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Short Review

The evolutionary genetics of ageing and longevity

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Evolutionary theories of ageing are based on the observation that the efficacy of natural selection decreases with age. This is because, even without ageing, individuals will die of environmental causes, such as predation, disease and accidents. Ageing is thought to have evolved as the result of optimising fitness early in life. A second process, namely the progressive accumulation of mutations with effects late in life, will reinforce this result. Longevity of a species is therefore determined by the amount of environmental mortality caused by the ecology of a species. The experimental data concerning the relative roles of both processes are reviewed here. Recent discoveries of the levelling of mortality curves, and of age specific mutations in mutation accumulation lines of *Drosophila melanogaster*, require adjustments to the original models of the evolution of ageing and species longevity. These adjustments do not invalidate the underlying rationale of evolutionary theories of ageing. With current developments in QTL mapping and genetic association studies, the unravelling of the ageing process has the potential to progress rapidly.

Keywords: ageing, antagonistic pleiotropy, life history, mortality, mutation.

Introduction

The ageing phenomenon

Ageing is a very common feature in metazoans (Bell, 1988; Finch, 1990) and can be described as the total effect of those intrinsic changes in an organism that adversely affect its vitality and that render it more susceptible to the many factors that can cause death. Typically, mortality rates accelerate with time, which is reflected in a rectangular survival-curve (Fig. 1). Acceleration of mortality rates has been documented in natural populations (Promislow, 1991; Gaillard *et al*., 1994; Ricklefs, 1998), but it is not clear whether this effect is the result of increases in external or internal causes of death. The full extent of ageing in a population will become apparent when most important external death hazards are removed. This can occur under captive or laboratory conditions, when average longevity is usually greatly extended. Note therefore that variation in longevity is not necessarily causally linked to variation in rate of ageing.

From an evolutionary perspective, ageing limits the reproductive potential of an individual and should as such be opposed by natural selection (Kirkwood & Rose, 1991; Partridge & Barton, 1993b). Therefore, the first issue evolutionary theories of ageing should explain is why has ageing evolved?

No doubt, internal and external damage contributes to an increase in mortality rate with age. With the advance of knowledge of physiology and molecular genetics, attention has turned to various sorts of damage to DNA, cells and tissues arising as a by-product of metabolism (Finch, 1990; Avise, 1993). The mechanisms contributing to ageing are as such stochastic. However, lifespan within species is uniform and under optimal conditions species have very different lifespans without any obvious differences in the risks of damage (Table 1). Clearly, species-specific longevities have a genetic basis and the ability to avoid or cope with internal and external damage has evolved (Finch, 1990; Avise, 1993; Partridge & Barton, 1993b). Therefore, the second issue evolutionary theories of ageing should explain is variation in lifespan among species.

Evolutionary explanation

Even if an organism is intrinsically immortal, it has a nonzero probability of dying because of extrinsic causes such as starvation, predation and accidents. The probability of survival decreases in the course of life, and, since natural selection is effective only through the reproductive output of surviving individuals, the strength of natural selection decreases with age (Fig. 2; Medawar, 1952; Williams, 1957; Hamilton, 1966). This observation underpins the evolution of ageing, for which two scenarios have been described.

The first scenario explains ageing through the accumulation of late-acting deleterious mutations. Medawar (1952) reasoned that mutations with late age-specific effects are subject to weaker selection than mutations with early age-specific effects. Mutations with deleterious effects on survival and fertility early in life will be swiftly eliminated from the population. However, late-acting deleterious mutations cannot be so easily

