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OPINION

Senescence is not inevitable

Owen R. Jones · James W. Vaupel

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Abstract Senescence, the physiological deterioration resulting in an increase in mortality and decline in fertility with age, is widespread in the animal kingdom and has often been regarded as an inescapable feature of all organisms. This essay briefly describes the history of the evolutionary theoretical ideas on senescence. The canonical evolutionary theories suggest that increasing mortality and decreasing fertility should be ubiquitous. However, increasing empirical data demonstrates that senescence may not be as universal a feature of life as once thought and that a diversity of demographic trajectories exists. These empirical observations support theoretical work indicating that a wide range of mortality and fertility trajectories is indeed possible, including senescence, negligible senescence and even negative senescence (improvement). Although many mysteries remain in the field of biogerontology, it is clear that senescence is not inevitable.

Keywords Senescence · Evolution · Non-human aging · Negligible senescence · Negative senescence

O. R. Jones (✉)
Department of Biology, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark
e-mail: jones@biology.sdu.dk

O. R. Jones · J. W. Vaupel
Max Planck Odense Center on the Biodemography of Aging, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark

J. W. Vaupel
Department of Public Health, University of Southern Denmark, J.B. Winsløws Vej 9B, 5000 Odense C, Denmark

Introduction

In the animal kingdom larger species tend to enjoy longer lives, but size is not everything: bat species weighing just a few grams can live for decades while similar-sized rodents are lucky to live 2–3 years (Munshi-South and Wilkinson 2010). In the plant kingdom, annual plant species grow, reproduce and die to complete their life cycle within a single year (if we overlook the remarkably long-lived seed banks of some species (Daws et al. 2007)), while others, including trees like bristlecone pines (e.g. *Pinus longaeva*) and giant redwood (*Sequoia sempervirens*) survive millennia (Lanner 2002). What drives this variation? The fact that humans, and our domesticated animals, tend to deteriorate with age must be an ancient observation, as must be the recognition that inanimate objects wear out with use. Thus it is no surprise that early thinkers believed differences in life span might be caused by differences in rates of inevitable "wear-and-tear" among species (Aristotle 1984). This idea has persisted and, even now, senescence (the catch-all term for physiological deterioration resulting in an increase in mortality and/or decline

in fertility with age) is often regarded by the layman as being driven by unavoidable wear-and-tear.

Mechanistic wear-and-tear theory, also known as "rate of living theory", was popularized by the physiologist Max Rubner in the early 1900s, who examined the metabolic rates of animals ranging in size from guinea pigs to cows (Speakman et al. 2002). He calculated that energy expenditure per unit body mass is fixed: each gram of body tissue consumes the same amount of energy before death, for all the species he studied. He thus concluded that variation in life span was driven by variation in metabolic rate. A related metabolic theory is that senescence is the inevitable result of toxic by-products of normal metabolism, such as by-products of cellular respiration, or reactive oxygen species (Harman 2009). Other theories such as telomere shortening (Sahin and DePinho 2010) and somatic mutation theories (Szilard 1959) are essentially more sophisticated versions of wear-and-tear and similarly imply that senescence is inevitable in all living things (self-repair mechanisms notwithstanding). The patchiness of support for the numerous mechanistic theories of aging suggests that senescence has multiple proximate causes. Indeed, the proximate specific mechanisms underlying senescence has become a major and diverse research line (Kirkwood 2005). Nevertheless, to understand the ultimate underlying causes of aging, which are likely to apply more generally across diverse taxa, one must examine evolutionary mechanisms.

Evolutionary theories

Around the time that researchers first addressed the proximate mechanisms of senescence, other scientists wrestled with its underlying evolutionary mechanisms. It seemed absurd that evolution, which had led to such boundless innovation in other areas, could retain such an apparently deleterious feature as aging. As George Williams (1957) put it, "it is remarkable that after a seemingly miraculous feat of morphogenesis, a complex metazoan should be unable to perform the much simpler task of merely maintaining what is already formed."

The first evolutionary theory of aging, proposed by August Weismann in the 1880s, argued that senescence was an adaptive mechanism for species to get rid of old individuals that could no longer "work towards the maintenance of the species" (Weismann 1891). This theory did not receive much attention until briefly mentioned by Medawar (1952) who dismissed it as being "circular" because it first assumes that older individuals are decrepit before explaining how this state came about. However, Weismann also suggested that senescence may have evolved because metazoans separate their immortal germline from the soma (body) (the "Weismann barrier") and invest resources in the germline at the soma's expense. Weismann did not expand on these ideas because the necessary analytical tools were yet to be developed, notably by R.A. Fisher (Charlesworth 2000) (see Kirkwood and Cremer (1982) for a review).

