PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Evolution of Senescence: Late Survival Sacrificed for Reproduction

T. B. L. Kirkwood and M. R. Rose

Phil. Trans. R. Soc. Lond. B 1991 **332**, 15-24
doi: 10.1098/rstb.1991.0028

Evolution of senescence: late survival sacrificed for reproduction

T. B. L. KIRKWOOD[1] AND M. R. ROSE[2]

[1] *National Institute for Medical Research, Mill Hill, London NW7 1AA, U.K.*
[2] *Department of Ecology and Evolutionary Biology, University of California, Irvine, California 92717, U.S.A.*

SUMMARY

In so far as it is associated with declining fertility and increasing mortality, senescence is directly detrimental to reproductive success. Natural selection should therefore act in the direction of postponing or eliminating senescence from the life history. The widespread occurrence of senescence is explained by observing that (i) the force of natural selection is generally weaker at late ages than at early ages, and (ii) the acquisition of greater longevity usually involves some cost. Two convergent theories are the 'antagonistic pleiotropy' theory, based in population genetics, and the 'disposable soma' theory, based in physiological ecology. The antagonistic pleiotropy theory proposes that certain alleles that are favoured because of beneficial early effects also have deleterious later effects. The disposable soma theory suggests that because of the competing demands of reproduction less effort is invested in the maintenance of somatic tissues than is necessary for indefinite survival.

1. INTRODUCTION

Senescence is a standard feature in the life histories of higher animals (Comfort 1979). It is usually defined in relation to the pattern of age-specific mortality, a population being said to experience senescence if it exhibits a progressive increase in the age-specific death rate even when the population is maintained under conditions that are ideal for survival (see, for example, Medawar 1955; Maynard Smith 1962). Underlying this progressive increase in the age-specific death rate is a generalized deterioration in a broad spectrum of physiological and metabolic functions (Finch & Schneider 1985). These physiological decrements leave the organism increasingly vulnerable to a variety of intrinsic and extrinsic factors that may cause death. An important correlate of the declining physiological competence of a senescing organism is that reproduction also generally declines with age. Taken together, the declines in survival and fecundity mean that a senescing organism experiences a major, and eventually total, loss in fitness during later ages. The puzzle, therefore, is to explain why this trait, which is deleterious to individual fitness, has evolved.

Senescence is most clearly seen in the case of a species with an iteroparous life history (Kirkwood 1985). In the iteroparous life history, the adult is capable of repeated reproduction after gaining sexual maturity (Cole 1954). This life-history pattern is potentially open-ended: it could in principle extend indefinitely, if senescence did not bring it to a close. This is in contrast to the semelparous life history, where death tends to follow closely upon reproduction, often as a direct result of endocrine and other changes which accompany the physiological commitment to reproduce (see, for example, Robertson 1961; Wodinsky 1977). Senescence is also most clearly seen in species where there is a clear distinction between germ-line and somatic tissue. When this distinction is lacking, organisms tend to be capable of reproducing vegetatively. Vegetative reproduction blurs the concept of individual survivorship and makes it harder to define whether or not senescence occurs. In fact, species capable of vegetative reproduction provide the best examples of organisms that do not senesce (Comfort 1979; Bell 1984).

Why does senescence occur and what determines its rate of progress? These questions require answers at both the proximate, physiological level and at the ultimate, evolutionary level. The field of gerontology is replete with physiological theories to account for senescence (Finch & Schneider 1985; Warner *et al.* 1987; Medvedev 1990). Evolutionary theories explain senescence in terms of the selection forces acting on the life history. There is a long tradition of evolutionary discussion of senescence, which began last century with the work of Weismann and Wallace (Kirkwood & Cremer 1982; Rose 1991).

In this paper, we describe two explanations of senescence which converge in the suggestion that its evolution can best be understood as a by-product of the priority that natural selection places on reproduction. One explanation, based in population genetics and owing mainly to Williams (1957), is the theory of 'antagonistic pleiotropy' (see also Charlesworth 1980; Rose 1984*b*). The other explanation is the 'disposable soma' theory (Kirkwood 1977, 1981; Kirkwood & Holliday 1979). The disposable soma theory is based on an optimality approach, consistent with the framework of physiological ecology (Townsend & Calow 1981). The

Phil. Trans. R. Soc. Lond. B (1991) **332**, 15–24
Printed in Great Britain

common element in both these theories is the conclusion that, in effect, natural selection trades late survival for enhanced early fecundity. The theories differ in the extent to which they also address the question of physiological mechanisms of senescence (see also Discussion).

2. EVOLUTION OF SENESCENCE

(*a*) *Population genetics*

The first hints of a population genetic approach to the problem of senescence come from Fisher (1930, pp. 28–29) and Haldane (1941, pp. 192–194). Both Fisher and Haldane suggested that the force of natural selection acting on allelic variants affecting survival should decline during adulthood. Hamilton (1966) and Charlesworth (1980) later showed mathematically that this intuition is often correct: under conditions where the Malthusian parameter defines fitness, the intensity of selection acting on an allele modifying survival probability by a fixed proportion will decline with age. That is, the force of natural selection acting on adult survival does indeed tend to decline with adult age. Comparable results also apply to selection acting on age-specific fertility, although the period of decline may be shifted (Hamilton 1966; Charlesworth 1980). Thus it may be generally concluded that the action of natural selection on age-specific fitness effects declines with age.

Given that natural selection is the force responsible for the adaptation of the organism, the evolutionary principle that the action of natural selection declines with age during the adult stage of the life cycle leads to the prediction that senescence should evolve (Medawar 1946, 1952; Williams 1957).

One population-genetic mechanism through which senescence might evolve is the accumulation of deleterious mutations that only act later in life, when the action of natural selection is extremely weak. This idea was discussed extensively by Medawar (1952). Even if senescence does not exist already in the life history, the lifespan of most animals is effectively curtailed by the mortality exacted by the environment. This provides the scope for late-acting deleterious mutations to accumulate relatively immune to the action of natural selection. When a rare individual lives long enough to encounter the effects of these late-acting mutations, they combine to generate the diverse pathologies of the aged adult. Thus, mutations accumulate and introduce senescence into the life history.