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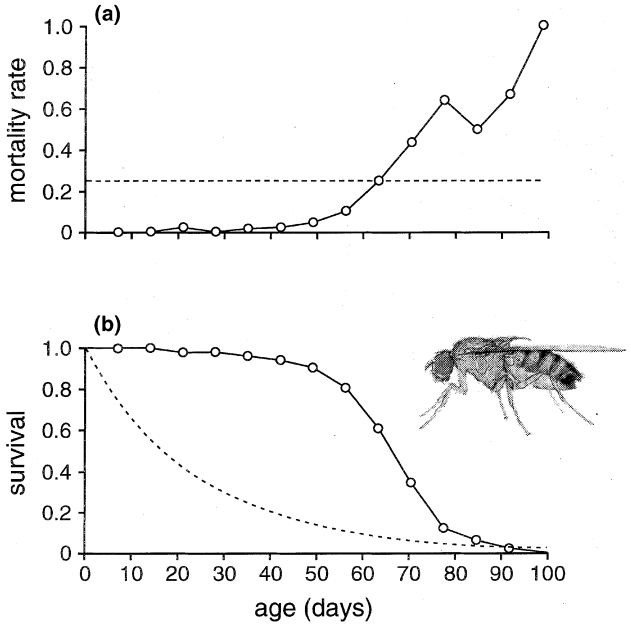

Fig. 1 Relationship between age and mortality rate (A), and between age and survival (B). The solid curve represents a population of *Drosophila melanogaster* males grown and kept at 25°C. The (exponential) increase in mortality rate with age (A) indicates the presence of ageing. For comparison the dashed curves are drawn; these represent a hypothetical non-ageing population (i.e. when the mortality rate is constant with age).

Table 1 Maximum lifespan for several species (data derived from Finch, 1990)

Species	Common name	Lifespan (years)
Lumbricus terrestris	Common earthworm	> 6
Lymnaea stagnalis	Pond snail	2
Drosophila melanogaster	Fruit fly	0.3
Acipenser fulvescens	Lake sturgeon	> 150
Lebistes reticulatus	Guppy	5
Apus apus	Common swift	21
Coturnix coturnix	Japanese quail	5
Mus musculus	House mouse	4–5
Myotis lucifugis	Little brown bat	> 32
Macaca mulatta	Rhesus monkey	> 35
Homo sapiens	Human (female)	> 110

removed, since most if not all of the individuals carrying such mutations will have reproduced and died from extrinsic mortality causes before the mutations have the chance to take effect. Thus, in the course of evolution there has been an opportunity for the accumulation of late-acting deleterious mutations. This will become apparent as ageing when extrinsic mortality is greatly reduced, as seen under favourable conditions in captivity.

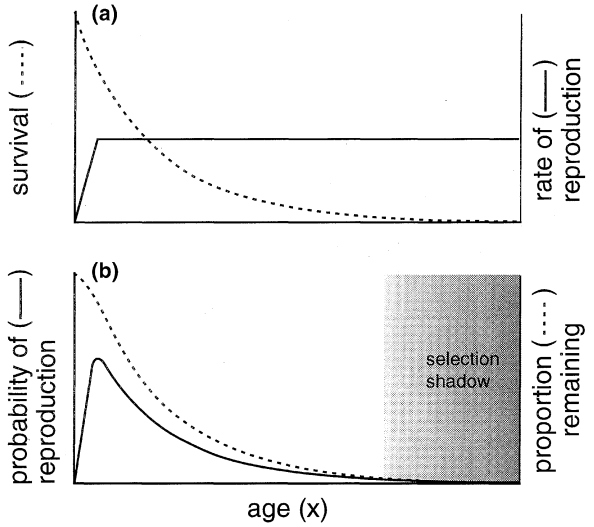

Fig. 2 (A) Survival (l_x) and reproductive rate (m_x), and (B) the probability of reproduction and proportion of reproduction remaining for an individual aged x, for a hypothetical non-ageing population. The probability of reproduction at age x, is taken as the product of l_x and m_x. The proportion of reproduction remaining can be taken as a measure for the strength of natural selection at age x. It appears that the strength of natural selection declines with age even in the absence of ageing. Genes can escape the scrutiny of natural selection if their effects occur in the selection shadow.

The second scenario introduces the idea of trade-offs (Kirkwood & Rose, 1991). Williams (1957) suggested that genes with beneficial effects on fitness early in life, but detrimental effects on fitness late in life would be selected for because of the diminishing power of natural selection with age. Williams' theory, which has become known as the antagonistic pleiotropy theory of ageing, suggests that ageing evolved as a by-product of natural selection for beneficial effects on early reproductive output. This optimization argument was developed further in the disposable soma theory which emphasized the trade-off between reproduction and somatic repair and maintenance (Kirkwood & Holliday, 1979; Kirkwood & Rose, 1991). This theory closes the gap between mechanistic and evolutionary views on ageing. Hence, the study of ultimate causation has the potential to indicate proximate causation and candidate processes (longevity assurance genes and processes).

