independent action of environmental sources and senescent declines in condition, as well as interactions between the two through the introduction of a multiplicative term:

$$\mu(k) = a_1\hat{\delta} + a_2\delta + a_3c(k) + a_4\delta c(k). \quad (2)$$

Here $\hat{\delta}$ is a measure of condition-independent environmental hazard, $\delta$ a measure of condition-dependent environmental hazard, and $c(k)$ a measure of an organism's age-specific state of physiological deterioration (so that high values of $c(k)$ imply a large degree of deterioration); and the positive constants $a_i$ convert these measures into mortality rates. Note that when $a_3 = 0$ all senescent mortality is effected through an interaction with environmental hazards, whereas $a_4 = 0$ corresponds to the case where senescent mortality is environment independent. By this definition of $\mu(k)$, the probability of survival through age class $j$ is given by

$$l(j) = \exp[-(a_1\hat{\delta} + a_2\delta)j - (a_3 + a_4\delta)jA(j)], \quad (3)$$

where $jA(j) = \Sigma_{k=1}^{j} c(k)$ is an individual's cumulative state of physiological deterioration over the first $j$ age classes. In general, an individual's state of physiological deterioration at age class $k$, $c(k)$, is the sum of the increments in deterioration at each age class up to and including age class $k$, which we denote by $\chi(1), \ldots, \chi(k)$, respectively, so that we can also write $jA(j) = \Sigma_{k=1}^{j}, (j - k + 1)\chi(k)$. By defining $c(k)$ in this way we follow Abrams's (1991, 1993) definition of a senescent change, in that any change in $\chi(i)$ alters an individual's age-specific state of physiological deterioration not only at age $i$ but for all subsequent ages as well.

## An Evolutionary Model of Antagonistic Pleiotropy

In our model of antagonistic pleiotropy, we consider the effect of selection upon the optimal level of senescent de-

terioration subject to some trade-off between age-specific fecundity and condition. To explore Williams's hypothesis, we first calculate the optimal level of senescent deterioration in the model and then calculate how this optimal level changes with an increase in the level of environmental hazard.

Our analysis considers alleles that affect some underlying character, $z$, which increases fecundity at some age $y$, $m(y)$, and also increases senescent deterioration at age $i$, $\chi(i)$, where $i > y$. Evidence for such a trade-off has appeared in numerous works with *Drosophila melanogaster* (Luckinbill et al. 1984; Rose 1984; Zwaan et al. 1995; Partridge et al. 1999) and other taxa (Rose 1991). For illustrative purposes, we offer the following as a possible mechanistic determinant of this kind of trade-off: the character $z$ is interpreted as activity rate; a fecundity benefit at age $y$ is obtained by increasing foraging (and hence activity) rate to meet the energy requirements for greater reproductive output. However, such increased activity rates cause irreversible metabolic and/or mechanical damage, and by definition an increase in senescence, whose effects are first felt at some later age, $i$.

Over evolutionary time, new alleles will continue to replace the resident alleles until a fitness maximum with respect to the character $z$ is reached. This maximum is defined by the conditions

$$\frac{\partial W}{\partial z} \equiv V = \frac{\partial W}{\partial m(y)}\frac{dm(y)}{dz} + \frac{\partial W}{\partial \chi(i)}\frac{d\chi(i)}{dz} = 0 \quad \text{and} \tag{4a}$$

$$\frac{\partial^2 W}{\partial z^2} = \frac{\partial V}{\partial z} < 0, \tag{4b}$$

where all terms are evaluated at the optimum, $z^*$. Here $V$ is the difference between the fecundity benefit obtained ($[\partial W/\partial m(y)][dm(y)/dz]$) and the senescent cost incurred ($-[\partial W/\partial \chi(i)][d\chi(i)/dz]$) given an increase in the trait value $z$, and condition (4a) states that at a maximum, $z^*$, these costs and benefits are balanced. Note that the fecundity-senescence trade-off implies that both $d\chi(i)/dz$ and $dm(y)/dz$ are positive.

In response to a sufficiently small change in environmental hazard level, $\zeta$ (where $\zeta$ is a dummy variable referring to either noninteractive, $\hat{\delta}$, or interactive, $\delta$, hazard level), this evolutionary optimum will increase, decrease, or remain the same according to whether

$$\frac{\partial z^*}{\partial \zeta} = -\frac{\partial V}{\partial \zeta}\Big/\frac{\partial V}{\partial z} \tag{5}$$

for $\zeta = \hat{\delta}, \delta$ (arrived at by implicitly differentiating condition 4a) is positive, negative, or zero, respectively. As long as condition (4b) for a maximum is met, equation (5) implies that the sign of $\partial V/\partial \zeta$ completely determines the sign of $\partial z^*/\partial \zeta$. Although we assume this condition holds in the following analyses, both the $m(y) - z$ and the $\chi(i) - z$ relationships must satisfy certain criteria for a maximum to exist (Appendix 1). Expanding the numerator of (5) gives

$$\frac{dz^*}{d\zeta} \propto \frac{\partial^2 W}{\partial \zeta \partial m(y)}\frac{dm(y)}{dz} + \frac{\partial^2 W}{\partial \zeta \partial \chi(i)}\frac{d\chi(i)}{dz}, \tag{6}$$

as the expression governing the direction of change in $z^*$. Now, because senescent deterioration, $\chi(i)$, is positively related to $z$, the direction of change in $\chi(i)$ is the same as that of $z$. Therefore, the sign of (6) tells us whether the degree of senescent deterioration has increased, decreased, or remained the same with an increase in environmental hazard.

In the following sections we explore the predictions of the above general model by considering two commonly employed fitness measures: the intrinsic rate of increase, $r$, and lifetime reproductive output, $R$.

## Measures of Fitness

### *Fitness Is Given by r*

Most classical discussions of senescence evolution (Hamilton 1966; Charlesworth 1994) have assumed the intrinsic rate of increase, $r$, given implicitly as the solution to the (discrete time) Euler-Lotka (E-L) equation, $\Sigma_{j=1}^{\infty} \exp(-rj)l(j)m(j) = 1$, to be the relevant measure of fitness. Note that, by this indexing system, an organism must survive through an age class to obtain the fecundity associated with that age class. Furthermore, because we consider only trade-offs between reproductive ages, indexing begins at the first reproductive age class. The sensitivity of $r$ to changes in age-specific fecundity and age-specific senescent deterioration that affects mortality can be calculated by implicitly differentiating the E-L equation to obtain

$$\frac{\partial r}{\partial m(y)} = \frac{1}{T}\exp(-ry)l(y) \quad \text{and} \tag{7}$$

$$\frac{\partial r}{\partial \chi(i)} = -\frac{(a_3 + a_4\delta)}{T}\sum_{j=i}^{\infty} F(i, j), \tag{8}$$

respectively, where $F(i, j) = (j - i + 1)\exp(-rj)l(j)m(j)$ and $T = \Sigma_{j=1}^{\infty} F(1, j)$, the mean age of mothers of a newly born set of individuals, measures generation time (Hamilton 1966).