A variant of the mutation accumulation idea, also discussed by Medawar (1952), is that natural selection acts on alleles at age-of-action modifier loci to postpone numerous genetic diseases from earlier to later ages. However, the magnitude of the selection pressure for postponement of genetic diseases is only on the order of the mutation rate (cf. Ewens 1979, pp. 195–198). For this reason, it is unlikely that such selection will overcome mutation pressure acting on the modifier locus, and this population genetic mechanism for the evolution of senescence is not given credence (Charlesworth 1980, p. 219).

Mutation accumulation is essentially a neutral process reflecting the inability of selection to exert tight control over the later portion of the lifespan. A stronger theory is obtained if it is assumed that the late deleterious effects are the pleiotropic consequences of genes that are favoured by selection because they confer early fitness benefits (Williams 1957). This is the theory of antagonistic pleiotropy.

Antagonistic pleiotropy introduces the idea of a trade-off between early benefit and late cost, and the important thing about the declining action of selection with adult age is that it takes only a small fitness benefit early in life to outweigh a substantial deleterious effect later on. An interesting technical point is that the presence of antagonistic pleiotropy may maintain variability in relation to age-specific fitness effects (Rose 1982, 1985). This will then make it difficult to detect the action of mutation accumulation when antagonistic pleiotropy has also been involved in the evolution of senescence. However, while the action of one of these population genetic mechanisms may impede the detection of the other, there is no theoretical difficulty with their simultaneous action in one species.

(*b*) *Physiological ecology*

The disposable soma theory for the evolution of senescence comes from looking at the problem physiologically and asking how an organism should best allocate resources among the various metabolic tasks it needs to perform (Kirkwood 1977, 1981; Kirkwood & Holliday 1979, 1986). In particular, the disposable soma theory addresses the question of the optimal investment of resources in somatic maintenance.

In physiological terms, an organism is an entity that takes in resources from its environment, primarily energy in the form of nutrients, uses these resources for a variety of metabolic tasks such as growth and maintenance, and in due course reproduces to generate an output of progeny. The problem of allocation of resources arises because resources used for one purpose are no longer available for other purposes. A central issue in physiological approaches to life-history evolution (see Sibly & Calow 1986; Partridge & Harvey 1988) is to understand which of the many different allocation strategies is optimal, i.e. maximizes fitness, for an organism subject to natural selection under a given set of ecological constraints. We might note that there is no implicit assumption here that resources are necessarily scarce. In practice, resources are often limiting. However, even where resources are abundant there are constraints on how fast they can be utilized. The point is that no matter what the gross intake of resources, there is always the problem of how best to divide them.

General solutions to the problem of optimal resource utilization are elusive, chiefly because the constraints that determine the option sets are as yet unknown (Partridge & Sibly, this symposium). Nevertheless, informative studies of specific trade-offs can be made. Senescence can be understood by focusing on the investment in maintenance of somatic, i.e. non-

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

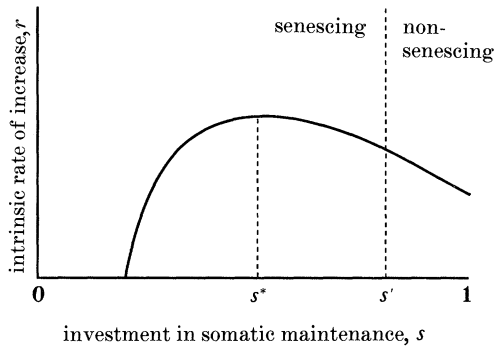

Figure 1. Relation between fitness, measured as the intrinsic rate of increase r, and the level of investment in somatic maintenance s. For $s > s'$, senescence does not occur. The optimum $s = s^*$ is predicted to be always less than s'.

reproductive, parts of the body. We ask two questions. First, for any given iteroparous species is there a best level of investment in maintenance? Secondly, is this sufficient to maintain the organism in a steady, non-senescing condition? The second of these questions presupposes that it is in fact possible to maintain the organism well enough for it to survive without progressive deterioration. If this is not the case, then there is nothing to explain about the evolution of senescence, as senescence is inevitable.

Formal ecological models can be used to answer these questions if we define fitness in terms of the Malthusian parameter, r, obtained from solving the standard Lotka equation

$$\int e^{-rx} l(x;s)\, m(x;s)\, dx = 1,$$

where survivorship $l(x;s)$ and fecundity $m(x;s)$ are written as functions depending not only on age, x, but also on the investment in maintenance, s (see, for example, Kirkwood 1990; see Appendix). From such models, we obtain fitness curves relating r to s. The typical form of the fitness curves is shown in figure 1, and it can be seen from figure 1 that an optimum value for s does exist at $s = s^*$, and that s^* is less than the minimum investment in maintenance ($s = s'$) required to be in the non-senescing condition.

This result establishes the conclusion that the optimum level of investment in somatic maintenance for an iteroparous species is less than the level required for indefinite survival. In other words, natural selection should favour a strategy that results in the progressive accumulation of unrepaired somatic defects, which in turn must result in senescence. This conclusion is robust to a wide range of variation in the specific assumptions of the ecological model used to generate figure 1, and can in fact be understood quite well without recourse to a formal model. This can be done by imagining what happens if an organism moves in from either of the ends of the horizontal scale in figure 1.

If nothing is invested in maintenance ($s = 0$), the organism will senesce with great rapidity. It is easy to see that raising the investment in maintenance increases fitness, at least initially. On the other hand, investing maximally in maintenance ($s = 1$) means that the organism is well inside the non-senescing region ($s > s'$). A small reduction in maintenance does not impose a survivorship cost but releases additional resources for growth and reproduction, and so leads to increased fitness. The same argument can be repeated until the boundary between the senescing and non-senescing states is reached. At this point, the organism is investing just enough in maintenance not to senesce, but is nevertheless subject to extrinsic hazards of the environment. If environmental mortality is, say, 50% a year, then the chance of surviving more than 20 years is less than one in a million. For practicable purposes this chance is negligible, so nothing is really lost if the investment in maintenance is reduced a little further so the organism now senesces at age 20 years. Not only is nothing lost in terms of survivorship, but further resources are released for growth and reproduction. This means that fitness continues to rise as the investment in maintenance is further reduced, in other words, as the boundary is crossed from the non-senescing to the senescing condition.