Evolutionary theories predict when ageing will evolve. The critical condition for the evolution of ageing is distinct parents and offspring (Partridge & Barton, 1993b). Metazoans generally fulfil this condition because they have distinct somatic and germinal tissues. This notion also applies to asexual multicellular organisms that reproduce through parthenogenesis. For example, in six freshwater oligochaetes the asexual egg-producing species showed senescent decline in survival rate, but the species that reproduced by binary fission did not (Bell, 1984). In the latter, parent and offspring cannot be distinguished, therefore the intensity of natural selection does not change through life and individual ageing will not evolve.

Genetic details

At the time of their historical development, both mutation accumulation and antagonistic pleiotropy were not specific about genetic details, such as the timing of gene transcription and the expression of gene effects. The consensus is that both processes are not mutually incompatible and therefore both forces are expected to contribute to present-day ageing (Partridge & Barton, 1993a). However, the interpretation of mutation accumulation becomes less clear when the origin of ageing is considered (Kirkwood & Holliday, 1979; Kirkwood, 1985; Hoekstra, 1993). Although development could provide a measure for the passage of time up to maturity, it is not clear why there would be early and late expression of genes in a life history that potentially can go on forever. This problem does not play a role in antagonistic pleiotropy for genes that are more or less continually expressed but whose negative side-effects accumulate in the course of life. Therefore, mutation accumulation is likely to be a reinforcing consequence of ageing, rather than a direct causal factor in the origin of ageing (Kirkwood, 1985).

Testing the alternatives

Central to the distinction between antagonistic pleiotropy and mutation accumulation is the nature of genetic correlation between early and late life history fitness components. Most experimental research on ageing has been limited to a few model systems such as *Drosophila melanogaster* (Mayer & Baker, 1985) and *Caenorhabditis elegans* (Lithgow, 1996). I will discuss the results of four approaches: selection experiments, analysis of (standing) genetic variation, major genetic effects and demography. The integration of these approaches will provide the future framework essential for our understanding of the ageing process in terms of evolution, genetics, physiology and proximate mechanisms.

Selection experiments

One of Williams's (1957) original deductions from antagonistic pleiotropy was that successful selection for increased longevity should result in decreased vigour in youth. In contrast, under mutation accumulation correlations between early and late life fitness components are not necessarily expected. These aspects have been submitted to extensive experimental testing in *Drosophila* species.

Following a pioneering study in *D. subobscura* (Wattiaux, 1968), Rose & Charlesworth (1981) reported exploratory selection experiments in *D. melanogaster* using an indirect procedure in which separate lines reproduced either at an early ('young' lines) or late ('old' lines) age. It was demonstrated that ageing could be postponed in the 'old' lines, but only at the expense of a loss in early reproduction relative to the 'young' lines (Rose, 1984). Coincidentally, Luckinbill and coworkers (Luckinbill *et al*., 1984) corroborated these findings in *D. melanogaster* and similar results were found in the flour beetle, *Tribolium castaneum* (Mertz, 1975), the bean weevil, *Acanthoscedelis obtectus* (Tucic *et al*., 1996) and the melon fly, *Bactro cucurbitae* (Miyatake, 1997). The apparent trade-off between lifespan and fecundity was taken to support the role of antagonistic pleiotropy in the evolution of ageing.

However, in another selection experiment on age at reproduction in *D. melanogaster*, increased longevity in the 'old' lines was not accompanied by a decrease in early fecundity (Partridge & Fowler, 1992). This observation was consistent with mutation accumulation, on the basis that the selection procedure in the 'old' lines was acting against late-acting deleterious genes that adversely affected both survival and fecundity. In addition, reversal of selection in the 'old' populations studied by Rose showed that longevity and starvation resistance declined towards the original values, but that this did not apply to alcohol and desiccation resistance (Service *et al*., 1988). This implied that selection on age at reproduction had removed accumulated mutations that negatively affected the ability to withstand alcohol and desiccation.

