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# Reviews

## Rapid development and a long life: an association expected under a stress theory of aging

P. A. Parsons

*Faculty of Science and Technology, Griffith University, Nathan, Brisbane, Queensland 4111 (Australia) and Department of Genetics and Human Variation, La Trobe University, Bundoora, Victoria 3083 (Australia), Fax +618 357 8197*

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**Abstract.** Life span and development time are considered in the context of the abiotic stresses to which free-living organisms are normally exposed. Under these circumstances, long life span depends upon metabolically efficient stress-resistance genes, which tend to be heterozygous. Similarly, rapid development time tends to be a feature of heterozygous stress-resistant individuals. Therefore, individuals who have high inherited stress resistance should develop fastest and live longest; in addition, they should show high homeostasis in the face of the energy costs of stress. In this way, the stress theory of aging can incorporate the developmental stage, based upon oxidative stress as an important major direct challenge.

**Key words.** Aging; development time; stress; energy cost; oxidative stress; *Drosophila*; homeostasis; life span.

### Introduction

Development time and adult life span are determined by the interaction of the environment with the genetic constitution of the individual. In this paper I adopt a realistic but far more stressful environment than is conventionally assumed[19,37].

To start with genetic considerations, long-lived strains of *Drosophila melanogaster* have been developed by directional selection[41], with suggestive evidence for major genes (sex-linked and autosomal) that determine longevity[8,27,54]. From crosses based on two inbred strains, one short-lived and one long-lived, it was found that early emergers tended to be long-lived and vice versa[54]. This suggests that longevity genes function prior to emergence, during the developmental stage. In contrast, in a comparison of long-lived strains developed by directional selection with control strains and with other strains varying in development rate, correlations between longevity and development time were not found[6,9]. A parallel conclusion was proposed from experiments on *Caenorhabditis elegans*[21]; however, detailed perusal indicates that a short-lived wild-type strain had the longest embryonic period, amounting to a statistically significant increase of 60–90 minutes over 20 hours, compared with some longer-lived strains.

Clearly, the above results are difficult to summarize. However, they were obtained under the presumably rather benign conditions found in the laboratory. In contrast, organisms in free-living populations are normally exposed to adverse physical (abiotic) factors, especially temperature extremes, drought, and inadequate resources. Since resources provide energy, and abiotic stress necessitates the utilization of energy, the normal scenario in free-living populations should envisage organisms struggling to survive in an environment that is at best barely adequate energetically[19,35]. Therefore, it is difficult to accommodate much detailed published laboratory data[26] on growth rate and life span under varying environments into this model.

Using this stressful model of the environment, I present here a case for an association between rapid development time and long life span in free-living populations.

Address for correspondence: P.O. Box 906, Unley, SA 5061 (Australia).

### Aging and energy costs

In humans, the body temperature oscillates between wider limits in the elderly than in the young, so that heat stroke increases dramatically in parallel[10,17]. Consequently, as aging proceeds, homeostatic mechanisms that ameliorate the effects of abiotic stress progressively deteriorate. This occurs for a wide variety of functions[7], including the ability of cells to express heat-shock proteins[17].

Turning to experimental organisms, in *D. melanogaster*, stress-resistant individuals obtained by selection for desiccation resistance were genetically long-lived[20]. Although it must be remembered that the rate-of-living theory of aging needs a stronger theoretical basis[26], metabolic rate is reduced in these strains, and this result is consistent with the theory. Reduced metabolic rate and increased longevity also occurred in the red flour beetle, *Tribolium castaneum*, in strains selected for resistance to low $O_2$ and high $CO_2$ concentrations[12]. This is

predictable, since many generalized stresses have several related effects[19]; in particular, desiccation and anoxia resistance are associated in natural populations of *D. melanogaster*[33]. More generally, evidence is accumulating from a range of organisms that longevity tends to be associated with relatively high stress resistance and homeostasis, and in some cases reduced metabolic rate[5,24,36,42], implying reduced energy costs per unit of time.

Assuming that free-living populations are normally exposed to substantial abiotic stress, changes in longevity may then be secondary to a primary selection of stress resistance at the level of energy carriers. This scenario has been generalized into a stress theory of aging[36]. This is a modification of the rate-of-living theory, which incorporates the energy cost to free-living populations of surviving and adapting to their environments. It is related to a recently proposed network theory of aging, which is an evolutionary approach based upon metabolic considerations emphasizing energy utilization as aging proceeds[23].

High stress resistance is associated with the efficient use of metabolic resources underlying growth and reproduction, especially under stressful circumstances when resources are limiting[22]. In other words, a genotype with a low maintenance requirement can support growth under a wide range of conditions. Taking account of the progressively accumulating energy costs during aging, an association between metabolic efficiency and stress resistance implies that genes for stress resistance[51] should underlie high homeostasis and a long life.

In the butterfly, *Colias philodice*, heterozygotes at the phosphoglucose isomerase (PGI) locus tend to be favoured as age increases, because they can fly faster over a broader climatic range than homozygotes, so enhancing survival[52,53]. Data from a wide range of taxa show the more anodal allozyme/isozyme at the PGI locus is favoured under stressful conditions including high temperature, high salinity, anoxia and desiccation[40]. The involvement of this locus in determining stress resistance is consistent with in vitro studies suggesting that the PGI enzyme is a target of selection for stress resistance at the level of energy carriers, where heterozygotes show superior catalytic abilities[53].