This verbal argument is sufficient to explain the form of the fitness curve in figure 1. Because fitness rises as the organism moves away from either extreme ($s = 0$ or $s = 1$), there is an optimum at some intermediate value. (The argument does not establish the uniqueness of the optimum, but for a simple life history a unique optimum is likely.) Secondly, the optimum occurs at a lower investment in somatic maintenance than is needed for indefinite survival. The optimum occurs at the point where the cost to survival of further reducing the investment in maintenance becomes large enough to cancel the benefit of any resulting increase in the rates of growth and reproduction.

This explanation for the evolution of senescence is termed the disposable soma theory for its analogy with the manufacture of disposable goods. In essence, the theory recognizes that all that is needed is a soma that remains in good condition through its normal expectation of life in the wild. Better maintenance than this is a waste, so the optimum is less than what is required for indefinite survival. This leads to the explicit predictions that (i) senescence is the result of the accumulation of somatic defects, and (ii) longevity is regulated through the efficiency of somatic maintenance processes.

3. EVOLUTION OF LIFESPAN

Species exhibit great variation in their lifespans. Among mammals alone, species' lifespans range over nearly two orders of magnitude. How does the evolution of species' lifespan differences relate to the theories on evolution of senescence?

We have just seen in the disposable soma theory that it is the presence of environmental mortality which makes it not worthwhile to invest in better maintenance than is needed to preserve somatic functions through the normal expectation of life in the wild. Expectation of life in the wild for an iteroparous species is largely determined by the prevailing level of environmental mortality. This is because most deaths occur in young animals through accidents, predation, and infectious

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Table 1. *Evolution of lifespan in response to varying the level of environmental mortality*

(The centre row corresponds to a life history fitted to data from the mouse, *Mus musculus* (see Appendix). The minimum maintenance level required for indefinite lifespan (s') is set at 0.8.)

environmental mortality[a]	maximum reproductive rate[b]	optimal maintenance level	lifespan[c]
10.0	8.2	0.37	20
5.0	5.2	0.45	29
3.2	4.0	0.50	36
2.0	3.2	0.56	45
1.0	2.2	0.65	70

[a] % per month.
[b] births female^{-1} month^{-1}.
[c] 99th percentile of adult survival (months).

disease, with many species showing little or no evidence of senescence in the wild (see, for example, Lack 1954; Promislow 1991).

When the level of environmental mortality is high, it is less worthwhile to invest heavily in maintenance and more worthwhile to invest in rapid growth and reproduction, and vice versa. Thus, it is clear that in the disposable soma theory the major driving force in the evolution of longevity is likely to be the prevailing level of environmental mortality. This can be studied in detail with the model described in the Appendix. The model is applied by requiring that the set of parameter values defining the survivorship and fecundity sechedules, $l(x;s)$ and $m(x;s)$, satisfy the constraint $r = 0$ for $s = s^*$, in other words, that a species should be at ecological equilibrium.

Starting from a point in the parameter space which satisfies this constraint, one can explore trajectories through this point which correspond to allowable evolutionary paths. An example is shown in table 1, where the trajectory tracks the effects of varying the level of environmental mortality. The centre row of the table defines a starting point based on data for the mouse, *Mus musculus* (see Appendix). Colonization of a more dangerous niche, equivalent to moving up the table, can occur successfully only if there is a concomitant increase in fecundity. The optimum level of investment in maintenance is reduced, together with lifespan. Moving in the other direction, down the table, a reduction in the level of environmental mortality is associated with increasing the optimum investment in maintenance, reducing fecundity, and increasing lifespan. The first, second and fourth columns of table 1 reveal correlations of the type that are familiar from the study of natural populations. What the disposable soma theory adds is the third column. This is an explicit prediction of the mechanism by which these correlations are generated physiologically, namely by varying the optimal investment in maintenance.

The level of environmental mortality plays a similarly central role in the evolution of lifespan in terms of antagonistic pleiotropy, although this theory's predictions with regard to the mechanism of lifespan determination are less explicit. Because most deaths in iteroparous adults are due to environmental causes, as already noted, the dominant factor influencing the rate of decline in the force of natural selection is the level of adult environmental mortality. The rate of decline in the force of natural selection is the key to determining what age is meant by 'late', in relation to the late deleterious fitness effects of antagonistically pleiotropic genes. Therefore, a high level of environmental mortality should be associated with short lifespan, and vice versa.

4. COSTS OF MAINTENANCE AND REPRODUCTION

The idea of costs of maintenance and reproduction has been used in this paper until now without specifying the sources and possible magnitudes of these costs. In the disposable soma theory, these costs form the basis of the theory and therefore play an essential part. In the antagonistic pleiotropy theory, as originally described by Williams (1957), a more general concept of pleiotropy was advanced. As an example, Williams cited a mutation arising that has a favourable effect on the calcification of bone in the developmental period but which expresses itself in a subsequent somatic environment in the calcification of the connective tissue of the arteries. During recent years, however, advocacy of the antagonistic pleiotropy theory has emphasized the trade-offs between survival and fecundity. With this shift in focus the antagonistic pleiotropy theory has become rather similar to the disposable soma theory and now also rests heavily on the idea of costs of maintenance and reproduction.

The recognition of a cost of reproduction has long been a major theme in ecology (Stearns 1976; Bell 1980; Partridge & Harvey 1988). Patently, there are substantial costs in the production of progeny and in the repertoire of morphological adaptations and behaviours associated with reproduction.