However, the evidence in favour of mutation accumulation could be the result of covert selection on other traits that confounded the analysis. In Partridge and Fowler's study, the 'old' lines had a longer developmental period, a larger adult body size and lower viability. This led the authors to suggest that trade-offs between the larval and adult life phase may underlie the selection response. This view is not supported by independent selection studies which have indicated that developmental time and adult longevity were not genetically correlated (Chippindale *et al*., 1994; Zwaan *et al*., 1995a). However, there is evidence that differences in larval densities caused inadvertent selection for developmental time in the Partridge and Fowler study (Roper *et al*., 1993; Tucic *et al*., 1996). The increase in body weight in the 'old' lines could have occurred because developmental time and body weight were positively genetically correlated as has been found consistently in other studies (Zwaan *et al*., 1995a; Nunney, 1996; Chippindale *et al*., 1997). Therefore, the lack of differences in early fecundity between the 'old' and 'young' lines (Partridge & Fowler, 1992) could have arisen because the loss of early fecundity in 'old' lines was offset by longer developmental time (Zwaan *et al*., 1995a) and larger size (Hillesheim & Stearns, 1992) which increased early fecundity.

The evidence in favour of antagonistic pleiotropy also has problems. When individuals reproduce at a late age, selection will not only be applied on survival to that age, but also on high fecundity at that age. Thus, the age at reproduction design is unable to separate selection for increased lifespan from selection for increased late fecundity (Clark, 1987; Curtsinger *et al*., 1995; Zwaan *et al*., 1995b). Thus, if early and late fecundity are negatively correlated, the decrease in early reproduction may be independent of changes in lifespan. In addition, reproduction itself reduces the longevity of an individual, without necessarily affecting ageing rates (Partridge & Andrews, 1985). Therefore, to separate cause and effect, selection should be applied such that the lines do not differ in parental age at reproduction or reproductive history. To date only one study has been performed using family selection directly on longevity (Zwaan *et al*., 1995b). After six

generations of selection, lifespan had diverged by 30% for short- and long-life selected lines, relative to controls. Long-life selected females produced about half the number of progeny over their lifetime as short-life selected females. Moreover, an analysis of the reproductive pattern showed that this difference was present at all ages in the females' life. This study strongly indicated that trade-offs are involved in the genetics of ageing. This conclusion was confirmed in a selection experiment on age at reproduction in which care was taken to avoid gene–environment interaction and inadvertent selection on other traits (Partridge *et al*., 1999). In contrast with earlier findings, late life fecundity was not higher in the 'old' lines compared to the 'young' lines and the base stock.

These laboratory selection experiments show that genetic variation of the kind postulated in antagonistic pleiotropy and mutation accumulation can be exploited by selection. They need to be complemented by observations under natural or semi-natural conditions to prove that the selective agents actually produce genetic change. Study of an introduced population of guppies, *Poecilia reticulata*, with a concomitant change from adult to juvenile predation, resulted in evolution towards a life history with late maturation, reduced reproductive effort and fewer and bigger offspring per brood (Reznick *et al*., 1990). In *Melanoplus* grasshoppers accelerated senescence has been reported in high-elevation populations, because severe winters at high altitude results in selection on reproductive schedules (Tatar *et al*., 1997). Finally, an experiment with *Drosophila melanogaster* has shown that individuals from populations which experience high experimenter-induced adult mortality have a shorter developmental time, a smaller size at eclosion, earlier and higher peak fecundity and have higher intrinsic mortality rates relative to low adult mortality populations (S. C. Stearns, M. Kaiser, M. Ackermann & M. Doebeli, personal communication).

Analysis of (standing) genetic variation

As selection weakens with age, the equilibrium allele frequency for age-specific deleterious alleles increases with the age of the gene effect. Therefore, the mutation accumulation hypothesis predicts that the additive (V_A) and dominance (V_D) genetic variance of fitness traits will increase with age (Charlesworth & Hughes, 1996). In addition, inbreeding depression should increase with age (Charlesworth & Hughes, 1996). This has led to a number of tests of mutation accumulation using data on age-dependent expression of genetic variation.