When all else is held constant, an increase in fecundity will increase fitness, and expression (7) measures the selection intensity acting to favor mutations that provide such a benefit. Similarly, equation (8) gives the fitness effect of an increase in senescent physiological deterioration beginning at age $i$, where the negative sign results from the fact that increases in senescent deterioration can only reduce fitness (or leave it unchanged). The absolute value of equation (8) (i.e. $-\partial r/\partial \chi(i)$) is the fitness cost of an increase in senescent deterioration and provides a measure of the degree to which selection will oppose such increases. Note that (7) and the absolute value of (8) are both decreasing functions of age, reflecting the diminishing strength of selection on late acting life history changes.

#### *Changes in environmental hazard levels*

*Condition-independent environmental hazard.*—Differentiating equations (7) and (8) with respect to condition-independent environmental hazard, $\hat{\delta}$, we find that

$$\frac{\partial}{\partial \hat{\delta}}\left(\frac{\partial r}{\partial m(y)}\right) = 0 \quad \text{and} \tag{9}$$

$$\frac{\partial}{\partial \hat{\delta}}\left(\frac{\partial r}{\partial \chi(i)}\right) = 0. \tag{10}$$

Hence, the evolutionary optimum, $z^*$, and thus the optimal level of senescent deterioration, is unaffected by changes in this component of environmental hazard. As previously dis-

cussed by Abrams (1993), this curious lack of accord with Williams's hypothesis arises due to compensatory changes in the fitness measure $r$. More exactly, increasing condition-independent hazard (from $\hat{\delta}$ to $\hat{\delta} + d\hat{\delta}$) increases period mortality rates (from $\mu(k)$ to $\mu(k) + a_1 d\hat{\delta}$), resulting in a greater discounting of future reproduction. But if $r$ measures fitness, then future reproduction is also discounted by this population growth rate at each age, and an increase in condition-independent hazard will decrease the population growth rate, from $r$ to $r + d\hat{\delta}(\partial r/\partial\hat{\delta}) = r - a_1 d\hat{\delta}$, exactly compensating for the increase in mortality: the period discounting rate (mortality rate plus growth rate) remains unchanged.

*Condition-dependent environmental hazard.*—Increases in condition-dependent environmental hazard produce effects on fecundity benefits and senescent costs given by

$$\frac{\partial}{\partial\delta}\left(\frac{\partial r}{\partial m(y)}\right) = a_4\left[y\left(\frac{Q}{T} - A(y)\right) + \frac{Q}{T}\left(\frac{\tilde{Q}}{Q} - \frac{\tilde{T}}{T}\right)\right]\frac{\partial r}{\partial m(y)} \qquad (11)$$

and

$$\frac{\partial}{\partial\delta}\left(-\frac{\partial r}{\partial\chi(i)}\right) = a_4\left\{\frac{(a_3 + a_4\delta)}{T}\left[\sum_{j=i}^{\infty} j\left(\frac{Q}{T} - A(j)\right)F(i, j) + \frac{Q}{T}\left(\frac{\tilde{Q}}{Q} - \frac{\tilde{T}}{T}\right)\sum_{j=i}^{\infty} F(i, j)\right] + \frac{1}{T}\sum_{j=i}^{\infty} F(i, j)\right\}, \qquad (12)$$

where $\tilde{T} = \Sigma_{j=1}^{\infty}, jF(1, j)$, $Q = \Sigma_{j=1}^{\infty}, A(j)F(1, j)$ (the expected state of cumulative deterioration experienced by mothers of a newborn set of individuals), and $\tilde{Q} = \Sigma_{j=1}^{\infty} jA(j)F(1, j)$. By equation (11), fecundity benefits will increase/decrease when the sign of the quantity in the square bracket is positive/negative. As was the case for condition-independent hazard, changes in the population growth rate affect all age classes equally (so that $r$ is reduced to $r + (\partial r/\partial\delta)d\delta = r - (a_2 + a_4 Q/T)d\delta$). However, period mortality rates do not change a constant amount (i.e., $\mu(k)$ becomes $\mu(k) + [a_2 + a_4 c(k)]d\delta$). In particular, those age classes characterized by greater senescent deterioration (i.e., older age classes) experience a greater discounting because the increased hazard affects them the most. The net effect of the changes in $r$ and $\mu(k)$ result in the total change in period discounting rates, $-a_4[Q/T - c(k)]d\delta$, and hence the cumulative effect of such changes, $-a_4 y[Q/T - A(y)]d\delta$, being negative for early age classes and positive for later ones. That is, in the high-hazard environment, early age classes are discounted less and later age classes are discounted more. The age at which this change in discounting rates switches from negative to positive is not easily determined, because it depends on how an organism's state of deterioration changes over time. Nevertheless, if fecundity benefits are received in the first age class (so that $y = 1$), the change in discounting must be negative (or zero, if an organism's state of senescent deterioration remains unchanged throughout its life), and discounting rate changes will increase (or not change, respectively) the value of fecundity benefits in the more hazardous environment.

The quantity $Q/T(\tilde{Q}/Q - \tilde{T}/T)$ arises from changes in generation time due to changes in both the population growth rate and period mortality rates (that is, changes in period discounting rates) and is positive (zero in the absence of senescent deterioration) as long as $A(j)$ is nondecreasing. This is because such changes decrease generation time and, when considered alone, smaller generation time elevates fecundity benefits (by expression 7).

Equation (11) states that the direction of change in fecundity benefits is determined by the sum of these two effects (changes in period discounting rates and changes in generation time), while indicating that an increase in fecundity will be more valuable in the more hazardous environment provided it occurs at an early enough age, but may possibly be less valuable if it occurs late enough.

A nearly identical analysis as the one above also holds for the terms in the square bracket of equation (12). However, here we have that, in addition to the effects due to altered period discounting rates and diminished generation time, an increase in condition-dependent hazard also increases the cost of a unit increase in senescent deterioration, given an individual has survived to the age at which this deterioration occurs, because the more senescent individuals will be more susceptible to the increased hazard. This tends to enhance the cost of senescent deterioration in the more hazardous environment, regardless of age, and accounts for the last positive sum in the braces of (12) (i.e., $\Sigma_{j=i}^{\infty} F(i, j)/T$). As a result, an increase in senescent deterioration will be more costly at early ages in the more hazardous environment, and this might be true at later ages as well, depending on the details of the situation. In particular, if senescent costs are paid starting in the first reproductive age class (so that $i = 1$), the left side of equation (12) reduces to $a_4$, and senescent costs will be greater in the high-hazard environment.