The evolution of senescence thus remained mysterious until the 1950s, when Peter Medawar (1952) made a breakthrough in his essay "An Unsolved Problem of Biology". He pointed out that after sexual maturity the remaining number of offspring an individual could expect to produce before death declines with age, even if its age-specific probability of death remains constant. Therefore, the fitness benefits of an extended life span declines with age: "The force of natural selection weakens with increasing age—even in a theoretically immortal population, provided only that it is exposed to real hazards of mortality. If a genetic disaster […] happens late enough in individual life, its consequences may be completely unimportant". Not only was this observation an explanation for why devastating late-onset genetic disorders like Huntington's disease are not eliminated by evolutionary forces, it also provided the first strong evolutionary framework to explain the existence of senescence. The idea that the force of natural selection weakens with age means mutations that are detrimental late in life, after most reproduction has happened, will tend to equilibrate at higher frequency than in those with deleterious effects early in life (*mutation accumulation theory*) (Medawar 1952). Thus, as individuals age they will tend to be challenged by increasing numbers of deleterious genes with an associated increase in mortality rate. A closely-related theory, dubbed *antagonistic pleiotropy*, was proposed by Williams (1957) who suggested, using similar arguments, that late-acting detrimental genes could be favoured by evolution and accumulate in the population, as long as they are sufficiently beneficial in early life. Therefore, senescence is the result of an unfortunate balancing of the trade-off between genes' positive effects early in

life and negative effects late in life. Hamilton (1966) soon provided the mathematical formalisation of these ideas in an influential article that emphasized that "senescence is an inevitable outcome of evolution". Hamilton later remarked that "no life schedule, even under the most benign ecology imaginable, could escape my spectrum of forces of senescence […] in the farthest reaches of almost any bizarre universe" (Hamilton 1998).

A third theory, advanced in 1977 by Kirkwood (1977), also argued that senescence is the result of balancing trade-offs, but of a different kind. Kirkwood argued that since genes in the germ line are the focus of selection, they must be carefully protected to ensure accurate replication from generation-to-generation. This involves energetically costly proofreading and repair. In contrast, he argued that the soma functions merely as a "disposable" vessel for carrying the germ line, and that energetic allocation to maintenance is adjusted to achieve an evolutionary stable strategy (ESS). His theory suggests that the ESS of the trade-off between resource allocation to processes of somatic maintenance and maintenance of the germ line inescapably favours the germ line, again resulting in inevitable senescence (at least in organisms that segregate the germ line and soma). The theory is complementary to antagonistic pleiotropy, but cannot be simply regarded as a special case of it (Kirkwood 2017).

Extrinsic mortality, longevity and senescence

Following these ideas it is a short step to appreciate that longer lifespans could evolve if populations are "protected" from death: If protected individuals live a little longer, the ESS of the trade-off will be shifted a little towards somatic maintenance. Species with long life expectancies must be those that have experienced lower mortality rates. For example, it is argued that small bats live longer than field mice of a similar size because they are able to escape predation thanks to their ability to fly (Munshi-South and Wilkinson 2010). In fact, this prediction has been validated empirically numerous times (Keller and Genoud 1997; Moller 2006) (though some have argued that flight may simply require a more robust physiology that coincidentally extends lifespan (Finch 1990)). Most recently, Healy et al. (2014) used a large dataset of mammal and bird life spans (de Magalhaes and Costa 2009) to show that life spans tended to be greater for flying or gliding species than non-volant ones. Furthermore, for birds, the *strength* of flying ability (presumably an important trait for escaping predation) was positively correlated with lifespan. Similar arguments have been made for the rate of senescence—as opposed to life span—(Abrams 1993; Williams et al. 2006; but see Caswell 2007). Thus, it seems that in the 1960s–1970s, Medawar's unsolved problem had been solved: senescence appeared to be inevitable, explainable by evolution, and the fingerprints of evolution were detectable in demographic patterns within available data.