The first test of the predictions failed to support the mutation accumulation hypothesis because V_A did not increase with age for female fecundity in *D. melanogaster* (Rose & Charlesworth, 1980). Recently, there has been a revival of studies of age-dependent expression of genetic variation. V_A and V_D significantly increase with age for mortality in male fruit flies (Hughes & Charlesworth, 1994). Similar increases were found in V_A for mortality and female fecundity in the first weeks of life (Tucic *et al*., 1988; Engstrom *et al*., 1989; Promislow *et al*., 1996; Tatar *et al*., 1996). In addition, inbreeding depression increased with age for male mortality and mating success in *D. melanogaster* (Charlesworth & Hughes, 1996) but not for fecundity in *Callosobruchus chinensis* (Tanaka, 1993). In contrast, in mutation accumulation lines, high positive mutational correlations between early and late life fitness appeared to contradict the mutation accumulation hypothesis, because mutations lack age-specificity (Houle *et al*., 1994). Similarly, analysis of standing genetic variance predominantly showed positive correlations between age classes for fecundity and mortality (Tatar *et al*., 1996). Recently, mutations affecting mortality limited to a narrow age-range have been described in mutation accumulation lines (Pletcher *et al*., 1998). The genetic characterization of these genes has the potential to uncover mechanisms underlying instantaneous increases and decreases in mortality.

Unlike the mutation accumulation hypothesis, antagonistic pleiotropy makes no specific predictions about genetic variation. Although V_A may increase with age (Charlesworth & Hughes, 1996), antagonistic pleiotropy does not require the maintenance of genetic variation (Partridge & Barton, 1993b; Charlesworth & Hughes, 1996). Nevertheless, the near absence of V_D for fitness related traits in outbreeding populations as well as mutation accumulation lines of *D. melanogaster* (Houle *et al*., 1994; Hughes, 1995; Houle *et al*., 1997) has been used as evidence against antagonistic pleiotropy, because substantial V_D/V_A ratios for early life history traits are expected (Curtsinger *et al*., 1994; Charlesworth & Hughes, 1996). In contrast, as was shown in a review including plants and animals, high dominance ratios appear to be the norm for life history traits (Crnokrak & Roff, 1995). The apparent contradiction between studies in the contribution of V_D to genetic variation for fitness related traits warrants more research (Roff, 1997).

The analysis of genetic variation is a valuable way of studying the genetics of ageing. The major drawback is that classical quantitative genetic methods and mutation accumulation experiments are only applicable in a limited number of species, because large sample sizes are required to obtain reliable parameter estimates. This may especially hinder the estimation of genetic variance components for early life history traits. Moreover, it needs to be confirmed that mutations accumulated under laboratory conditions play a role in nature as well.

Major genetic effects

Research on *Caenorhabditis elegans* has revealed classes of single genes (e.g. *age-1, clk-1, spe-26, daf-2*) that spectacularly extend the lifespan without apparent trade-offs (Lithgow, 1996). Many of these genes are involved in dauer-formation: an alternative developmental programme initiated in the first larval-instar that results in a hardy phenotype at the third larval-stage adapted to survive periods of stress. The link between lifespan extension and dauer-formation is illustrated by the finding that the longevity mutants also show increased stress tolerance (Lithgow *et al*., 1995; Murakami & Johnson, 1996). *daf-2* is a temperature sensitive mutation that causes constitutive dauer larvae formation at the permissive temperature (Kenyon *et al.,* 1993). Adults can be produced, however, when mutants are shifted to nonpermissive temperatures in the later larval stages. These adults live about twice as long and

