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To Age or Not to Age--What Is the Question?

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The terms "aging" and "senescence" refer to the deterioration in physiological condition that occurs as an organism gets older (1-4). The very existence of this interdisciplinary journal is a testament to the level of interest and research effort devoted to understanding aging from a multitude of perspectives (see "Aging Research Grows Up"). Many of these research perspectives examine the proximate physiological and biochemical causes of aging, but evolutionary biologists have also had a longstanding interest in providing an ultimate or evolutionary explanation for the existence of aging (5-8). One of the primary motivations for attempting to develop an evolutionary theory of aging arises from the maladaptive consequences of physiological deterioration. Natural selection is expected to preserve those genotypes that enjoy the highest reproductive success. Why then do genotypes coding for physiological deterioration, and the resultant decrease in reproductive success that this causes, persist in natural populations (5)?

It is clear that aging can and has evolved, both in the lab and in natural populations (1, 3, 9). This fact has driven the development of the theory of aging over the past 50 years, to the point where we now have a body of evolutionary explanations that are generally accepted. A recent paper by Sozou and Seymour (10), however, questions one of the most basic tenets of this evolutionary theory of aging.

Two main hypotheses compose the currently most strongly supported general theory about the evolution of aging (2). These are referred to as the mutation accumulation (MA) and antagonistic pleiotropy (AP) hypotheses. These hypotheses are not mutually exclusive, and both rest on the more general fact that the ability of natural selection to weed out deleterious alleles from a population declines as the age at which the deleterious allele is expressed increases. Alleles that are not expressed until late in life will often never be expressed, because individuals harboring such alleles will tend to die of unrelated, extrinsic causes, such as predation or accidents, before late age is reached. Thus, the efficacy of selection acting on any allele with age-specific effects is determined by the effect of that allele on reproductive success, weighted by the likelihood that an individual carrying that allele will actually survive to the age at which it is expressed (8, 11).

The MA hypothesis asserts that the equilibrium frequency of deleterious alleles in a population is determined by the

balance between mutational input and the removal of deleterious alleles by natural selection. Therefore, all else being equal, late-acting deleterious alleles will reach a higher equilibrium frequency than will early-acting alleles, leading to a pattern of aging. The AP hypothesis asserts that high reproductive success at any age can be bought only at the expense of decreasing reproductive success at later ages (7) (see Williams Classic Paper). As a result, an allele that increases reproductive success at an early age, at the expense of an equivalent decrease in reproductive success at a later age, will nevertheless be favored by natural selection because of the differential weighting of the age-specific effects (Fig. 1A). In essence, the optimal strategy is to live for today, because tomorrow might never come.

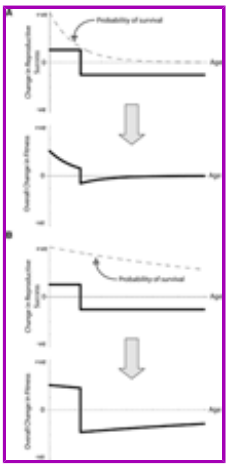

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Fig. 1. A stylized graphical portrayal of the AP hypothesis and the main results of Sozou and Seymour (10). (**A**) The top panel gives the change in reproductive success at each age that is caused by a mutation with antagonistic age-specific effects (solid curve), along with the probability that the individual survives to any given age (dashed curve). The bottom panel gives the net effect of selection on the mutation at each age once its age-specific effects are weighted by the probability of surviving to each age. The allele will spread if the benefits (that is, the positive area bounded by the curve) exceed the costs (that is, the negative area bounded by the curve). In this case, the allele would spread. (**B**) Same as (A), but used to illustrate how a non-aging strategy can be optimal as found by Sozou and Seymour (10). Suppose we start with a non-aging organism, and the same mutation considered in (A) appears. The top panel of (B) again gives its age-specific effects on reproductive success. The bottom panel gives the net effect of selection on the mutation at each age once its age-specific effects are weighted by the probability of surviving to each age. If the probability of survival to late ages is quite high (as it is here), then the benefits of the allele (that is, the positive area bounded by the curve) are smaller than the costs (that is, the negative area bounded by the curve). Thus, the allele cannot spread, and a non-aging strategy has the highest fitness.

There are a number of predictions that can be derived from this general body of theory, some of which have been subject to experimental tests as well as to tests using comparisons across different populations and/or species (1, 3). One common prediction found in much of this evolutionary literature is that aging is an inevitable consequence of natural selection in any organism for which there is a distinction between parents and offspring (1, 4, 7, 8). This latter stipulation ensures that there is a definable age structure to the population, and, therefore, that alleles can have age-specific effects. The paper by Sozou and Seymour (10) focuses on the AP hypothesis and steps back for a moment to ask: Is aging really inevitable under such conditions? Their answer to this question is no, and thus the near universality of aging in such organisms would suggest that further considerations are required to explain these empirical patterns.