Costs of maintenance, although mentioned passingly as the obverse of reproductive effort, have received considerably less attention. Kirkwood (1981) reviewed the general problem of the evolution of maintenance and repair capabilities. For any repair or maintenance process to evolve, three basic conditions must be fulfilled. First, the organism must be able to survive the damage at least for long enough for repair to take place. Secondly, the information to restore the damaged part to its undamaged form must be available (the requirement of 'repeatability'). Thirdly, the overall benefit of repair, in terms of its effect on fitness must outweigh its cost. For severe forms of damage the fulfilment of all three conditions is less likely than for minor damage. Thus, the phylogenic distribution of major repair functions is likely to be less uniform than for correction of minor defects. This is presumably the reason why regeneration ability varies markedly between species (Kirkwood 1981; Reichman 1984). Basic maintenance processes, on the other hand, are expected to be more evenly distributed, and we observe similar mechanisms in virtually all species.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Maintenance costs arise at three principal levels. The first comprises the costs incurred in those aspects of the construction of non-renewing parts, like teeth, which are concerned with durability. It might be argued that these are not really costs of maintenance, as such. They are, however, a part of the overall maintenance picture so we include them here. The second level comprises the cost of maintenance involving cell renewal. The way skin maintains itself is one example, the immune system another. The third level involves the processes of intracellular maintenance. These are particularly important because of their ubiquity. All cells require them, and there are striking similarities between basic cell maintenance processes among very different forms of life. Basic cell maintenance processes are also being found to be quite costly (see Kirkwood *et al.* 1986). Maintenance of DNA, for instance, involves several different repair systems, each tailored for particular types of damage (Sedgwick 1986). The fidelity of DNA replication is maintained by the highly tuned proofreading capacity of DNA polymerases. Proofreading is metabolically expensive, as can be shown by *in vitro* studies on mutant polymerases with altered proofreading capabilities (see Kirkwood *et al.* 1986, pp. 5–6). Accuracy in protein synthesis is also important in maintaining cell viability, and this too is costly. The cost of proofreading the charging of tRNA by aminoacyl-tRNA synthetases has been estimated to account for as much as 2% of the energy budget of a cell (Savageau & Freter 1979), and this is just one of several operations in accurate protein synthesis. Similarly, there are energy-consuming enzymic processes to degrade abnormal proteins (Hipkiss 1989) and to protect cells against the highly reactive oxygen radicals that arise as by-products of aerobic metabolism (Halliwell & Gutteridge 1989).

Given that each of these maintenance processes has its costs, some quite considerable, we expect the investment in them to be optimized at a level below that which permits indefinite survival. What we also expect is some degree of harmonization between rates of accumulation of different types of damage, which is probably part of the reason why attempts to explain senescence in terms of just DNA damage, or just protein errors, for example, have yielded inconclusive results (see, for example, Warner *et al.* 1987).

5. TESTS OF THE EVOLUTIONARY THEORIES

(*a*) *Evolutionary versus non-evolutionary theories*

Non-evolutionary theories of senescence are those which suggest that senescence does not require an evolutionary explanation and arises, for example, as the inevitable result of wear-and-tear. Although there are logical arguments that can be advanced against the inevitability of wear-and-tear in a biological organism (see, for example, Williams 1957), the evolutionary theories could be falsified if it was shown that the presence and absence of senescence failed to correlate with the basic requirements of the evolutionary theories.

Bell (1984) addressed this point. By examining several freshwater invertebrates, Bell found that those species that reproduced vegetatively did not senesce, whereas those that laid eggs did. This confirms the importance of the soma/germ-line distinction and supports the idea that senescence evolves as a consequence of natural selection acting upon age-specific rates of reproduction and survival.

(*b*) *Comparative studies*

A second approach to testing the evolutionary theories is through comparative studies, particularly of somatic maintenance mechanisms. In an often-cited study Hart & Setlow (1974) found a strong positive correlation between a particular form of DNA repair – excision repair of pyrimidine dimers – and lifespan, and this result has been confirmed in other laboratories (see Rattan 1989). However, the criticism can be made of these and most other comparative studies to date that they have failed to take proper account of potentially confounding variables, such as body size, age of cell donor, and biopsy site.

In spite of the limitations of current comparative data on somatic maintenance mechanisms, it is probably safe to conclude that long-lived organisms look after their cells better than short-lived organisms, one clear example being that the lifetime risk of cancer is similar for mice and humans, despite their great differences in body size and lifespan. However, better comparative studies would be welcome.

(*c*) *Selection for altered lifespan*

The third approach to testing the evolutionary theories is to select for altered lifespan. Because many things can shorten life, and not all of these have to do with senescence, the most interesting challenge is to select for increased lifespan. This was first done successfully using *Drosophila* spp. by Wattiaux (1968*a*, *b*), and has since been repeated several times in *Drosophila melanogaster* (e.g. Rose & Charlesworth 1980, 1981*b*; Rose 1984; Luckinbill & Clare 1985). The basic procedure followed in these experiments has been to select indirectly for longevity by selecting for late female fecundity. This is particularly likely to work where there is a trade-off between early fecundity and late survival, and Rose & Charlesworth (1981*a*) showed that in outbred populations the necessary negative genetic covariance in life-history characters appears to exist. The importance of using outbred populations is both to ensure the necessary genetic variation and to avoid inbreeding depression. Inbreeding depression can cause artifactual strong positive correlations between survival and fecundity (see Giesel 1979; Rose 1984*a*).

The general experimental strategy involves raising two sets of populations. The 'young' control lines are reproduced under standard conditions, breeding from young females. The 'old' lines are reproduced from old females by selecting only eggs laid towards the end of the reproductive period. Because the selection does in fact work, the egg collection in the 'old' lines can take place later and later in successive generations.

A necessary feature of the experimental procedure is that the culture must be grown at high larval density (Luckinbill & Clare 1985; Clare & Luckinbill 1985). Failure to control the larval density among 'young' and 'old' lines can produce genotype-by-environment interactions that interfere with the selection for postponed senescence. These probably explain earlier discordant results of Lints & Hoste (1974, 1977). The need to control larval density at high rather than low levels is that when exposed to a rich, non-competitive environment, the larvae respond with rapid growth and early reproduction, vitiating the effects of selection for late fecundity. Replication of the selected lines is also important because if there are only one or two selected lines used for comparison, then they may have spuriously differentiated in response to selection due to linkage and related finite-population effects.

A study by Rose (1984*b*) gave results typical of the above selection procedure. Rose (1984*b*) found that (i) mean adult lifespan in the 'old' lines was increased compared with the 'young' lines, and (ii) females in the 'old' lines laid fewer eggs early in life and somewhat more eggs late in life than the females in the 'young' lines. The mean lifespan for females in the 'old' lines of Rose (1984*b*) was increased by 29% after 15 generations of selection. A smaller increase was seen in the mean lifespan of males.