have near-normal fertility. Mutation of the *daf-16* gene suppresses the lifespan extension effect of *daf-2* mutants (Kenyon *et al.,* 1993). Evidence has shown that *age-1* and *daf-2* act in the same genetic pathway (Dorman *et al*., 1995) consistent with the suggestion that *age-1* may be the same gene as *daf-2* (Malone *et al*., 1996). There is growing evidence that suggests that *age-1*, *daf-2* and *daf-16* form an insulin-like pathway that transduces signals about nutrition and metabolism (Kimura *et al*., 1997; Ogg *et al*., 1997). However, it is unclear how this determines ageing rate, and further genetic and physiological characterization of the mutants may shed light on this issue and on their effects on life history traits (Gems *et al*., 1998) and the processes of repair and maintenance. The increase in lifespan of the mutants could be the result of altered metabolism affecting the amount of oxygen free radicals produced and/or the amount of damage prevented (e.g. through heat shock proteins). The same explanation might apply to the dauer-unrelated extended lifespan phenotype of *clk* mutants (Wong *et al*., 1995).

Similar to *C. elegans* is the finding in P-element insertion lines of *D. melanogaster* that mutations of the *methuselah* (*mth*) gene have extended longevity and increased resistance to several stresses (Lin *et al*., 1998). The gene was identified as a G-protein receptor. Receptors from this gene family register a variety of signals, including hormone physiology and external stimuli.

All the genes thus far identified appear to be involved in repair, maintenance and stress resistance mechanisms. These genes are central to the 'disposable soma' theory. For instance, null mutants of *mth*, resulting from imprecise excision of the P-element, do not survive past the second larval instar, suggesting a crucial role during development. It is possible that the longevity decreasing effect of wild type *mth* is a negative pleiotropic effect of the gene. A full picture of the fitness of the mutant flies and the phenotypic and genetic correlations between fitness traits is essential for understanding the role of this gene in the evolution of ageing. It would be extremely interesting to search for genetic variants of *mth* in selection lines with divergent longevities. In addition, for *C. elegans*, the lifespan genes are involved in developing an alternative life history, thus the relevant level to study ageing is in separate dauer and nondauer phenotypes.

Further evidence for the role of damage production and prevention comes from the study of genes involved in neutralising oxygen free radicals. For instance, over-expression of super oxide dismutase (SOD) extends lifespan by a third in *D. melanogaster* (Orr & Sohal, 1994), whereas urate-null mutants in the same species (Hilliker *et al*., 1992) and defective succinate dehydrogenase mutants in *C. elegans* (Ishii *et al*., 1998) have markedly reduced lifespans. Caution is needed when interpreting studies of under- or over-expression in transgenic animals. For example, in *D. melanogaster* it has been shown that P-element insertion size, position and interactions with the genetic background can have effects similar in magnitude to the actual over–expression of the inserted gene (Kaiser *et al*., 1997). In addition, most insertions reduce fitness because they disrupt vital processes that are unrelated to ageing. In this sense, the discovery of *mth* is extraordinary because excision of the P-element and its insertion into the third intron leaves the gene function intact but probably reduces gene expression by interfering with RNA splicing (Lin *et al*., 1998).

Applying the candidate gene approach to divergent selection lines may prove a powerful tool. Analysis of allozymic variation in *D. melanogaster* populations has shown allelic differentiation for certain enzymes, including SOD (Deckert-Cruz *et al*., 1997) and glucose-6-phosphate dehydrogenase (Luckinbill *et al*., 1990). Moreover, increased paraquat resistance indicated enhanced levels of antioxidant defences (Force *et al*., 1995). All these examples need more careful examination of the genetic and physiological mechanisms to be convincing, as does the proposed role of fat in the trade-off between longevity and fecundity (Service, 1987; Zwaan *et al*., 1995b).

QTL studies have been reported in *C. elegans* (Shook *et al*., 1996) and *D. melanogaster* (Nuzhdin *et al*., 1997). In the latter case, two unrelated homozygous strains were used as parental lines and the recombinant inbred lines were derived from backcrossed F_1 progeny. Using this approach there is a serious risk of mapping genes involved in inbreeding/heterosis, and this in general applies to species that are sensitive to inbreeding. A better approach would be to use selected lines as source material. Nevertheless, five QTLs were found that mapped to similar positions as certain candidate genes, among which was SOD. As a technical note, one has to realize that the QTL approach is strongly biased against genes with small effect (Kearsey & Farquhar, 1998), and, thus, biased against mutation accumulation.