In parallel, in the coot clam, *Mulinia lateralis*, and the mussel, *Mytilis edulis*, heterozygotes have lower energy requirements than homozygotes because they are more efficient in the metabolic processes releasing energy for ingestion and absorption[16,22]. Such heterozygous individuals should therefore be able to maintain growth and reproduction over a wider range of environmental conditions than homozygotes, especially under stressful circumstances. This means that heterozygosity should increase from younger to older adult individuals – a conclusion generalized from substantial data mainly from marine bivalves[2], but also from organisms such as reptiles[47].

A manifestation of reduced homeostasis with age is increased susceptibility to disease. On the above arguments, heterozygotes should be favoured following exposure to disease, which normally increases energy costs. This has been documented in the rainbow trout, *Oncorhynchus mykiss*, in surviving bacterial gill disease, a potentially lethal epizootic for fresh water fish[14]. Furthermore, there was an association between low oxygen consumption and heterozygosity, and hence metabolic efficiency. This translates into reduced energy costs in the face of stress in heterozygotes.

## Development time

The level of heterozygosity of organisms in populations tends to correlate with measures of performance or fitness, in particular development time[28]. Enzyme loci influencing metabolism and contributing to the amount of energy available for development and growth show the most significant positive associations with heterozygosity[28].

This is clearest under extreme conditions, when the energy demands from the environment would be highest. Examples include heterozygote growth advantage under the stress of limited food and low moisture in juvenile manure worms, *Eisenia foetida*[11], an enhancement of heterozygote growth rate in *Mulinia lateralis* under temperature and salinity stress[43], and an enhancement of feeding efficiency in heterozygotes of the oldfield mouse, *Peromyscus polionotus*, when food quality was low[45]. These represent a few of the many studies that have reported enhanced correlations between heterozygosity and fitness, in particular development time under stress[2,28].

Even under apparently less stressful circumstances, such relationships appear not uncommon. The normal assumption is that the environments of managed domesticated species are less stressful than conditions in the wild. However, in commercial pigs, feed conversion – a trait correlated with growth rate – increased with heterozygosity[29].

## Discussion

In summary, rapid development time and long life span appear to be features of genetically stress-resistant individuals that are likely to be more heterozygous than those developing slower and dying earlier. This association should be most obvious under extreme environments, when fitness differences between genotypes tend to be maximized[19,33,37].

There is much correlative evidence that oxidative stress, causing damage from free radicals, contributes to the rate of aging[3]. Furthermore, since the level of oxidative damage is roughly proportional to the basal metabolic rate among a range of mammalian species[1], the rate-of-living theory of aging can be reformulated as the free-radical theory of aging[4,44]. In *C. elegans*, mutants with

extended life span have increased starvation and oxidative stress resistance[24,50], which is associated with high superoxide dismutase (SOD) and catalase levels. In *D. melanogaster*, there are parallel results for resistance to the superoxide anion-generating drug, paraquat, and to irradiation[5,48]. Furthermore, in transgenic flies with overexpression of SOD and catalase, life span increased substantially[31]. Finally, in human centenarians, relatively high resistance of peripheral blood lymphocytes to oxidative stress[15] is consistent with the results from experimental organisms.

Many senescencent changes in *Drosophila* and in the dipteran, *Musca domestica*, implicate oxidative stress as a major force underlying aging[13,39,44]. Predictably, *Drosophila* mutants in which specific components of the oxygen defence mechanism are disrupted have a short life span, and are sensitive to paraquat, ionizing radiation and hypoxia[18,38].

Based upon a study of such mutants, it has been proposed[18] that metamorphosis in *Drosophila* imposes a crisis of oxygen stress on the developing imago, focussing principally on the malpighian tubules, one of the few larval tissues to function in the adult. The ability to cope with the high metabolic costs of development to emergence is at a premium, so this is a time when metabolic efficiency is important. Under these circumstances, stress-resistant individuals, especially heterozygotes, should be favoured. After emergence, this advantage translates into long-lived adults. Rapid emergence should therefore be the forerunner of a long life in free-living populations. In other words, a proposed oxidative stress hypothesis of aging[44] is a major component of the stress theory of aging[36], which can accommodate the developmental phase.

Fluctuating asymmetry (FA), representing small random deviations from bilateral symmetry, is a measure of the extent to which an individual can control development under given environmental and genetic conditions[25,32,34]. Indeed, one manifestation of the energy dissipation caused by stress is increased FA[28]. Hence, developmental homeostasis, expressed by low FA, should be maximal in organisms where metabolic efficiency is highest. In agreement, there is an increasing volume of data showing an association between protein heterozygosity and developmental homeostasis, especially under stressful conditions[2,28]. While longevity needs additional study in this regard, there is accumulating evidence in insects that individuals with large morphological FA tend to have reduced longevity compared with more symmetrical individuals[30,46,49]. Therefore, individuals that have inherited high stress resistance should develop fastest, live longest and should be the most symmetrical at any given age, because of high metabolic efficiency.

In conclusion, development and aging have been considered assuming a world dominated by abiotic stress, where habitats of organisms are determined from an energy balance between the costs of stress and energy from resources. The validity of this environmental model is suggested by (1) the rarity of creatures in free-living populations that normally die of old age, perhaps only certain humans in recent times[10,36], and (2) its predictive value in developing insights into some major patterns of evolutionary change[35,37]. This implies that selection on development rate underlain by stress should be primary, and that in many cases, the life span achieved would be a secondary consequence of such selection. In any case, relationships between development rate, life span and the level of homeostasis, which are predictable and have increasing empirical support, are beginning to emerge.


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