The above arguments provide some insight into how fitness benefits and costs change when condition-dependent hazard increases, with the general trend that both tend to increase when they are experienced early enough. Late in life, benefits will tend to decrease, while costs might or might not decrease. But the decisive factor in determining how selection will act on the optimal level of senescent deterioration is how these benefits and costs change relative to one another. Substituting the fitness sensitivity equations (11) and (12) into expression (6), we find that the evolutionarily optimal level of senescent deterioration will increase/decrease when the sign of

$$\frac{dz^*}{d\delta} \propto -a_4\frac{d\chi(i)}{dz}\left\{(a_3 + a_4\delta)\sum_{j=i}^{\infty}\left[j\left(\frac{Q}{T} - A(j)\right) - y\left(\frac{Q}{T} - A(y)\right)\right]F(i, j) + \sum_{j=i}^{\infty} F(i, j)\right\} \qquad (13)$$

is positive/negative. Note that, as indicated by Abrams (1993), generation time effects vanish when cost and benefit expressions are combined in a pleiotropy model (this fact also follows directly from equations 4a and 5: see Appendix 2).

Ignoring the second sum in (13) for the moment, and restricting our attention to the case when $y < i$, it is clear that, if senescent costs are paid at a late enough time so that $(Q/T - A[i])$ is negative, then the expression in the square bracket

of (13), and hence the first sum in (13), is guaranteed to be negative. This is true regardless of the age at which the fecundity benefit is obtained (with the proviso that it occurs before the senescent deterioration), although the result is strengthened when it occurs early enough so that $(Q/T - A[y])$ is positive (i.e., early enough so that the fecundity benefit is more valuable in the high-hazard environment). This implies that, for a fixed benefit age, it becomes more likely for the first sum in (13) to be negative as the age-of-onset of the senescent cost is increased and suggests the following general statement: Given an increase in condition-dependent hazard, the likelihood that Williams's hypothesis will give the correct evolutionary prediction increases with the lag time between when the fecundity benefit is obtained and the senescent cost is paid. Note that this statement assumes some degree of pre-existing senescence, since in the absence of any change in senescent deterioration (so that $A(j)$ is constant) the expression in the square bracket of (13) vanishes, resulting in a negative sign for (13) and giving a prediction that runs counter to Williams's hypothesis. This result suggests a second general statement: Given an increase in condition-dependent hazard, the likelihood that Williams's hypothesis gives the correct evolutionary prediction increases as the rate of pre-existing senescence increases.

Of course, when we include the second positive sum in (13) it can change the sign of the whole expression in the braces to positive, and so predict a decrease in senescent deterioration (because this whole expression is multiplied by the parameter $-a_4$). However, prior to any increase in condition-dependent hazard, the increase in period mortality rates due to an increase in physiological deterioration is given by $(a_3 + a_4\delta)dc(k)$, while after such an increase in condition-dependent hazard (so that $\delta$ becomes $\delta + d\delta$) the increase in mortality rate is $(a_3 + a_4\delta)dc(k) + a_4 d\delta dc(k)$. The extra increase in mortality rate due to increased hazard, $a_4 d\delta dc(k)$, is fixed with respect to $a_3$ and $\delta$, and so increases in either of these parameters diminishes the relative contribution of this extra increase to mortality rate increases. Thus, in a situation where the expression in the square bracket is negative, a large direct mortality effect (i.e., mortality not mediated by external hazard) due to physiological deterioration (i.e., large $a_3$) and/or large condition-dependent hazard (i.e., large $\delta$) would increase the likelihood for (13) to be positive, and hence for Williams's hypothesis to give the correct prediction.

Although the above statements do provide some very general ideas about how we might expect optimal senescence patterns to respond to changes in condition-dependent deterioration, they clearly do not rule out the possibility of other behaviors. In view of this, we will explore the issue further by considering a number of numerical examples. First, however, we present the corresponding results when using total reproductive output to measure fitness.

### *Fitness Is Given by R*

Determining the conditions under which expected lifetime reproductive output, $R = \sum_{j=1}^{\infty} l(j)m(j)$, provides an appropriate measure of fitness has received the attention of numerous authors (reviewed in Brommer 2000). In general, the use of $R$ assumes that generation time is irrelevant (implying that the intrinsic rate of increase is close to zero), so that it is only the total number of offspring produced during an individual's lifetime that determines fitness (Stearns 1992). Furthermore, the way that density dependence acts to keep population numbers at a steady state (so that $R$ is approximately one) also has an influence on which fitness measure is maximized by natural selection (Mylius and Diekmann 1995).

Results obtained from using expected lifetime reproductive output as the relevant fitness measure are somewhat more transparent than those obtained using the intrinsic rate of increase, because we do not have to deal with any compensatory changes in the population growth rate. In this case our sensitivity expressions are

$$\frac{\partial R}{\partial m(y)} = l(y) \quad \text{and} \tag{14}$$

$$\frac{\partial R}{\partial \chi(i)} = -(a_3 + a_4\delta) \sum_{j=i}^{\infty} \tilde{F}(i, j), \tag{15}$$

where $\tilde{F}(i, j) = (j - i + 1)l(j)m(j)$. Here we again consider how these sensitivities change in response to changes in the different types of environmental hazard separately.

#### *Changes in environmental hazard levels*

*Condition-independent environmental hazard.*—Increases in condition-independent hazard levels induce the responses

$$\frac{\partial}{\partial \hat{\delta}}\left(\frac{\partial R}{\partial m(y)}\right) = -a_1 y \frac{\partial R}{\partial m(y)} \quad \text{and} \tag{16}$$

$$\frac{\partial}{\partial \hat{\delta}}\left(-\frac{\partial R}{\partial \chi(i)}\right) = -a_1(a_3 + a_4\delta) \sum_{j=i}^{\infty} j\tilde{F}(i, j) \tag{17}$$

in the benefit and cost expressions. Equations (16) and (17) show that both benefits and costs are reduced in the high-hazard environment, because the probability of experiencing either is reduced when the mortality rate due to increased hazard level increases. In other words, the period discounting rates are now simply the period mortality rates rather than the mortality rate plus the population growth rate. Therefore, the period discounting rates now decrease, rather than remain unchanged as they did in the case when $r$ measured fitness. However, assuming that the fecundity benefits are obtained earlier than the senescent costs are paid (so that $y < i$), the reduction in the benefits is less than that of the costs, because the left side of (17) will be less than $-a_1 y[-\partial R/\partial \chi(i)]$. The prediction, in this case, is thus for the optimal level of senescent deterioration to increase, in agreement with Williams's hypothesis. This result, in conjunction with the situation when $r$ measured fitness, suggests that an implicit assumption in verbal arguments in support of Williams's hypothesis is a notion of how density dependence acts to regulate populations (Abrams 1993), and hence which fitness function accurately measures evolutionary success.