Genetic components of longevity have been studied in populations of human centenarians. It was shown that the ε4 allele of apolipoprotein E (*APOE*) that promotes premature arteriosclerosis had a significantly lower frequency in the centenarians relative to control groups (Schächter *et al*., 1994). Surprisingly, an allelic variant of the angiotensin-converting enzyme, associated with an increase in coronary heart disease, was more frequent in centenarians. This led the authors to suggest that pleiotropic effects of this allele may outweigh its detrimental effects. The ε2 allele of *APOE* had an increased frequency in centenarians despite being a risk factor for ischaemic heart diseases (Schächter *et al*., 1994). The same allele is suggested to protect against late-onset Alzheimer's disease and, hence, the *APOE* gene is the first convincing example that antagonistic pleiotropy may play a role in human ageing (Charlesworth, 1996). Genetic marker association studies in human (sub)populations should provide a promising addition to this candidate gene approach.

Demography

The demographic approach concentrates on changes in the shape of mortality curves with age rather than mean lifespan alone. For instance, *D. melanogaster* lines selected for lifespan have been subjected to demographic analysis (Zwaan *et al*., 1995b). For both females and males the age-independent mortality was decreased in the long lived lines and increased in the short lived lines relative to controls (Fig. 3). The age-dependent mortality was not significantly affected by selection

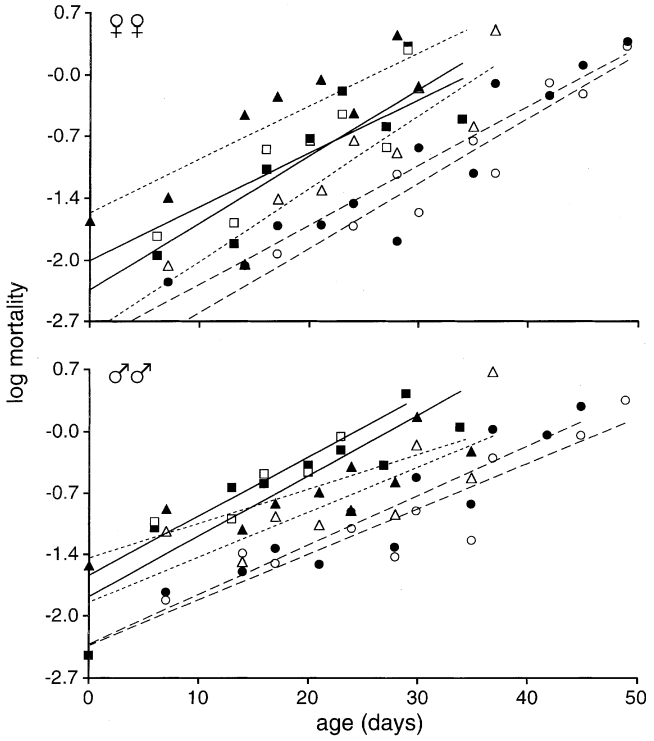

Fig. 3 The logarithm of age-specific mortality with age for females and males after six generations of selection (compare with figure 2 in Zwaan *et al*., 1995b). Solid curves represent short-lived lines (open squares replicate 1, closed squares replicate 2); dotted curves represent control lines (open triangles replicate 1, closed triangles replicate 2); hatched curves represent long-lived lines (open circles replicate 1, closed circles replicate 2).

for lifespan, corroborating previous results on selected populations (Curtsinger *et al*., 1995; Partridge *et al*., 1999), or for the *mth* mutant (Lin *et al*., 1998). Divergence in age-independent mortality rate has been taken as support for mutation accumulation (Pletcher *et al*., 1998). However, this result is consistent with antagonistic pleiotropy as well, because genes might have been selected that differ in the relative allocation of resources between maintenance and reproduction throughout life. Moreover, differences between selected *D. melanogaster* lines have been reported for age-dependent mortality (Service *et al*., 1998).