The theory presented by Sozou and Seymour is somewhat mathematical, but the underlying logic of their argument can be easily understood using the graphical caricature in Fig. 1. To begin, Sozou and Seymour introduce an age-specific quantity referred to as "vitality." This quantity encompasses both fecundity and the survival consequences of declining physiological conditions with age. Intuitively, it represents the expected reproductive output of a newly matured individual at each future age, in the absence of any extrinsic source of mortality. More specifically, the vitality at age a is obtained by multiplying the probability of surviving to age a (in the absence of extrinsic sources of mortality) with the fecundity realized at age a. For non-aging individuals, the probability of survival to any given age is constant for all ages (in the absence of extrinsic mortality). Therefore, assuming that reproductive prospects do not increase with age through growth or increased experience, the vitality of a non-aging individual will be constant across all ages. We can view such a non-aging strategy within the context of Fig. 1 by simply taking it to

be the baseline state (that is, zero change in reproductive success at all ages) when determining whether an antagonistic allele with age-specific effects is favored by natural selection. An aging individual, on the other hand, will have a vitality that is higher at early ages, but lower at late ages. Again, in the context of Fig. 1, we can view this strategy as one that has a positive effect on reproductive success early in life at the expense of reduced success late in life, owing to a decrease in physiological condition with age.

With this graphical setup, the conditions under which a non-aging strategy is optimal can be found by simply determining the conditions under which an allele coding for such aging cannot invade (that is, the conditions under which the non-ageing strategy has a higher fitness than an aging strategy). The net effect of selection on the allele that causes aging will depend on the magnitude of the benefit in early life relative to the cost in late life (Fig. 1). Bigger benefit-to-cost ratios are more conducive to the mutation's spreading by natural selection. Remember, however, that the effect of the allele at each age must also be weighted by the likelihood of an individual surviving to that age in order to determine the overall efficacy of selection acting on the allele at that age. As a result, small beneficial effects early in life can sometimes outweigh large costs late in life. Sozou and Seymour show, however, that this is not always the case. In fact, if the magnitude of the benefit is small and the cost and/or the likelihood of surviving to late ages is relatively high, then such mutations will not be favored by natural selection. The optimal strategy is to maintain a constant physiological condition throughout life (that is, no aging; Fig. 1B).

At the most fundamental level, the results of Sozou and Seymour are so simple as to border on the obvious. Under the AP hypothesis, an allele that causes physiological deterioration in late life will spread in a population only if its early-life benefits outweigh its late-life costs. Sometimes this will be true and sometimes it will not. At the same time, however, one is then led to wonder why most evolutionary biologists have taken aging to be an inevitable evolutionary outcome for most organisms. Further still, if aging really isn't an inevitable outcome according to the current body of evolutionary theory, then why does aging appear to be so universal? Is the current theory inadequate or incomplete? Or do the conditions under which most organisms have evolved happen to fall within the region of parameter space where this theory really does predict the evolution of aging?

The answers to these questions are probably not simple, but I believe that at least part of the solution lies in how we ask the question "to age or not to age" in the first place. If we ask this question within the context of a simple model of the AP hypothesis, then the results of Souzou and Seymour speak clearly: Aging is not necessarily an inevitable consequence of natural selection. But the general conceptual body of evolutionary theory on aging encompasses some important factors that are not included in the mathematical formalization of Sozou and Seymour. These factors will probably lessen the sting of their results and make the evolution of aging much more certain.

To begin, most formalizations of the AP hypothesis (including that of Sozou and Seymour) examine a situation in which there is a single tradeoff between early-age benefits and late-age costs. In reality, there are likely to be many loci, each with a suite of potential alleles that mediate such tradeoffs in different ways. The coevolutionary dynamics of such a set of loci will display very different behavior than the evolutionary dynamics of a single tradeoff. At the very least, if we consider all of the potential tradeoffs that might occur for the various alleles at all relevant loci, then undoubtedly some of these will be able to spread by natural selection. Of course, those alleles that satisfy the conditions detailed by Sozou and Seymour will not spread (because the overall costs are greater than the benefits), but some senescence will nevertheless evolve through the spread of alleles for which the benefits do outweigh the costs. Once some senescence has evolved, this will relax the conditions for the future spread of other such antagonistic alleles. The reason is that, once some senescence exists, it decreases the likelihood of an individual surviving to late ages, and this thereby reduces the effective cost of other, antagonistic alleles by placing less weight on the costs relative to the benefits. Consequently, although it is possible that a non-aging strategy is optimal, if even one allele with antagonistic age-specific effects does spread, then this event can produce a positive feedback that will cause other such alleles to spread as well. In this way, an aging strategy might usually (always?) be optimal if we ask the question "to age or not age" in a more realistic evolutionary context.

Second, because the AP and MA hypotheses are not mutually exclusive, the processes that underlie these theories

are likely to interact in interesting ways. This is particularly relevant to the study by Sozou and Seymour. Even if it were true that a non-aging strategy is optimal for some organisms (according to the Sozou and Seymour model), the MA process would likely still operate. Consequently, some aging would evolve through the increased frequency of late-acting deleterious mutations. Once this event occurs, it again relaxes the conditions under which antagonistic alleles can spread for the reasons outlined above. As a result, these conditions should also lead to a positive feedback or snowballing effect, in which most populations evolve further aging through both processes.

The work by Sozou and Seymour illustrates why the common assumption that aging is an inevitable consequence of natural selection in age-structured populations need not be true. It remains to be seen, however, whether this finding stands up against a more complete formalization of the evolutionary theory of aging. My guess is that it will not, but given the ubiquity of aging in natural populations, these results clearly call for further work to reconcile the theory with the data.

March 10, 2004

Comment on Article

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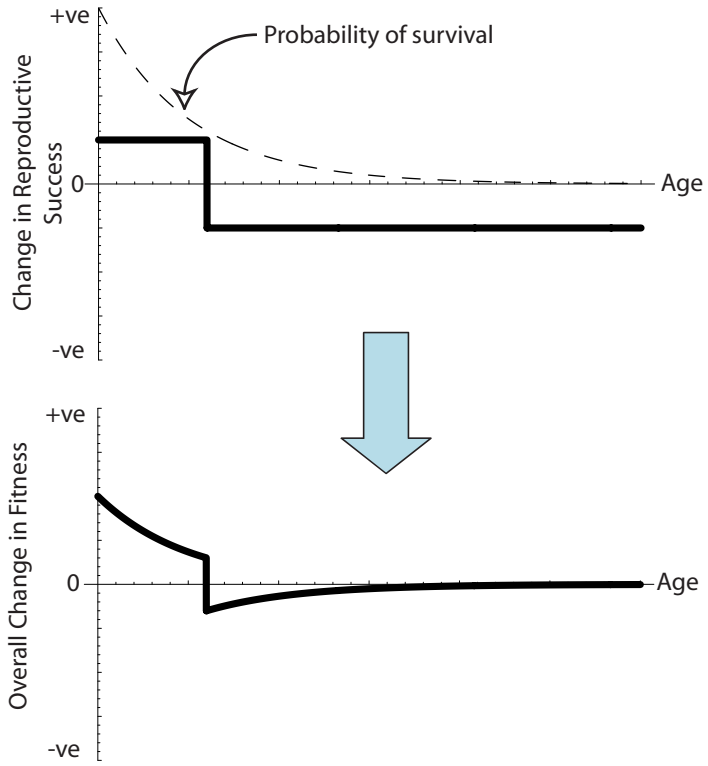
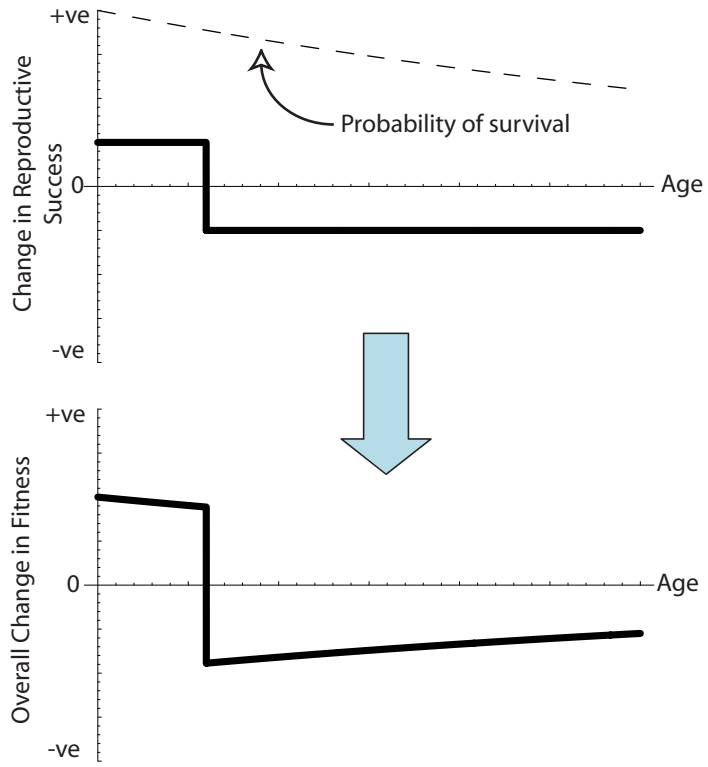
Figure 1

(a)


+ve
Probability of survival
Change in Reproductive Success
0
Age
-ve
+ve
Overall Change in Fitness
0
Age
-ve

(b)


+ve
Probability of survival
Change in Reproductive Success
0
Age
-ve
+ve
Overall Change in Fitness
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Age
-ve