*Condition-dependent environmental hazard.*—When environmental hazard is condition-dependent, the sensitivity expressions change according to

$$\frac{\partial}{\partial \delta}\left(\frac{\partial R}{\partial m(y)}\right) = -a_4 y\left(\frac{a_2}{a_4} + A(y)\right)\frac{\partial R}{\partial m(y)} \quad \text{and} \tag{18}$$

$$\frac{\partial}{\partial \delta}\left(-\frac{\partial R}{\partial \chi(i)}\right) = a_4\left[-(a_3 + a_4\delta)\sum_{j=i}^{\infty} j\left(\frac{a_2}{a_4} + A(j)\right)\tilde{F}(i, j) + \sum_{j=i}^{\infty}\tilde{F}(i, j)\right]. \tag{19}$$

In this case we again have that the fitness benefit expression decreases. The reason is that, again, the period discounting rates (which consist solely of the period mortality rates) increase at all ages in the more hazardous environment. Similarly, the effect of this increase in period discounting rates is to lessen the cost of senescent deterioration (which accounts for the first sum in eq. 19), because the probability of ever having to experience its negative fitness effect has diminished. The first sum in (19) is strictly less than $-a_4 i[a_2/a_4 + A(i)][-\partial R/\partial \chi(i)]$, and restricting our attention to the case when benefits are received at some time before costs must be paid (so that $y < i$) implies that, in the absence of any other effects, costs will be reduced more than benefits, and greater senescent deterioration will be favored. This observation simply recapitulates the result of the preceding section. In the present case, however, a positive term appears in expression (19), as it did when $r$ measured fitness, again because increases in condition-dependent hazard elevate the cost of a unit increase in senescent deterioration and therefore raise the cost of senescent deterioration in the more hazardous environment. How costs change thus depends on the sum of these two opposing effects.

Substituting the sensitivity expressions (18) and (19) into equation (6) we obtain

$$\frac{dz^*}{d\delta} \propto a_4\frac{d\chi(i)}{dz}\left\{(a_3 + a_4\delta)\sum_{j=i}^{\infty}\left[jA(j) - yA(y) + \frac{a_2}{a_4}(j - y)\right]\tilde{F}(i, j) - \sum_{j=i}^{\infty}\tilde{F}(i, j)\right\}, \tag{20}$$

as the expression governing the direction of change in the evolutionarily optimal level of senescent deterioration. The first sum in the braces of (20) is the total amount of extra discounting that the cost expression experiences, relative to the benefits, in the high-hazard environment and is clearly always nonnegative. Thus, the larger this extra discounting is, the more likely it is that Williams's hypothesis will correctly predict the direction of evolution of senescent deterioration. Additionally, as was the case when $r$ measured fitness, an increase in condition-dependent hazard increases the fitness cost of a unit increase in senescent deterioration, given that an individual has survived to the age at which this deterioration occurs, and this effect is quantified by the second sum in (20). This implies that any parameter combinations that inflate this extra discounting, relative to the extra cost, or decrease the extra cost, relative to the discounting, will tend to make Williams's hypothesis more likely to be realized.

By (20) we have that $z^*$ will certainly increase whenever the inequality $(a_3 + a_4\delta)[iA(i) - yA(y)] \geq 1$ implying that: Given an increase in condition-dependent mortality, Williams's hypothesis is more likely to be realized when pre-existing senescence proceeds rapidly. Thus, as was the case with $r$, rapid senescence increases the likelihood that Williams' hypothesis provides the correct evolutionary prediction. This occurs because senescent deterioration contributes toward the greater discounting of both fecundity benefits and senescent costs in the high-hazard environment, but because costs feel this discounting for a longer period, increased senescent deterioration discounts costs more.

Also by (20) we have that the optimum will certainly increase whenever the inequality $(a_2\delta + a_2a_3/a_4)(i - y) > 1$ is satisfied. Since the expression on the left increases as $(i - y)$ increases, we again have a prediction identical to the case when $r$ measured fitness: Given an increase in condition-dependent hazard, the likelihood that Williams's hypothesis will give the correct evolutionary prediction increases with the lag time between when the fecundity benefit is obtained and the senescent cost is paid. This inequality also implies that large values for any or all of $a_2$, $a_3$, and $\delta$ increase the probability that Williams's hypothesis will be realized. An argument identical to the one when $r$ measured fitness shows that large $a_3$ and/or $\delta$ diminish the relative contribution of the extra increase (due to increased hazard) in period mortality rate increases due to increased deterioration, $a_4 d\delta dc(k)$, assuming an organism survives to pay the fitness cost of increased physiological deterioration. Large values for $a_2$ also make Williams's prediction more likely for an identical reason as rapid senescent deterioration: the discounting of costs and benefits due to $a_2$ (or $\delta$) is greater for costs and increases in this parameter make this difference greater. Since $a_2\delta$ is the condition-independent component of mortality due to condition-dependent hazard, this result, coupled with that of the previous section, suggests another general observation: Given an increase in condition-dependent hazard, a high risk of condition-independent mortality and/or a large direct mortality effect due to physiological deterioration increase the likelihood that Williams's hypothesis will give the correct evolutionary prediction.

Again, as was the case when $r$ measured fitness, the preceding statements are not meant as rigorously derived predictions. Rather, they are meant to provide a rough indication of the environmental and/or organismal conditions under which we might expect Williams's hypothesis to correctly predict evolutionary outcomes. In the next section we consider a number of numerical examples to more completely explore alternate outcomes.

We close this section by noting that, although we lack precise results about how the optimal level of senescent deterioration should respond to condition-dependent environmental hazard manipulations, the discussions of the preceding sections do highlight two important themes: (1) The age at which costs and benefits are expressed (i.e., timing effects) are important determinants of how these costs and benefits change given an increase in condition-dependent hazard; and (2) pre-existing patterns of senescent deterioration are likely to strongly influence the way that costs and benefits will respond to altered environmental hazard levels.

## Numerical Examples

In this section we use some numerical calculations to consider how pre-existing senescence and fecundity schedules