Study of morphological differences between 'young' and 'old' lines revealed no overall size change (Rose *et al.* 1984; Luckinbill *et al.* 1988*a*). Early ovary mass in the 'old' lines was found to be substantially reduced (Rose *et al.* 1984), consistent with the reduced early fecundity. Studies of stress resistance in the 'old' lines (Service *et al.* 1985; Service 1987) found that postponed senescence was associated with increased resistance to starvation, desiccation, and low levels of ambient alcohol. In addition, flight duration is increased in the longer-lived lines (Luckinbill *et al.* 1988*a*; Graves *et al.* 1988; Graves & Rose 1990).

The findings from the selection experiments in *Drosophila* provide a body of evidence consistent with the idea that selection has exploited a trade-off between survival and fecundity. This fits with the predictions of the antagonistic pleiotropy theory, and will also be consistent with the disposable soma theory if it turns out that the reason for the increased longevity in the old lines is that the flies invest more resources in somatic maintenance.

6. LEVELS OF TRADE-OFF BETWEEN SURVIVAL AND FECUNDITY

Theory and evidence support the idea of trade-offs between late survival and early fecundity. But at what level might these trade-offs be operating?

First, the trade-offs might be non-metabolic. For instance, if reproductive activity reduces survival by increased risk exposure, or wear-and-tear, then simply rescheduling fecundity to later ages will increase survivorship. Secondly, the trade-offs might be direct metabolic trade-offs. These are trade-offs that can happen if reproduction and maintenance draw directly from the same supply of resources within the organism, so that reducing the demand for one automatically increases the supply to the other. Thirdly, the trade-offs might be indirect metabolic trade-offs, such that resources are shared but not directly convertible between reproduction and maintenance. For instance, reducing the level of proofreading DNA replication may mean that cells consume less energy in maintenance, but it does not necessarily mean that the organism can produce larger or more frequent litters. Each investment is independently regulated, and reducing one merely provides a more favourable opportunity for adaptations increasing the other.

In general, non-metabolic and direct metabolic trade-offs are likely to be associated with greater plasticity of the life history, both genotypic and phenotypic. Indirect metabolic trade-offs will be slower to respond to altered circumstances, including those imposed in selection experiments.

With this perspective, what might be going on in the selection for postponed senescence in *Drosophila melanogaster*? It has been known for some time that in *Drosophila* spp. sexual activity and reproduction are directly detrimental to survival (Maynard Smith 1958; Kidwell & Malick 1967; Partridge & Farquhar 1981; Partridge *et al.* 1986, 1987; Fowler & Partridge 1989). This non-metabolic trade-off, whatever its physiological basis, means that simply postponing fecundity in the 'old' lines may be a major contributor to their increased mean lifespan. Luckinbill *et al.* (1987) reported that a single genetic factor appeared to be mainly responsible for the delay in senescence, consistent with a predominating non-metabolic trade-off. This estimate rested, however, on a method of calculation which questionably assumed an equal influence of the genes measured. Luckinbill *et al.* (1988*b*) later performed a more direct study using chromosome substitution, which suggested that longevity is under polygenic control with contributing elements on all chromosomes. However, one chromosome, the third chromosome, was found to be by far the most influential, accounting for two thirds of the observed effect in females.

The exact basis of the trade-offs between survival and fecundity in *Drosophila* remains to be discovered, and as Luckinbill *et al.* (1988*b*) point out, this will depend on locating and functionally analysing the individual genes that are involved. We note here, however, that although selection for postponed senescence has proved valuable in generating lines to compare, selection will expose most strongly those trade-offs that are most amenable to change and which respond quickest. These will tell us part, but not necessarily all of the story.

7. DISCUSSION

Two different approaches to understanding evolution of senescence lead to the same general conclusion, namely that a major factor is likely to have been the sacrifice of late survival in favour of enhanced early reproduction. One approach is through population genetics, particularly inspired by Medawar (1952) and

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Williams (1957). The foundation of this approach is the recognition that the force of selection declines with age. Because of this, genes that have beneficial effects early in life can be favoured by selection even if they produce major deleterious effects later on (antagonistic pleiotropy). The second approach stems from studies on the physiology of senescence, particularly of theories proposing that stochastic molecular damage is responsible. From asking how much an organism ought to invest in maintaining itself comes the disposable soma theory (Kirkwood 1977, 1981; Kirkwood & Holliday 1979), which asserts that the optimum investment in maintenance is less than the mimimum level required for indefinite survival.

The difference between the disposable soma theory and antagonistic pleiotropy is partly a difference between an optimality theory approach (see Parker & Maynard Smith 1990) and a quantitative genetics approach, and partly about the level at which the two theories seek to explain senescence. The disposable soma theory assumes a trade-off of resources between maintenance (survival) and reproduction and shows that with this assumption the evolutionary optimum leads directly to senescence. The theory gives broad insights into the physiological basis of senescence and the genetic control of longevity, and it thus combines ultimate and proximate factors in a unified theory. The antagonistic pleiotropy theory assumes a more formal principle that trade-offs can occur between early beneficial and late deleterious effects of genes influencing the life history; the nature of the genes' action is not specified.

Is the disposable soma theory a causal subset of the antagonistic pleiotropy theory? One can answer yes to this question if the genes responsible for somatic maintenance functions are regarded as having the pleiotropic effects that they (i) prolong survival and (ii) consume resources which might otherwise be used for reproduction. It is then necessary to invert these effects to fit the antagonistic pleiotropy theory. In other words, it is by depressing the action of somatic maintenance genes that the benefit of enhanced early reproduction is generated at the expense of late senescence. The optimality approach obviates the need for such indirect reasoning. The two theories are more accurately seen as complementary than overlapping. The antagonistic pleiotropy theory is appropriate to the study of variance and covariance of life-history characters within a population and the effects of selection upon them. The disposable soma theory leads more directly to predictions about physiological and comparative aspects of longevity and senescence.

In suggesting that the sacrifice of late survival for early reproduction is the major factor in the evolution of senescence, we must not lose sight of other explanations. For instance, there may be pleiotropic effects not involving the trade-off of survival for fecundity, as was clearly envisaged by Williams (1957). Also, the iteroparous life history always provides scope for mutation accumulation, even if this is not the main driving force in the evolution of senescence. Mueller (1987) reported that preventing *Drosophila melanogaster* from breeding late led to reduced late fecundity, which he suggested was best explained as the result of mutation accumulation, arising from the absence of selection against mutations affecting late fecundity. Service *et al.* (1988) have also reported results in *D. melanogaster* consistent with mutation accumulation. After selecting successfully for postponed senescence, they reversed the direction of selection in some old lines. The original survival and fecundity patterns were restored, but some of the increased stress resistance remained unaltered. This, they suggested, was because the original selection had shifted some late-acting deleterious effects which were the result of mutation accumulation rather than pleiotropy.