Positive, negligible and negative senescence

But can this be the whole story? If senescence is truly inevitable, we should expect the mortality rates of all organisms to inexorably increase with age as physiological deterioration takes its toll. However, biologists have long been aware of organisms whose mortality rates appear to buck this trend (e.g. long-lived fish species like rockfish (*Sebastes* spp.) in Finch 1990). Perhaps some of these observations could be attributed to the difficulty of collecting enough data to provide sufficient statistical power to even detect senescence in wild animals. In fact, Medawar (1952) himself remarked, "whether animals can, or cannot, reveal an innate deterioration is almost literally a domestic problem; the fact is that under the exactions of natural life they do not do so. They simply do not live that long". This idea was popular for some years (Promislow 1991; Ricklefs 1998; Kirkwood and Austad 2000) but it is incorrect. A growing body of literature now convincingly demonstrates that senescence is common, and commonly detected, in wild populations of mammals and birds (Jones et al. 2008) and even insects (e.g. Zajitschek et al. 2009) (though decrepit individuals may indeed be relatively uncommon). So if we *can* detect and quantify senescence with appropriate methods, and can therefore confidently assert that some species do indeed avoid senescence, what should be made of these non-senescent species?

In many cases, the lack of senescence may be a real phenomenon. In the 1990s, Caleb Finch and colleagues (Finch 1990) gave serious consideration to

organisms that exhibit "negligible senescence". These are organisms that experience no, or very small, increases in mortality rate with age. Finch noted that high-quality demographic data were lacking for most species at the time, but his contenders with supporting evidence included sexually reproducing species known to reach advanced age such as the trees bristlecone pine and yew (*Taxus baccata)*, lobsters (e.g. *Homarus* spp.), bivalves such as the quahog (*Arctica islandica*), marine fish including rockfish (*Sebastes* spp.) and halibut (*Hippoglossus* spp.), and the Testudinidae (tortoises) (Finch 1990).

But why stop at negligible senescence? Could mortality rates even *decline* with age? And would their existence fit into the "Hamiltonian" understanding of the universality of senescence? The first serious mathematical examination of this phenomenon, dubbed negative senescence, was undertaken by Vaupel et al. (2004) and later built upon by Baudisch (2008). They pointed out that Hamilton's models, which describe how the magnitude of the force of natural selection to oppose deleterious mutations is influenced by age (Hamilton 1966), examined just two out of several plausible indicators of senescence—both of which Hamilton proved can only decrease with age. Hamilton's indicators were the rate of change in fitness (the intrinsic population growth rate r), with respect to a change in the natural log of probability of survival p_a with age, (i.e. $dr/d\ln p_a$), and with respect to the rate of change in fertility (m_a) with age (i.e. dr/dm_a). Vaupel and Baudisch demonstrated that other equally reasonable indicators (e.g. dr/dp_a and $dr/d\ln m_a$) can remain constant or increase with age, depending on the shape of the age trajectories fertility and mortality (Baudisch 2005). Similarly, it is now known that selection gradients for fertility and mortality for organisms including plant species whose life history is better-predicted by size, rather than age, do not adhere to Hamilton's predictions (Caswell and Salguero-Gómez 2013). Hamilton also assumed that deleterious mutations are frequent, that their rate of occurrence remains constant with age, that they can affect either mortality or fertility (not both), and that the negative effects of these mutations only occur after a particular age. These assumptions are far from certain—in fact, for example, in most cases there is no proposed mechanism that would allow age-specific effects (Kirkwood and Melov 2011). In addition, the models are only suitable for unitary organisms (where individuals are well-defined) that reproduce non-clonally (e.g. all arthropods and vertebrates), nor do they consider the potential impact of parental care and other intergenerational transfers (Lee 2003). Finally, but perhaps most importantly, Hamilton's models implicitly ignore species where mortality and fertility are highly-dependent on body size (Caswell and Salguero-Gómez 2013). Therefore, these models do not encompass the broad diversity of life history patterns and there is, as Vaupel and colleagues insist, plenty of scope to be sceptical of Hamilton's robust statement on the universality of senescence.

The crux of Vaupel et al.'s (2004) case for negative senescence is that, for many species, age per se is relatively unimportant compared to size or developmental stage, a fact also pointed out by Caswell (2001). Thus, in numerous species, mortality risk declines with increasing size and, since size generally increases with age, mortality risk may consequently fall with advancing age. At the same time, for many species, fecundity is correlated with size (e.g. teleost fish, turtles). Vaupel et al. (2004) outlined mathematically the conditions under which evolution could favour mortality trajectories that declined with age. From their analyses, they hypothesized that the aging patterns after maturity depended largely on growth pattern, echoing Bidder's Hypothesis, advanced in 1932, that senescence is a by-product of growth termination (Bidder 1932). Species with indeterminate growth (those that continue to grow and increase in reproductive capacity long after maturity, such as teleost fish and many plant species) would tend to be characterized by either negligible or negative senescence. Note, however that growth patterns themselves are an active area of research and assigning species to discrete categories may not be quite so simple. Surprisingly, for example, many tree species show mass growth rates that continue to increase with size (Stephenson et al. 2014), many plants (Salguero-Gómez and Casper 2010; Wikelski and Thom 2000) are capable of adaptive shrinkage with important implications for survival though harsh times.

A diversity of senescence trajectories

One reason for the continued acceptance that senescence was inevitable was a lack of data, and lack of comparative studies illustrating the great demographic

diversity that exists across multicellular organisms. In 2014, we published an article that illustrates the diversity of demographic trajectories across a wide taxonomic scope (Jones et al. 2014). By necessity we used several data types—all of high quality—ranging from life tables for modern humans, to individual-based data on e.g. Soay sheep and red deer, to trajectories derived from matrix population models (Cochran and Ellner 1992; Caswell 2001). It is clear that there is an astonishing diversity in qualitative patterns of demography across the tree of multicellular life.[1] Many of the species in our sample showed the kind of mortality trajectories that Hamilton would expect—e.g. mammals and birds—but others (e.g. hydra, abalone, coral and tortoise) showed negligible or even negative senescence of the kind discussed by Finch (1990) and Vaupel et al. (2004). Similar analyses on angiosperm plants have also found that 93% of species show declining mortality with age, and that tree species are more likely to senesce than herbs and other plant growth forms (Baudisch et al. 2013).

It is remarkable that some of these exemplars had been predicted decades before this finding was reported. Finch's (1990) book documents numerous species with negligible senescence, albeit without the benefits of high-quality demographic data. Furthermore, even in the 1920s Hydra, a small fresh-water Cnidarian, was the subject of controversy over whether it senesced or not (Comfort 1979), decades before it was shown convincingly that Hydra raised in the laboratory did not show senescence (Martinez 1998; Schaible et al. 2015). Indeed, most elementary ecology textbooks contain a figure showing the archetypical Type I, II and III survivorship curves originally proposed by (Pearl and Miner 1935) and which correspond to increasing, constant and decreasing mortality trajectories (i.e. senescence, negligible, and negative senescence) respectively.

Jones et al. (2014) demonstrated that the senescence predicted by the canonical evolutionary theories of aging is not universal, but this analysis only offers a small glimpse of the true diversity of demographic trajectories. Even a cursory survey of the biodemographic literature reveals huge biases in the taxa studied. It is perhaps no surprise that the concept of inevitable senescence dominated the discourse for so long given that most biodemographic studies on aging focus on organisms with Type I survivorship curves (increasing mortality rates with age). Researchers are now striving to broaden this view by assembling demographic data sets for diverse taxa across the plant and animal kingdoms (e.g. Salguero-Gómez et al. 2014), developing measures to better quantify mortality trajectories (Baudisch 2011), and developing models that can examine the bivariate effect of age and size on mortality (Colchero and Schaible 2014). The biodemographic community is thus making great progress towards understanding the puzzle of senescence but significant challenges nevertheless remain: A crucial one is to resolve how best to deal with eusocial, clonal or modular species where we are unsure how to identify an "individual", the standard unit of demography and where growth may sometimes be considered a form of reproduction (and vice versa). This challenge notwithstanding, a profitable avenue of exploration, in addition to studying variation in more proximate mechanisms in a more diverse range of taxa, will be to return to the heart of life history theory and examine, in diverse taxa with varying constraints, the compromises made in resource allocation among processes of growth (and shrinkage), maintenance and reproduction, across the life course and in differing environments (Baudisch and Vaupel 2012). One thing is already clear though—senescence is not inevitable.

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[1] Diversity also exists within species: this is clearly shown by the human trajectories in our 2014 study, but there are also non-human examples. For example, painted turtles (*Chrysemys picta*) (not included in our study) show more rapid mortality senescence in some populations (Warner et al. 2016) than others (Congdon et al. 2003), a difference that Warner et al. (2016) attribute to differences in extrinsic mortality between the populations. It is also likely that differences in methodology among studies can cause variation in apparent senescence trajectories.

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