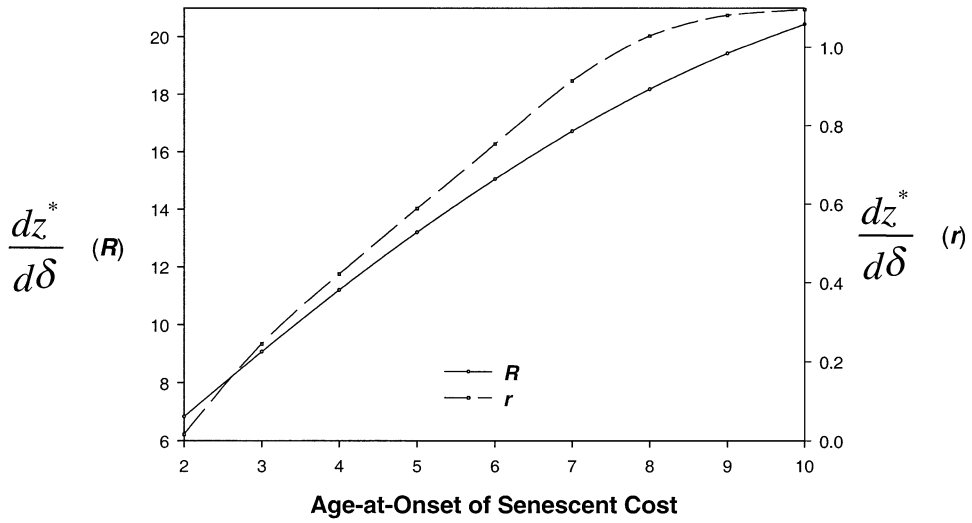


FIG. 1. Plot of the change in the optimum, $z^*$, given a change in condition-dependent environmental hazard level versus age-at-onset of senescent cost. For these particular sets of parameter values, the optimum always increases given an increase in environmental hazard level. *r*: $\alpha_1 = 1$; $\beta_1 = 1$; $\beta_2 = 1$; $\beta_3 = 0.25$; $a_1 = 0.01$; $a_2 = 0$; $a_3 = 0.05$; $a_4 = 0.05$; $\hat{\delta} = 0$; $\delta = 1$. *R*: $\alpha_1 = 1$; $\beta_1 = 0.5$; $\beta_2 = 0.5$; $\beta_3 = 2$; $a_1 = 0.1$; $a_2 = 5$; $a_3 = 0.01$; $a_4 = 0.1$; $\hat{\delta} = 0$; $\delta = 0.1$.

can affect predictions of senescence evolution given an increase in condition-dependent hazard level. In all examples, fecundity benefits are obtained during the first reproductive age class ($y = 1$), and the change in the evolutionary optimum given a change in condition-dependent environmental hazard levels, $dz^*/d\delta$, is plotted for all possible ages-at-onset of senescent deterioration.

As indicated in the discussion of equation (5), some choices must be made regarding the functional forms of the $m(y) - z$ and $\chi(i) - z$ relationships. For all calculations, we assume that senescent deterioration is a linearly increasing function of $z$ so that $\chi(i) = \alpha_1 z$, for some $\alpha_1 > 0$, and that fecundity has a diminishing returns relationship with $z$, so that $m(y) = \beta_1 + \beta_2(1 - e^{-\beta_3 z})$, where $\beta_1 \geq 0$ and $\beta_2, \beta_3 > 0$. We choose a linear $\chi(i) - z$ relationship since this is the simplest form that does not violate the conditions required for a maximum to exist (see Appendix 1). The diminishing returns $m(y) - z$ relationship, where each unit increase in fecundity requires successively greater investment in the trait of interest ($z$), is likely a reasonable description for many systems. Such a relationship could result from, for example, the existence of a maximum reproductive output at any given age. This maximum might be set by a strictly mechanical limit to the number of zygotes that can be carried. If this were the case, then an organism might continue to invest in increased foraging effort without obtaining any fecundity benefit.

For simplicity, fecundity is assumed to be constant for all ages other than the first age class ($y = 1$), when a fecundity benefit can be obtained via the trade-off with senescent deterioration, so that $m(n) = \beta_1$ for all $n \neq y$. Senescent deterioration beginning at all ages other than the age of interest (age $i$) is assumed to be zero, so that $c(k)$ is a step function at age $i$ given by

$$c(k) = \begin{cases} 0, & \text{for } j < i \\ \alpha_1 z^*, & \text{for } j \geq i. \end{cases} \tag{21}$$

The maximum attainable age class for all calculations was set at 10. Calculations were performed using the Mathematica 4.1 (Wolfram 1999) software package, and all parameter values used for each example are given in the figure captions (notebooks available upon request).

The results of all calculations using both total reproductive output and intrinsic rate of increase as measures of fitness are presented in Figures 1, 2, and 3. For some parameter values (Fig. 1) the evolutionarily optimal level of senescent deterioration is seen to increase for all possible ages-at-onset, in agreement with verbal statements of Williams's hypothesis. However, for other parameter values (Fig. 2) the exact opposite behavior, where the optimum decreases for all ages-at-onset, can be observed. Finally, and perhaps most notably, still other parameter choices can produce a switching phenomenon, where a decrease in senescent deterioration is favored for some early age classes but increases result when the age-at-onset occurs at later ages (Fig. 3).

## DISCUSSION

Previous theoretical work (Abrams 1993) has shown that, when population growth is density-dependent, optimal senescence schedules can exhibit a broad range of qualitative behaviors in response to changes in condition-independent mortality risk. In this paper we have developed a model of physiological senescence evolution, via the antagonistic pleiotropy mechanism, focusing our analyses on the two fitness measures, $r$ and $R$, since one of the two often provides the appropriate index of evolutionary success under various forms of population regulation (Mylius and Diekmann 1995). Our results indicate that a similarly diverse array of evolutionary outcomes in response to changes in extrinsic hazard level can be obtained when senescent deterioration increases an organism's susceptibility to such hazards. In particular, the results summarized in Figures 1–3 suggest that different parameter combinations can be found such that increased senescent deterioration is favored at all ages, decreased de-

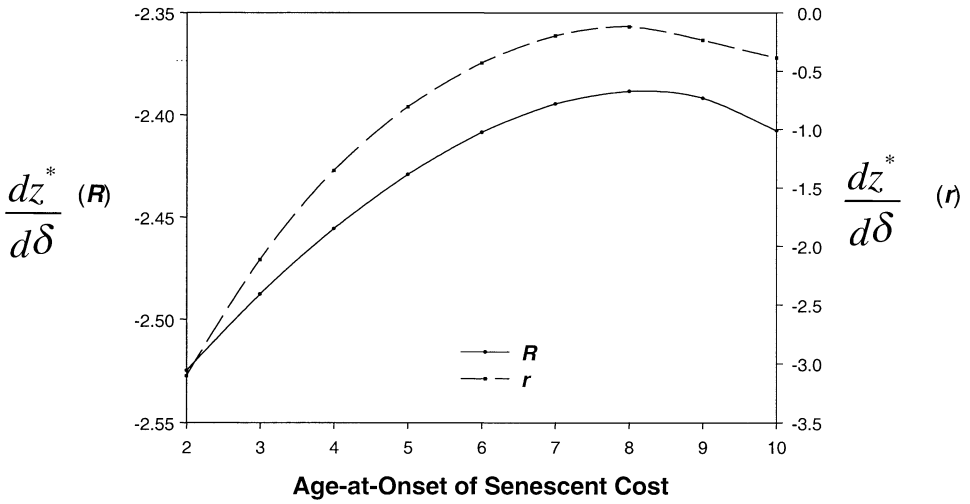


FIG. 2. Plot of the change in the optimum, $z^*$, given a change in condition-dependent environmental hazard level versus age-at-onset of senescent cost. These sets of parameter values result in an optimum that decreases for all ages-of-onset in response to an increased environmental hazard level. $r$:$\alpha_1 = 10$; $\beta_1 = 0.5$; $\beta_2 = 0.5$; $\beta_3 = 2$; $a_1 = 0.1$; $a_2 = 0$; $a_3 = 0.01$; $a_4 = 0.1$; $\hat{\delta} = 0$; $\delta = 0.1$. $R$:$\alpha_1 = 1$; $\beta_1 = 0.5$; $\beta_2 = 0.5$; $\beta_3 = 2$; $a_1 = 0.1$; $a_2 = 0$; $a_3 = 0.01$; $a_4 = 0.1$; $\hat{\delta} = 0$; $\delta = 0.1$.

terioration is favored at all ages, or decreased deterioration is favored at early ages, but increased deterioration at later ones.

Despite this apparently broad range of possible evolutionary outcomes, our analyses of the way that fitness sensitivity expressions change in response to increases in condition-dependent hazard levels indicates that timing effects can have important general consequences for the predicted direction of evolution in senescent deterioration. For either fitness measure considered, our results suggest that, if both benefits and costs occur early in the life history, selection will often favor decreased senescent deterioration, whereas large time lags between receiving fecundity benefits and paying senescent costs can favor increased senescent deterioration. Consequently, we predict that, in response to increased condition-dependent hazard, optimal senescence schedules should often show a pattern of decreased age-specific deterioration early in life, but a steeper rate of change in age-specific deterioration, and possibly greater age-specific deterioration, at late ages. This type of adjustment in age-specific physiological deterioration cannot be easily characterized as the evolution of either faster or slower senescence; rather, more abrupt senescence seems the most appropriate description.

Recent work with Trinidadian guppies (Reznick et al. 2001) provides a good example to illustrate the potential significance of this last result. The scenario outlined above suggests that, if we compared the pattern of physiological senescence in traits related to predator escape and/or avoid-

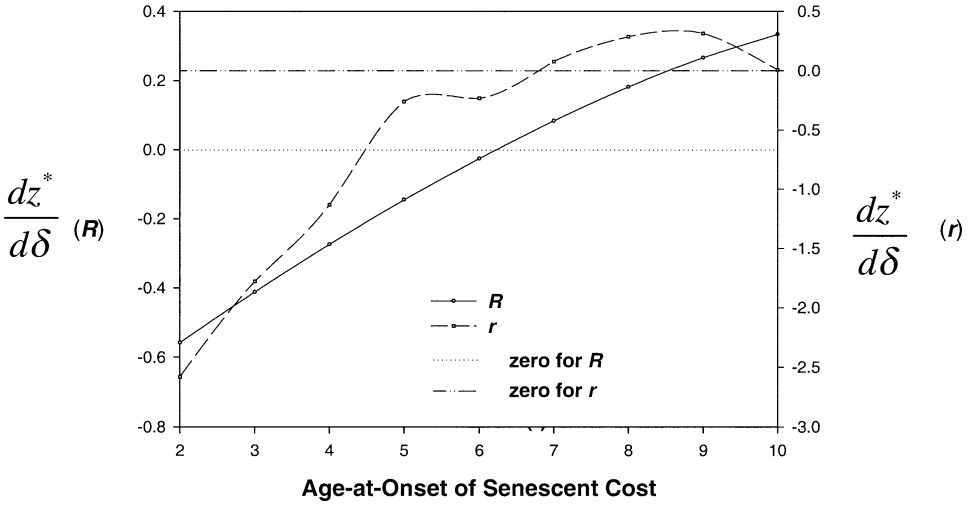


FIG. 3. Plot of the change in the optimum, $z^*$, given a change in condition-dependent environmental hazard level versus age-at-onset of senescent cost. These sets of parameter values result in an optimum that decreases for all ages-of-onset less than or equal to age class 6, but increases for all greater age classes in response to an increased environmental hazard level. $r$:$\alpha_1 = 10$; $\beta_1 = 1$; $\beta_2 = 0.05$; $\beta_3 = 2$; $a_1 = 0.1$; $a_2 = 0$; $a_3 = 0.01$; $a_4 = 0.1$; $\hat{\delta} = 0$; $\delta = 0.1$. $R$:$\alpha_1 = 1$; $\beta_1 = 0.5$; $\beta_2 = 0.5$; $\beta_3 = 2$; $a_1 = 0.1$; $a_2 = 0.6$; $a_3 = 0.01$; $a_4 = 0.1$; $\hat{\delta} = 0$; $\delta = 0.1$.

ance in fish from high- and low-predation areas, we might expect to see those fish from high-predation areas being physiologically more effective in this regard early in life and less so late in life. In other words, fish from high-predation areas might display a more abrupt pattern of senescence in the ability to escape predation than fish from low-predation areas, a pattern that has recently been found using populations of guppies (C. Ghalambor, pers. comm.). Previous theory that has ignored condition-dependent mortality sources would not make such a prediction.

### *Measures of Senescence*

Typical procedure in laboratory tests of Williams's hypothesis is to compare age-specific mortality rates of two closely related populations, one having evolved under high-hazard and the other under low-hazard conditions, in a common, low-hazard environment. Some authors cite greater age-specific mortality rates in the high-hazard population as confirmation of Williams's hypothesis (Stearns et al. 2000), whereas others require an increase in the slope of the age-specific mortality curve (Tatar et al. 1997; Dudycha and Tessier 1999). Williams's original statement (1957) was phrased in terms of rates of senescence, suggesting that the latter interpretation is the more exact test of the prediction. The distinction may not have seemed to Williams an important one, however, since the former might have been thought to imply the latter. Indeed, Williams (1957, p. 405) later asserted that ''The evolutionary cause of the low rate of bird senescence must be that birds can fly, are thereby less liable to predation and accidents, and therefore have lower mortality rates''. It is important to note, however, that this need not be the case. The slope of the age-specific mortality curve can change independently of its magnitude at any given age. For example, some conditions might well select for the evolution of higher age-specific mortality rates but a slower rate of increase in mortality rate across ages. Therefore, whether or not this is termed increased senescence depends on which measure is actually employed. Importantly, many theoretical results (e.g., Abrams 1993) as well as those presented here quantify increased senescence as a higher mortality rate rather than a higher rate of increase in mortality. Therefore, empirical measurements of the latter do not provide relevant tests of such predictions.