The success of selection for postponed senescence in *Drosophila* has confirmed one of the main predictions of the theory that senescence has evolved by trading late survival for early reproduction. It has also provided us with a valuable experimental model to study senescence in this species. Just how far this model will take us remains to be seen. Recent studies by K. Fowler & L. Partridge (unpublished data) have reported a different pattern of response to selection for postponed senescence, where 'old' and 'young' did not differ in fecundity early in the lifespan, and where it was also found that the larval period was affected, with increased larval development time and lowered larval survival under competitive conditions. The effects of selection and the nature of the trade-offs that result need further study, including the effects on the larval stage of the life cycle.

Can similar selection work in other species, such as the mouse? Theory predicts it should, but it will of course be a much longer and more expensive experiment. Should we attempt it? Serious discussion of the feasibility of such a project has been taking place (Charlesworth 1988; Johnson 1988; Rose 1988, 1990). Will the response per generation of selection be as fast as in *Drosophila*? This will depend on the genetic variance and covariance in the population, and on the levels of trade-off which can be exploited.

Although selection experiments provide one avenue to explore the genetic basis of senescence, other avenues are provided by careful comparative studies between different species (see, for example, Sacher & Hart 1978), by genetic analysis of longevity mutants within a single species (see, for example, Johnson 1987), and by gene transfer studies in transgenic animals (see, for example, Epstein *et al.* 1987). The evolutionary view described in this paper leads us to predict that genes involved in regulating the trade-offs between costs of maintenance and costs of reproduction should be principal candidates for intensive study. The disposable soma theory leads us to understand senescence as the result of tuning the investment in somatic maintenance at a level that is enough to survive the natural expectation of life in the wild, but not higher. This is a prediction which is eminently testable. We must recognize, however, that evolutionary theory also tells us that in iteroparous organisms no single physiological process is likely to cause senescence on its own. The practical problem of teasing out individual contributions to the overall process of senescence remains a major challenge.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

APPENDIX

This appendix outlines the model used to obtain the results in figure 1 and table 1 (this is a modified version of an earlier model by Kirkwood & Holliday (1986) and Kirkwood (1990)). Survivorship $l(x;s)$ and fecundity $m(x;s)$ are defined as functions that depend on age x and investment in maintenance s. The form of $l(x;s)$ is determined by specifying juvenile and adult mortality. The age-distribution of juvenile mortality does not matter in the model and total juvenile mortality is defined as V, independent of s. Adult mortality rate μ is assumed to follow the Gompertz–Makeham equation

$$\mu = \alpha\, e^{\beta x} + \gamma,$$

where the exponential term represents intrinsic, age-dependent mortality, and the constant γ represents extrinsic, age-independent 'environmental mortality'. When $\beta > 0$, the adult mortality rate increases with age and senescence occurs. This mortality pattern provides a good fit to survival data in several species (Sacher 1978; Finch *et al.* 1990). The resulting form for $l(x;s)$ is

$$l(x;s) = (1-V)\exp\left[-\alpha(e^{\beta x}-e^{\beta a})/\beta - \gamma(x-a)\right].$$

The dependence on s is introduced by making β a decreasing function that reaches zero at $s = s'$ (e.g. $\beta = \beta_0(s'/s-1)$ for $s < s'$; $\beta = 0$ for $s \geqslant s'$). This has the required property that senescence occurs more slowly as s is increased, until for $s \geqslant s'$ senescence does not occur at all.

Fecundity is specified by assuming that reproduction begins at peak rate h at age a, and that if $\beta > 0$ (i.e. if senescence occurs) the reproductive rate declines like a survival curve driven by the intrinsic, exponential component of the adult mortality rate. This has the advantage of linking the effects of senescence on survival and fecundity through the same parameter β, and gives

$$m(x;s) = h\exp\left[-\alpha(e^{\beta x}-e^{\beta a})/\beta\right] \quad \text{for} \quad x \geqslant a.$$

The parameters h and a are made to depend on s, because increasing the investment in maintenance leaves fewer resources for growth and reproduction, and vice versa. For example, we assume $a = a_{\min}/(1-s)$ and $h = h_{\max}(1-s)$. Provided that β and h are decreasing functions of s, and a is an increasing function of s, the precise forms of these functions are not critical for the general pattern of results which is obtained.

The example of the mouse (table 1, centre row) was fitted using data on age at first reproduction a (taken as 6 weeks), maximum reproductive rate h (taken as 1.0 birth female^{-1} week^{-1}), and the pattern of intrinsic age-dependent adult mortality (taken as a Gompertz function of the form $0.01e^{0.1x}$, where x is age in months; see Sacher (1978)). From these data, and applying the constraint $r = 0$ for $s = s^*$, values for juvenile mortality (95%), environmental mortality ($\gamma = 0.032$), and lifespan (36 months) were determined. The value of s' was set at 0.8, and the value of s^* found to be 0.5. A degree of freedom is available to define the arbitrary scale for s so that s^* takes a convenient reference value, but whatever scaling is chosen s^* is always well below s'.

REFERENCES

Bell, G. 1980 The costs of reproduction and their consequences. *Am. Nat.* **116**, 45–76.

Bell, G. 1984 Evolutionary and nonevolutionary theories of senescence. *Am. Nat.* **124**, 600–603.

Charlesworth, B. 1980 *Evolution in age-structured populations*. Cambridge University Press.

Charlesworth, B. 1988 Selection for longer-lived rodents. *Growth, Dev. Aging* **52**, 211.

Clare, M. J. & Luckinbill, L. S. 1985 The effects of gene–environment interaction on the expression of longevity. *Heredity, Lond.* **55**, 19–29.

Cole, L. C. 1954 The population consequences of life history phenomena. *Q. Rev. Biol.* **29**, 103–137.

Comfort, A. 1979 *The biology of senescence*, 3rd edn. Edinburgh: Churchill Livingstone.