In addition, males have higher age-independent but lower age-dependent mortality rates relative to females (Fig. 3). These differences indicate that males have a higher chance of dying throughout their life, but age at a slower rate. Future research should focus on identifying the genetic, physiological and behavioural factors that may underlie mortality differences between the sexes. Potentially, the sex differences and the underlying factors are important for the interpretation of experimental results. Furthermore, the above shows that equating age-independent mortality with environmental mortality and age-dependent mortality with true ageing rates may not be valid.

Much attention in demographic research has been given to how mortality rates vary late in life. By studying cohorts of fruit flies, medflies, nematodes and humans, it was discovered that mortality rates level off at advanced ages, and in some cases even decreased (Charlesworth & Partridge, 1997; Vaupel *et al*., 1998). This effect had previously been missed because very large sample sizes are required. First attempts to explain these findings concentrated on the role of temporal environmental heterogeneity (e.g. lower densities in fruit fly vials with time), statistical power changes because of falling numbers, genetic variation between individuals and the role of reproduction.

Careful experimentation has ruled out density as a sole explanation and statistical artefacts are not likely (Pletcher *et al*., 1998; Vaupel *et al*., 1998). Abstaining from reproduction early in life might result in increased life expectancy that could be reflected in decreased mortality rate late in life. Using single sex cohorts in experimental animals may avoid this problem.

Significant V_A for age-dependent (Hughes & Charlesworth, 1994; Promislow *et al*., 1996) and age-independent (Promislow *et al*., 1996) mortality rate has been reported in *D. melanogaster*, and it is conceivable that the mortality deceleration reflects this genetic variation. Using genetically homogeneous lines showed that the mortality deceleration was significantly reduced in *C. elegans*, but unchanged in *D. melanogaster* (Charlesworth & Partridge, 1997). Even genetically identical individuals may not have the same chance of dying at a certain age (frailty). They live different lives, and their frailty is affected by factors such as accidents, reproduction and feeding levels. Differences in environmentally induced frailty in (genetically homogeneous) populations can entirely account for the decline of mortality with age (Service *et al*., 1998; Vaupel *et al*., 1998).

Recent findings suggested significant V_A for the deceleration of mortality in *D. melanogaster*, and, after an initial increase with age, V_A for mortality decreased again at advanced ages (Promislow *et al*., 1996). Moreover, mutations with age-specific effects appeared not to occur at these late ages (Pletcher *et al*., 1998). A frailty model alone cannot explain these findings. It is feasible that (very) late acting mutations are prevented from accumulating because immediate death would follow, possibly as a result of interactions with previously accumulated mutations and/or because the late life mutational load in the lines was already high (Pletcher *et al*., 1998; Promislow & Tatar, 1998). In addition, V_A for mortality may be lacking because levels of gene regulation and maintenance processes may be very low and equally poor in all genotypes (Promislow *et al*., 1996) because the ageing process becomes increasingly irreversible (Ricklefs, 1998). Alternatively, mutations in vital functions needed for survival late in life are prevented because these functions are essential early in life as well (Charlesworth & Partridge, 1997). These suggestions warrant further investigation.

If one assumes that mortality rates decelerate at late ages even when individual heterogeneity has been taken into account, what explains it? Several modelling attempts have

been used (Abrams, 1995; Mueller & Rose, 1996; Pletcher & Curtsinger, 1998; B. Charlesworth, personal communication). The outcome of the models is very sensitive to the genetic details (Pletcher & Curtsinger, 1998), but, in general, details of genes, their interactions and window of effect are lacking for quantitative traits (Falconer & Mackay, 1996; Lynch & Walsh, 1998). It is therefore imperative to further characterize the genes with and without age-specific properties found in mutation accumulation, QTL and candidate gene studies and determine their role in late life survival and ageing in *D. melanogaster* and in other species.

Conclusions

On the basis of its track record, it is becoming widely accepted that an evolutionary genetic approach to ageing is crucial for understanding why ageing evolved and how species-specific lifespan and ageing are regulated. The current developments in integrating genetic and demographic observations into theoretical models, together with the availability of sophisticated techniques in gene mapping and gene identification, should prove invaluable for fully understanding the ageing process.

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