### *Empirical Tests of Williams's Hypothesis*

Our results also suggest that, given the ubiquity of condition-dependent mortality sources, Williams's hypothesis should often not be correct. Why, then, have empirical results provided support for its predictions? One possible answer is simply that most empirical systems examined to date happen to satisfy the conditions under which Williams's hypothesis *is* valid. For example, by experimentally imposing different levels of extrinsic mortality on laboratory populations of fruit flies in such a way as to prevent it from being condition-dependent, Stearns et al. (2000) found evidence for greater intrinsic mortality in flies from high extrinsic mortality treatments. Such experimental conditions are the most conducive to obtaining support for the hypothesis (issues of population regulation aside; see Abrams 1993), but their relevance to evolutionary responses in natural populations, where much extrinsic mortality is condition-dependent, is unclear. Nevertheless, interactions could be effectively explored in the laboratory environment by extending the experimental protocol of Stearns et al. (2000) to include a treatment in which mortality is imposed in condition-dependent fashion. This could be achieved by, for example, assaying all individuals in both treatments for some condition-dependent motor skill (like escape response), then preferentially removing the slowest individuals in the interactive treatment while randomly removing individuals in the noninteractive treatment.

The presence of condition-dependent hazards requires that extra care be exercised when using age-dependent increases in mortality rate as a surrogate measure of physiological senescence. The reason is that, in such cases, the mortality rate at any given age, and therefore the pattern of mortality throughout an individual's life, will depend on the environment in which it is measured. For example, cases do exist where age-related degenerative changes produce a mortality increase only within certain stressful environments (Roach 2001). This dependence of the age-specific mortality pattern on environmental conditions is a hallmark of condition-dependent hazards, and it introduces an additional level of complexity to studies of aging that is sometimes ignored.

With this in mind, we now consider why spurious support for Williams's hypothesis might be found in some cross-taxa comparative studies. Such studies typically quantify patterns of senescence by measuring age-specific mortality rates for populations in the environments in which they evolved. One then obtains an estimate of the extrinsic mortality rate, as well as the rate of increase in age-specific mortality over an individual's lifetime, for several different populations or species and then looks for a relationship between the two. A positive relationship would then be taken as support for Williams's hypothesis. Suppose, however, that extrinsic mortality is mediated through condition-dependent hazards and that physiological senescence has actually evolved to be lower (see Fig. 2) in response to higher hazard (i.e., organisms in the high-hazard environment have evolved decreased levels of age-specific physiological deterioration when compared to those of the low-hazard population). Because mortality arises through an interaction between physiological state and extrinsic hazard, however, it is possible for the age-specific mortality rate of the more physiologically degenerate population to be less, when tested in the low-hazard environment it evolved in than that of the more physiologically robust population when tested in the high-hazard environment. Thus, even though the age-specific mortality rate patterns would support Williams's hypothesis, the age-specific pattern of physiological deterioration that has evolved in response to extrinsic mortality might, nevertheless, run counter to Williams's prediction.

We close by noting that in one recent comparative study (Ricklefs 1998) the author tested Williams's hypothesis after first using statistical techniques and concluded that condition-dependent extrinsic hazards are not important in natural populations of birds. We would suggest that this conclusion is tentative at best for two reasons. First, this conclusion was reached by comparing the fit of two models with particular functional forms to age-specific mortality patterns, one that

embodied some condition-dependence and one that did not, with the latter appearing to fit the data better. It remains unclear, however, whether models with other functional forms involving condition-dependence might fit the data even better.

Second, the very existence of an interaction between condition and extrinsic hazard means that it will often be very difficult to detect using comparisons between high- and low-hazard conditions. The reason is that few individuals in the high-hazard environment will survive very long relative to those in the low-hazard environment. Thus, the ages for which we might expect the most pronounced difference in mortality rates between the groups as a result of interactions will tend to be those for which only the low-hazard group will have survivors, leaving little data for comparison. In view of these points, as well as the abundant direct empirical evidence for interactions between physiological state and extrinsic hazard, we feel that the issues explored in this article warrant further consideration.

## Acknowledgements

We thank P. Abrams and L. Rowe for their comments. We also thank M. Morgan and two anonymous reviewers for comments that helped to clarify some of the issues dealt with in the manuscript. This work was funded by a grant from the Natural Science and Engineering Research Council of Canada and a Premier's Research Excellence Award to TD.

## Literature Cited

Abrams, P. A. 1991. The fitness costs of senescence: the evolutionary importance of events in early adult life. Evol. Ecol. 5: 343–360.

———. 1993. Does increased mortality favor the evolution of more rapid senescence? Evolution 47:877–887.

Ashman, R. B., J. M. Papadimitriou, and A. Fulurija. 1999. Acute susceptibility of aged mice to infection with *Candida albicans*. J. Med. Microbiol. 48:1095–1102.

Austad, S. N. 1993. Retarded senescence in an insular population of Virginia opossums. J. Exp. Zool. 229:695–708.

Austad, S. N., and K. E. Fischer. 1991. Mammalian aging, metabolism, and ecology: evidence from the bats and marsupials. J. Gerontol. Biol. Sci. 46:B47–B53.

Bakker, T. C. M., D. Mazzi, and S. Zala. 1997. Parasite-induced changes in behavior and color make *Gammarus pulex* more prone to fish predation. Ecology 78:1098–1104.

Boyd, D. K., R. R. Ream, D. H. Pletscher, and M. W. Fairchild. 1994. Prey taken by colonizing wolves and hunters in the Glacier National Park area. J. Wild. Manage. 58:289–295.

Bjorge, R. R., and J. R. Gunson. 1989. Wolf, *Canis lupus*, population characteristics and prey relationships near Simonette River, Alberta. Can. Field-Nat. 103:327–334.

Brommer, J. E. 2000. The evolution of fitness in life-history theory. Biol. Rev. 75:377–404.

Charlesworth, B. 1994. Evolution in age-structured populations. Cambridge Univ. Press, Cambridge, U.K.

Charlesworth, B., and K. A. Hughes. 1996. Age-specific inbreeding depression and components of genetic variance in relation to the evolution of senescence. Proc. Natl. Acad. Sci. USA 93: 6140–6145.

Dudycha, J. L., and A. J. Tessier. 1999. Natural genetic variation of life span, reproduction, and juvenile growth in *Daphnia*. Evolution 53:1744–1756.

Edney, E. B., and R. W. Gill. 1968. Evolution of senescence and specific longevity. Nature 220:281–282.

Finch, C. E. 1990. Longevity, senescence, and the genome. Univ. of Chicago Press, Chicago, IL.

Fuller, T. K., and L. B. Keith. 1980. Wolf population dynamics and prey relationships in northeastern Alberta. J. Wild. Manage. 44: 583–602.

Gray, D. A., and W. H. Cade. 2000. Senescence in field crickets (Orthoptera; Gryllidae): examining the effects of sex and a sex-biased parasitoid. Can. J. Zool. 78:140–143.

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

Holmes, D. J., and S. N. Austad. 1995. The evolution of avian senescence patterns: implications for understanding primary aging processes. Am. Zool. 35:307–317.

Keller, L., and M. Genoud. 1997. Extraordinary lifespans in ants: a test of evolutionary theories of ageing. Nature 389:958–960.

Lafferty, K. D., and A. K. Morris. 1996. Altered behavior of parasitized killifish increases susceptibility to predation by bird final hosts. Ecology 77:1390–1397.

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

Medawar, P. B. 1952. An unsolved problem of biology. Lewis, London.

Mech, L. D., T. J. Meier, J. W. Burch, and L. G. Adams. 1995. Patterns of prey selection by wolves in Denali National Park, Alaska. Pp. 231–243 *in* L. D. Carbyn, S. H. Fritts, and D. R. Seip, eds. Ecology and conservation of wolves in a changing world. Canadian Circumpolar Institute, Edmonton, Alberta.

Miller, R. A., J. M. Harper, R. C. Dysko, S. J. Durkee, and S. N. Austad. 2002. Longer life spans and delayed maturation in wild-derived mice. Exp. Biol. Med. 227(7):500–508.

Møller, A. P., and F. de Lope. 1999. Senescence in a short-lived migratory bird: age dependent morphology, migration, reproduction and parasitism. J. Anim. Ecol. 68:163–171.

Mueller, L. D. 1987. Evolution of accelerated senescence in laboratory populations of *Drosophila*. Proc. Natl. Acad. Sci. USA 84:1974–1977.

Mylius, S. D., and O. Diekmann. 1995. On evolutionarily stable life histories, optimization and the need to be specific about density dependence. Oikos 74:218–224.

Partridge, L. 1989. Lifetime reproductive success and life-history evolution. Pp. 421–440 *in* I. Newton, ed. Lifetime reproduction in birds. Academic Press, New York.

———. 2001. Evolutionary theories of ageing applied to long-lived organisms. Exp. Gerontol. 36:641–650.

Partridge, L., and N. H. Barton. 1993. Optimality, mutation and the evolution of ageing. Nature 362:305–311.

———. 1996. On measuring the rate of ageing. Proc. R. Soc. Lond. B 263:1365–1371.

Partridge, L., N. Prowse, and P. Pignatelli. 1999. Another set of responses and correlated responses to selection on age at reproduction in *Drosophila melanogaster*. Proc. R. Soc. Lond. B 266: 255–261.

Pletcher, S. D., D. Houle, and J. W. Curtsinger. 1998. Age-specific properties of spontaneous mutations affecting mortality in *Drosophila melanogaster*. Genetics 148:287–303.

Promislow, D. E. L. 1991. Senescence in natural populations of mammals: a comparative study. Evolution 45:1869–1887.

Reznick, D., G. Buckwater, J. Groff, and D. Elder. 2001. The evolution of senescence in natural populations of guppies (*Poecilia reticulata*): a comparative approach. Exp. Gerontol. 36:791–812.

Ricklefs, R. E. 1998. Evolutionary theories of aging: confirmation of a fundamental prediction, with implications for the genetic basis and evolution of life span. Am. Nat. 152:24–44.

Roach, D. A. 2001. Environmental effects on age-dependent mortality: a test with a perennial plant species under natural and protected conditions. Exp. Gerontol. 36:687–694.

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

———. 1991. Evolutionary biology of senescence. Oxford Univ. Press, New York.

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

———. 1981. Genetics of life-history evolution in *Drosophila melanogaster*. Part II. Exploratory selection experiments. Genetics 97:187–196.
Stearns, S. C. 1992. The evolution of life histories. Oxford Univ. Press, New York.
Stearns, S. C., M. Ackermann, M. Doebeli, and M. Kaiser. 2000. Experimental evolution of aging, growth, and reproduction in fruitflies. Proc. Natl. Acad. Sci. USA 97:3309–3313.
Tatar, M., D. W. Gray, and J. R. Carey. 1997. Altitudinal variation for senescence in *Melanoplus* grasshoppers. Oecologia 111: 357–364.
Walker, D. W., G. McColl, N. L. Jenkins, J. Harris, and G. J. Lithgow. 2000. Natural selection: evolution of lifespan in *C. elegans*. Nature 405:296–297.
Williams, G. C. 1957. Pleiotropy, natural selection, and the evolution of senescence. Evolution 11:398–411.
Wolfram, S. 1999. The Mathematica book. 4th ed. Wolfram Media/ Cambridge Univ. Press, Cambridge, U.K.
Zwaan, B., R. Bijlsma, and R. F. Hoekstra. 1995. Direct selection on life span in *Drosophila melanogaster*. Evolution 49:649–659.

Corresponding Editor: M. Morgan

## Appendix 1

### *Maximum Conditions*

To clarify the maximum/minimum status of $z^*$, for either fitness measure considered, the denominator of equation (5) must be calculated. Suppressing the age dependence of the fecundity and senescent deterioration terms and denoting derivatives with respect to $z$ as subscripts (so that $dm(y)/dz = m_z$, $d^2m(y)/dz^2 = m_{zz}$, etc.) yields the two similar conditions:

$$\frac{\partial^2 r}{\partial z^2} \propto \chi_z(a_3 + a_4\delta)\left[\left(\frac{m_{zz}}{m_z} - \frac{\chi_{zz}}{\chi_z}\right)\sum_{j=i}^{\infty} F(i,j) + \chi_z(a_3 + a_4\delta)\sum_{j=i}^{\infty}(j - i + 1)F(i,j)\right] \quad \text{or} \quad \text{(A1)}$$

$$\frac{\partial^2 R}{\partial z^2} = \chi_z(a_3 + a_4\delta)\left[\left(\frac{m_{zz}}{m_z} - \frac{\chi_{zz}}{\chi_z}\right)\sum_{j=i}^{\infty} \tilde{F}(i,j) + \chi_z(a_3 + a_4\delta)\sum_{j=i}^{\infty}(j - i + 1)\tilde{F}(i,j)\right] \quad \text{(A2)}$$

where $F(i, j) = (j - i + 1)e^{-ri}l(j)m(j)$ and $\tilde{F}(i, j) = (j - i + 1)l(j)m(j)$. These expressions must be negative if the stationary point $z^*$ is to correspond with a fitness maximum, which requires that the inequality $(m_{zz}/m_z - \chi_{zz}/\chi_z) < 0$ must hold. Necessary (though not sufficient) conditions for $z^*$ to maximize fitness are therefore $m_{zz} < 0$, $\chi_{zz} > 0$, or both.

## Appendix 2

### *Justification for Ignoring Changes in Generation Time*

By condition (4a) we have that $V(z^*) = 0$ and so $\partial(TV)/\partial\psi = T(\partial V/\partial\psi)$ when evaluated at $z^*$, for $\psi = \zeta, z$. It follows that, when $r$ measures fitness, equation (5) can be written as

$$\frac{\partial z^*}{\partial \zeta} = -\frac{\partial V}{\partial \zeta}\Big/\frac{\partial V}{\partial z} = -\frac{\partial(TV)}{\partial \zeta} - \frac{\partial(TV)}{\partial z}, \quad \text{(A3)}$$

when $\zeta = \hat{\delta},\delta$ and hence that the $1/T$ factor that appears in the sensitivity expressions (7) and (8) can be disregarded.