Epstein, C. J., Avraham, K. B., Lovett, M., Smith, S., Elroy-Stein, O., Rotman, G., Bry, C. & Groner, G. 1987 Transgenic mice with increased Cu/Zn-superoxide dismutase activity: animal model of dosage effects in Down syndrome. *Proc. natn. Acad. Sci. U.S.A.* **84**, 8044–8048.

Ewens, W. J. 1979 *Mathematical population genetics*. Berlin: Springer-Verlag.

Finch, C. E. & Schneider, E. L. 1985 *Handbook of the biology of aging*. 2nd edn. New York: Van Nostrand Rheinhold.

Finch, C. E., Pike, M. C. & Witten, M. 1990 Slow mortality rate accelerations during aging in some animals approximate that of humans. *Science, Wash.* **249**, 902–905.

Fisher, R. A. 1930 *The genetical theory of natural selection*. Oxford University Press. (Page numbers in text refer to the 1958 2nd edn, New York: Dover.)

Fowler, K. & Partridge, L. 1989 A cost of mating in female fruitflies. *Nature, Lond.* **338**, 760–761.

Giesel, J. T. 1979 Genetic co-variation of survivorship and other fitness indices in *Drosophila melanogaster*. *Exp. Geront.* **14**, 323–328.

Graves, J. L. & Rose, M. R. 1990 Flight duration in *Drosophila melanogaster* selected for postponed senescence. In *Genetic effects on aging* II (ed. D. E. Harrison), pp. 59–65. Caldwell, New Jersey: Telford Press.

Graves, J. L., Luckinbill, L. S. & Nichols, A. 1988 Flight duration and wing beat frequency in long- and short-lived *Drosophila melanogaster*. *J. Insect Physiol.* **34**, 1021–1026.

Haldane, J. B. S. 1941 *New paths in genetics*. London: George Allen & Unwin.

Halliwell, B. & Gutteridge, J. M. C. 1989 *Free radicals in biology and medicine*, 2nd edn. Oxford University Press.

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

Hart, R. W. & Setlow, R. B. 1974 Correlation between deoxyribonucleic acid excision-repair and lifespan in a number of mammalian species. *Proc. natn. Acad. Sci. U.S.A.* **71**, 2169–2173.

Hipkiss, A. R. 1989 The production and removal of abnormal proteins: a key question in the biology of ageing. In *Human ageing and later life* (ed. A. M. Warnes), pp. 15–28. London: Edward Arnold.

Johnson, T. E. 1987 Aging can be genetically dissected into component processes using long-lived lines of *Caenorhabditis elegans*. *Proc. natn. Acad. Sci. U.S.A.* **84**, 3777–3781.

Johnson, T. E. 1988 Thoughts on the selection of longer-lived rodents. *Growth, Dev. Aging* **52**, 207–209.

Kidwell, J. F. & Malick, L. E. 1967 The effect of genotype, mating status, weight and egg production on longevity in *Drosophila melanogaster*. *J. Hered.* **58**, 169–172.

Kirkwood, T. B. L. 1977 Evolution of ageing. *Nature, Lond.* **270**, 301–304.

Kirkwood, T. B. L. 1981 Repair and its evolution: survival versus reproduction. In *Physiological ecology: an evolutionary approach to resource use* (ed. C. R. Townsend & P. Calow), pp. 165–189. Oxford: Blackwell Scientific Publications.

Kirkwood, T. B. L. 1985 Comparative and evolutionary aspects of longevity. In *Handbook of the biology of aging*, 2nd edn (ed. C. E. Finch & E. L. Schneider), pp. 27–44. New York: Van Nostrand Reinhold.

Kirkwood, T. B. L. 1990 The disposable soma theory of aging. In *Genetic effects on aging* II (ed. D. E. Harrison), pp. 9–19. Caldwell, New Jersey: Telford Press.

Kirkwood, T. B. L. & Cremer, T. 1982 Cytogerontology since 1881: a reappraisal of August Weismann and a review of modern progress. *Hum. Genet.* **60**, 101–121.

Kirkwood, T. B. L. & Holliday, R. 1979 The evolution of ageing and longevity. *Proc. R. Soc. Lond.* B **205**, 531–546.

Kirkwood, T. B. L. & Holliday, R. 1986 Ageing as a consequence of natural selection. In *The biology of human ageing* (ed. A. J. Collins & A. H. Bittles), pp. 1–16. Cambridge University Press.

Kirkwood, T. B. L., Rosenberger, R. F. & Galas, D. J. 1986 *Accuracy in molecular processes: its control and relevance to living systems*. London: Chapman & Hall.

Lack, D. 1954 *The natural regulation of animal numbers*. Oxford University Press.

Lints, F. A. & Hoste, C. 1974 The Lansing effect revisited. I. Life-span. *Exp. Geront.* **9**, 51–69.

Lints, F. A. & Hoste, C. 1977 The Lansing effect revisited. II. Cumulative and spontaneously reversible parental age effects on fecundity in *Drosophila melanogaster*. *Evolution* **31**, 387–404.

Luckinbill, L. S. & Clare, M. J. 1985 Selection for life span in *Drosophila melanogaster*. *Heredity, Lond.* **55**, 9–18.

Luckinbill, L. S., Clare, M. J., Krell, W. L., Cirocco, W. C. & Richards, P. A. 1987 Estimating the number of genetic elements that defer senescence in *Drosophila*. *Evol. Ecol.* **1**, 37–46.

Luckinbill, L. S., Graves, J. L., Tomkiw, A. & Sowirka, O. 1988*a* A qualitative analysis of some life-history correlates of longevity in *Drosophila melanogaster*. *Evol. Ecol.* **2**, 85–94.

Luckinbill, L. S., Graves, J. L., Reed, A. H. & Koetsawang, S. 1988*b* Localizing genes that defer senescence in *Drosophila melanogaster*. *Heredity, Lond.* **60**, 367–374.

Maynard Smith, J. 1958 The effects of temperature and of egg-laying on the longevity of *Drosophila subobscura*. *J. exp. Biol.* **35**, 832–842.

Maynard Smith, J. 1962 Review lectures on senescence. I. The causes of ageing. *Proc. R. Soc. Lond.* B **157**, 115–127.

Medawar, P. B. 1946 Old age and natural death. *Mod. Quart.* **2** (new series), 30–49.

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

Medawar, P. B. 1955 The definition and measurement of senescence. In *Ciba Foundation Colloquia on ageing*, vol. 1 (ed. G. E. W. Wolstenholme & M. P. Cameron), pp. 4–15. London: Churchill.

Medvedev, Z. A. 1990 An attempt at a rational classification of theories of ageing. *Biol. Rev.* **65**, 375–398.

Mueller, L. D. 1987 Evolution of accelerated senescence in laboratory populations of *Drosophila*. *Proc. natn. Acad. Sci. U.S.A.* **84**, 1974–1977.

Parker, G. A. & Maynard Smith, J. 1990 Optimality theory in evolutionary biology. *Nature, Lond.* **348**, 27–33.

Partridge, L. & Farquhar, M. 1981 Sexual activity reduces longevity of male fruitflies. *Nature, Lond.* **294**, 580–582.

Partridge, L. & Harvey, P. H. 1988 The ecological context of life-history evolution. *Science, Wash.* **241**, 1449–1455.

Partridge, L., Fowler, K., Trevitt, S. & Sharp, W. 1986 An examination of the effects of males on the survival and egg-production rates of female *Drosophila melanogaster*. *J. Insect Physiol.* **33**, 745–749.

Promislow, D. 1991 The evolution of senescence in mammals: comparative evidence. *Evolution*. (submitted.)

Rattan, S. I. S. 1989 DNA damage and repair during cellular ageing. *Int. Rev. Cytol.* **116**, 47–88.

Reichman, O. J. 1984 Evolution of regeneration capabilities. *Am. Nat.* **123**, 752–763.

Robertson, O. H. 1961 Prolongation of the lifespan of Kokanee salmon (*Oncorhynkus nerka kennerlyi*) by castration before beginning of gonad development. *Proc. natn. Acad. Sci. U.S.A.* **47**, 609–621.

Rose, M. R. 1982 Antagonistic pleiotropy, dominance, and genetic variation. *Heredity, Lond.* **48**, 63–78.

Rose, M. R. 1984*a* Genetic covariation in *Drosophila* life history: untangling the data. *Am. Nat.* **123**, 565–569.

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

Rose, M. R. 1985 Life history evolution with antagonistic pleiotropy and overlapping generations. *Theor. Popul. Biol.* **28**, 342–358.

Rose, M. R. 1988 Response to 'Thoughts on the selection of longer-lived rodents' *Growth, Dev. Aging* **52**, 209–211.

Rose, M. R. 1990 Should mice be selected for postponed aging? A workshop summary. *Growth, Dev. Aging* **54**, 7–15.

Rose, M. R. 1991 *Evolutionary biology of aging*. New York: Oxford University Press.

Rose, M. R. & Charlesworth, B. 1980 A test of evolutionary theories of senescence. *Nature Lond.* **287**, 141–142.

Rose, M. R. & Charlesworth, B. 1981*a* Genetics of life history in *Drosophila melanogaster*. I. Sib analysis of adult females. *Genetics* **97**, 173–186.

Rose, M. R. & Charlesworth, B. 1981*b* Genetics of life history in *Drosophila melanogaster*. II. Exploratory selection experiments. *Genetics* **97**, 173–186.

Rose, M. R., Dorey, M. L., Coyle, A. M. & Service, P. M. 1984 The morphology of postponed senescence in *Drosophila melanogaster*. *Can. J. Zool.* **62**, 1576–1580.

Sacher, G. A. 1978 Evolution of longevity and survival characteristics in mammals. In *The genetics of aging* (ed. E. L. Schneider), pp. 151–167. New York: Plenum.

Sacher, G. A. & Hart, R. W. 1978 Longevity, aging and comparative cellular and molecular biology of the house mouse, *Mus musculus*, and the white-footed mouse, *Peromyscus leucopus*. In *Genetic effects on aging* (ed. D. Bergsma & D. E. Harrison), pp. 71–96. New York: Alan Liss.

Savageau, M. A. & Freter, R. R. 1979 On the evolution of accuracy and cost of proofreading tRNA aminoacylation. *Proc. natn. Acad. Sci. U.S.A.* **76**, 4507–4510.

Sedgwick, S. G. 1986 Stability and change through DNA repair. In *Accuracy in molecular processes: its control and relevance to living systems* (ed. T. B. L. Kirkwood, R. F. Rosenberger & D. J. Galas), pp. 233–289. London: Chapman & Hall.

Service, P. M. 1987 Physiological mechanisms of increased stress resistance in *Drosophila melanogaster* selected for postponed senescence. *Physiol. Zool.* **60**, 321–326.

Service, P. M., Hutchinson. E. W., MacKinley, M. D. & Rose, M. R. 1985 Resistance to environmental stress in *Drosophila melanogaster* selected for postponed senescence. *Physiol. Zool.* **58**, 380–389.

Service, P. M., Hutchinson. E. W. & Rose, M. R. 1988 Multiple genetic mechanisms for the evolution of senescence in *Drosophila melanogaster*. *Evolution* **42**, 708–716.

Sibly, R. M. & Calow, P. 1986 *Physiological ecology of*

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

animals: an evolutionary approach. Oxford: Blackwell Scientific Publications.

Stearns, S. C. 1976 Life-history tactics: a review of the ideas. *Q. Rev. Biol.* **51**, 3–47.

Townsend, C. R. & Calow, P. 1981 *Physiological ecology: an evolutionary approach to resource use*. Oxford: Blackwell Scientific Publications.

Warner, H. R., Butler, R. N., Sprott, R. L. & Schneider, E. L. 1987 *Modern biological theories of aging*. New York: Raven Press.

Wattiaux, J. M. 1968*a* Parental age effects in *D. pseudoobscura*. *Exp. Gerontol.* **3**, 55–61.

Wattiaux, J. M. 1968*b* Cumulative parental age effects in *D. subobscura*. *Evolution* **22**, 406–421.

Williams, G. C. 1957 Pleiotropy, natural selection and the evolution of senescence. *Evolution* **11**, 398–411.

Wodinsky, J. 1977 Hormonal inhibition of feeding and death in *Octopus*: control by optic gland secretion. *Science, Wash.* **198**, 948–951.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES