

Update on Slow Aging and Negligible Senescence – A Mini-Review

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Abstract

This review updates developments of the concept of negligible senescence, proposed in *Longevity, Senescence, and the Genome* in 1990, with new information for turtles, rockfish, and the naked mole-rat. However, centenarians certainly do not show negligible senescence.

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The concept of negligible senescence was developed two decades ago while writing *Longevity, Senescence, and the Genome*, 1990 [1]. I sought to define the spectrum of species differences in senescence as part of their total life history across a broad phyletic sample. This effort was built upon the curation and synthesis of Alex Comfort in the three editions of *The Biology of Senescence*: 1956, 1964, and 1979 [2–4]. Besides broadening the phyletic representation from Comfort's great monographs, I sought to develop a life history framework for aging that included developmental stages. My monograph characterized senescence in a range of eukaryotes by phenotypes at two levels: physico-chemical-cellular changes of individual organisms (molecules to organ pathology) and mortality rate patterns of age-stratified populations (tim-

ing and acceleration). Two main demographic parameters were calculated that define the Gompertz model of survival curves: the Gompertz rate of mortality acceleration (G) after maturation and the initial mortality rate at maturation (IMR). The code was developed with Malcolm Pike and Matthew Witten (now Tarryn M. Witten) [5, 6]. This sampling across the animal kingdom (5 phyla, 75 species) [1, appendix I, II] demonstrated the wide range of differing schedules of demographic and physiological aging in species sampling from the broad range of diverse body plans and life histories. Moreover, many species of animals and plants also have great ecological diversity between populations that may reproduce asexually (vegetatively) or sexually with a range from semelparity to iteroparity. Human populations also differ remarkably in the distribution of early and later mortality, and in the IMR. The diversity in rates and types of senescence between species and between populations implies that lifespans and rates of aging have shifted innumerable times during evolution within most if not all phyla.

During the last 18 months before *Longevity, Senescence, and the Genome* was submitted for publication, I realized that the available data on lifespans and mortality rates allowed a new category of life histories distinguished by negligible changes in adult mortality rates over extended periods of time at advanced adult ages. This seemed to me a demographic equivalent to 'negligible senescence', which may be conceptualized as the extreme of slow aging in a continuum, with the other ex-

treme of rapid senescence representing very short-lived adults. If humans did not experience aging with accelerating mortality, their median lifespan could be estimated as 1,200 years, assuming 0th order kinetics like radioactive decay, and the decay constant from the IMR of a typical 20th century population [1, pp. 28–29]. Additional criteria included maintenance of reproduction and other organ functions at levels of fully mature adults. I identified and analyzed a number of candidate species for negligible senescence, including rockfish, turtles, and bristlecone pines. Several reviewers of drafts of these chapters warned me that this concept was rash, undocumented, and would damage my credibility, because ‘nothing escapes aging’.

Fair enough! For at that time, few if any had challenged William D. Hamilton’s 1966 brilliant analysis of population reproduction and mortality during aging, ‘The moulding of senescence by natural selection’, which mathematically investigated how natural selection acts on age-specific survival and fecundity, with arguments based on the widely accepted Euler-Lotka model for population growth [7]. Hamilton’s highly influential model indicates for all sexually reproducing species that ‘... phenomena of senescence will tend to creep in’. The rate of senescence is made explicitly scalable, varying by the intensity of Darwinian selection for the reproductive contribution (reproductive value), which commonly declines with age because of two factors: reproductive (physiological) senescence and the ever diminishing survival to later ages in all populations. Natural selection acts on life expectancy through the reproductive schedule, and by implication on the schedule of aging. In essence, the lifespan and pattern of aging is under natural selection for a sufficient proportion of the population to survive just long enough with sufficiently slow somatic aging to propagate the next generation. During the next 4 decades, the Hamilton model has had major sway on biogerontology through further mathematical developments of the Euler-Lotka model [8, 9] and experimental studies with artificial selection for the reproductive schedule in studies led by Michael Rose [10–12]. Lifespans (mean, maximum) and both Gompertz parameters responded to artificial selection for the reproductive schedule in outbred lab fly populations within about 10 generations [10, 12, 13]. These powerful effects are reversible, and are attributed to changes in the frequency of existing alleles without fixation. This front of biogerontological research defined a new era in theory and experiment, by showing that the schedules of aging and lifespans were highly plastic and influenced by existing

genetic variation in natural populations, as well as by induced mutations.

To find further candidates for negligible senescence, I organized a series of meetings supported by the NIA and the Ellison Medical Foundation: the Workshops on Negligible Senescence (WONS-1, 1997; WONS-2, 1999) and the Symposia on Slow Aging (SOSA-1, 2000; SOSA-2, 2003). The SOSA proceedings, published as special issues of *Experimental Gerontology* [14, 15], compile a broad range of eukaryotes from three kingdoms (fungi, animals, and plants). I also reviewed evidence that negligible senescence is recurrent in life history evolution in a separate article [16]. I also outline here several paths to adult mortality rate decreases that are at work in postmaturational aging of sexually reproducing species: (a) individual learning to avoid predation and nutritional deficits; (b) somatic growth, which may also improve survival in competition; (c) increased adaptive immunity to pathogens, in which survivors have greater resistance, and, lastly and less likely, (d) increased somatic repair and regeneration, which might derive from postmaturational changes in gene expression that are independent of (a), (b), and (c).

Concurrently, further theory is being developed. Since 2000 at the Max Planck Institute for Demography in Rostock, James Vaupel, Annette Baudisch and colleagues have reexamined the Hamilton paper and argue from different assumptions and parameterizations that senescence was not inevitable under natural selection. These arguments were developed in two journal articles [17, 18] and in Baudisch’s monograph ‘Inevitable Aging?’ [19]. It is proposed that species with indeterminate growth with continuing increase in reproductive capacity after maturity might show negative senescence with decreasing adult mortality rates [17, 19, p. 8]. Candidate organisms include perennial trees and modular organisms like sponges which can reproduce both sexually and asexually, but also sexually reproducing vertebrates that continue somatic growth after maturation, like fish and turtles [16]. These new developments based on the Lotka model are controversial. Rose et al. [9] briefly comment in a penetrating review of Hamilton’s theory that the Rostock Group models are ‘interesting for life history theory [but not applicable] to Hamiltonian theories’. The terms of engagement need to be developed for debating these contending views. We need several high-level symposia and special journal issues to unfold the issues with greater participation by the experimentalist community. Meanwhile, it is timely to update two of the candidates for negligible senescence discussed at WONS and SOSA,

turtles and rockfish. I consider their relevance to the naked mole-rat, a new long-lived model, and to human centenarians, and briefly link these data to the current discussions of how to achieve negligible senescence for humans at large.

Turtles

For more than 4 decades, Justin Congdon has led unique longitudinal studies of two long-lived turtles on the E.S. George Reserve of Michigan State University: Blanding's turtle (*Emydoidea blandingii*) [20] and the painted turtle (*Chrysemys picta*) [21]. In these protected populations, ages exceed 70, but the maximum lifespan is unknown. Both species mature slowly and begin reproduction after about 20 years, with a cohort generation time longer than 30 years. Their ecology is well defined as a detailed 'environgram' with a hierarchy of risk factors and trophic chains [22]. Remarkably, older females lay more eggs and have more consistent annual reproduction than the average younger adult. There are no exterior indications of loss of vigor. Mortality rates, so far as can be judged for such a small sample, do not indicate increase at later ages. The two oldest fertile females, both Blanding's, were at least aged 73 and 73 in 2007, and were first marked as adults in 1953 by Owen Sexton. Because maturation takes typically 20 years, these are minimum ages [Congdon, pers. commun.]. Nothing is known about the ovary: even a basic histological survey of oocyte and follicle populations would be valuable. Congdon has recently retired, and tragically for many areas of science, the project has been completely shut down. Further papers are in preparation.

Rockfish

Long lifespans exceeding 100 years are accepted for some species of deep-dwelling marine fish (groundfish) by combinations of radio-isotope and growth ring measurements [23, 24]. In the genus *Sebastes* (rockfish), at least 30% of the 102 described species can live beyond 50 years. The maximum age recorded is for *S. aleutianus* (rougeye rockfish), 205 years. Other species may be shorter lived based on maximum recorded age: *S. wilsoni* (pygmy rockfish), 26 years; *S. mystinus* (blue rockfish), 30 years. The greatest ages are recorded for fish caught in the deepest waters >300 m, which also support shorter-lived species. These ages underestimate the maximum lifespan

because of sampling issues and because the individuals caught were healthy fish in natural habitats. No gross organ degeneration has been seen; tumors are very rare (<0.1%) [1, p. 217; Leaman, pers. commun.]. Tissue histology has not been systematically evaluated in aged individuals, except for ovary and liver.

The oldest fish examined in the breeding season consistently have normal loads of gametes. Ovarian oocyte and follicles were characterized in detail in a project I organized, based on Bruce Leaman's pioneering collection of ovaries from age-dated individual fish from *S. aleutianus* and *S. aleutus* (Pacific Ocean perch). These specimens were sent to Jan-Pieter de Bruin and Roger Gosden for quantitative histology by their group [25]. In both species, the oldest age class >50 years had slightly smaller body mass than those aged 30–49 years, but nonetheless had the normative ratio of eggs:body mass. The oldest fish had ovaries with enlarged oocytes and follicles, which are characteristic of reproductive activity just before mating. However, some findings differed between the species. For *S. aleutianus*, age did not alter the density of follicles or their size distribution; the oldest individual at 80 years is young relative to the record of 205 years. However, for *S. aleutus* the smallest size class of oocytes and follicles was absent in fish aged >50 years. This deficit may be attributed to a relatively later time of sampling, closer to ovulation than for *S. aleutianus*. As the time of ovulation approaches, follicular growth is complete. Only one crop of follicles is generated each year, at least in younger adults. Thus, *Sebastes* clearly differs in ovarian follicle dynamics from some other fish with shorter lifespans: Lampreys, one of the two surviving classes of agnatha, have fixed numbers of oogonia, like mammals, but are semelparous, unlike mammals, and do not survive their single spawning [1, p. 81]. Another potential example of fixed oogonia is *Cynolebias* (South American annual killifish).

Sebastes reproduction is notable for internal fertilization. The storage of sperm allows maternal determination of the onset of fertilization to optimize according to individual physiological and ecological factors. Development varies 30–50 days before parturition of free swimming larvae about 5 mm long. Recent studies from the National Marine Fisheries Service [27, 28] showed that in the initial years after maturation in several other *Sebastes* species, ova quality increases with maternal age. The volume of oocyte oil globules increases, a stored energy source rich in lipids containing triacylglycerol. The larger oocyte oil stores are hypothesized to account for the positive maternal age effect on larval growth rates and

greater larval resistance to starvation. Increased maternal age also shortens the duration of parturition (rockfish have internal fertilization and are oviparous); there are also progressive increases in the maternal yield of larvae (larval weight per maternal weight). Thus, maternal age increases fecundity and is expected to increase larval survival. Further experiments could use *in vitro* fertilization on much older fish to evaluate if aging alters ova fertilizability and developmental abnormalities, which increase prominently in middle-aged mammals.

Other tissues are being studied. Ana Maria Cuervo and colleagues are examining the liver lysosomes in three age groups of *Sebastes* (young adult, 14–23 years; middle-aged, 27–37 years; older, 40–77 years). For several markers of liver lysosomes, aging rockfish did not show declines in lysosomal functions that are typical of aging rodent livers [pers. commun.]. These fish were freshly obtained from Alaska through Kristan Munk (Alaska Department of Fish and Game, Division of Commercial Fisheries) [24]. John Guerin merits much appreciation for his leadership in promoting research on rockfish and attempts to set up a tissue bank [28]. Despite major efforts over the last decade, no federal peer review panel has yet given his proposals a fundable rating score.

Two decades after my initial proposal [1], some species of fish have gained plausibility as candidates for negligible senescence. More tissues are being characterized for possible molecular aging changes and histopathology. However, we cannot expect to know much about mortality rates, which are needed for the actuarial definition of rates of senescence. Rockfish populations are subject to global ecological disturbances in ocean temperature and nutrients, and to commercial fishing, whether or not a particular species is a commercial target. Throughout the world, commercial fisheries are going to progressively greater depths to harvest the larger fish, which also tend to be the older age classes [29]. From 1990 to 2000, the mean age of bottom fish caught globally has increased on a linear trajectory from 21 to 25 years [29, fig. 4a]. In the Southern Ocean's deep waters, the long-lived orange roughy has been depleted below sustainability in most populations [8]. Nonetheless, there is some hope for sustainable populations of the Patagonian toothfish (*Dissostichus eleginoides*), a delicious and popular food which is marketed as the Chilean sea bass [www.icefish.neu.edu/specialtopics/toothfish]. Illegal fishing of managed oceanic fisheries is also rampant and difficult to control. The next decade may be the final opportunity to characterize the very slow aging of fish species that can not be easily adapted to laboratory culture. Current fisheries models

do not consider protection of the largest size classes, which is critical because the oldest individuals may be the most effective breeders for sustainable fisheries.

The search for further candidates of slow aging in fish should be continued while there is still time before these treasures of evolution are gone forever. According to the model of Vaupel et al. [17, fig. 6], candidates for negligible senescence mature at 'somewhat less' less than the asymptotically limiting size. A puzzle is that the oldest individual rockfish and toothfish tend to be smaller than the median largest size class [1, p. 218]. My preliminary calculation indicates that demographic criteria for negligible senescence could be found in populations with Gompertz mortality rate doubling times >100 years. In reality, it is difficult to define mortality rates at later ages in natural populations of fish because of the small sample sizes, which are necessarily sacrificed for observation of age. Moreover, mortality rate plateaus must be evaluated in terms of the pathophysiological phenotypes in a population.

Mammalian Candidates for Negligible Senescence

The naked mole-rat (*Heterocephalus glaber*) has recently entered the gero-bestia with a lifespan of 28 years or longer in captivity which departs remarkably from allometric trends for lifespan predicted from its small size of 30–80 g [1, pp. 267; 30, 31] and lipid composition with extensive oxidation [32–34]. When I published, *Longevity, Senescence, and the Genome*, its lifespan was already clearly exceptional for a small rodent and its eusociality was noted [1, p. 152], but its lifespan was not yet documented to exceed 25 years.

Rochelle Buffenstein has evaluated the naked mole-rat by my original criteria for negligible senescence [1]. (1) Mortality rates. There was no detectible mortality acceleration up to age 25. Between ages 5–25, annual mortality averaged 1.5%/year by my calculation. This background mortality rate may be lower than the 'initial mortality rate' (IMR) at puberty in most laboratory rodent colonies [6]. A full demographic analysis of the several naked mole-rat colonies is urgently needed. (2) Reproduction. In Buffenstein's colony, litter size has not declined in the oldest females, although there is decreased maternal success in maintaining pup survival to weaning; 'many pups born to elderly females die before weaning'. However, in another colony, a wild-caught female of >26 years at death '... had ceased reproducing 3 years earlier' [35]. This brief observation raises the possibility of

ovarian oocyte decline or depletion, as observed in all other mammals, but the discussion is still in want of ovarian follicular data. (3) Physiological functions besides reproduction. Buffenstein's lab and others have investigated a number of vital parameters, reviewed in reference [30]. No age changes up to about 25 years were found in basal metabolic rate, glucose-insulin tolerance, arterial elasticity, and bone mineral content. At a biochemical level, glycosylated hemoglobin and lipid oxidation did not increase, consistent with maintained glucose homeostasis. Extensive published and unpublished data are cited in references [30–33]. Tumors have not been found (800 animals) and sickly animals are unusual. Thus, the naked mole-rat appears to satisfy most criteria for negligible senescence, with the important exception of lower pup survival to weaning in the older mothers. Poorer pup survival could arise from deficient maternal care, or from congenital defects which increase with maternal age in all mammals examined [1, chapter 8].

A fascinating new observation is that the oldest male in this colony has gradually developed a frail appearance, yet is still highly functional [R. Buffenstein, pers. commun.]. At the advanced age of 27–28 years, this individual gradually lost weight with apparent sarcopenia and kyphosis (hunched appearance). Despite surviving several years of apparent frailty, this male nonetheless retained his social dominance, siring a recent litter and getting first access to daily food, etc. The viability of this phenotype of frailty with maintenance of some vital functions raises important questions on the evolution of aging. Has the naked mole-rat evolved a behavioral ecology that is permissive for frail phenotypes of aging? This example is also relevant to the debate by anthropologists on benefits of experience that elderly humans bring to their group that could have been a factor in the evolution of the long human lifespan.

Naked mole-rats pose many other challenges to molecular biogerontology theory. Their levels of oxidized lipids and proteins are very high, without further age changes after maturation [32, 33], which would not predict long lifespan in the usual model of critical oxidative load. Two other anomalies may join the discussion about oxidative stress. In culture, primary fibroblasts are sensitive to hydrogen peroxide relative to mouse [36]; however, for some other cytotoxic agents, naked mole-rats conform to general correlations cell vulnerability with species lifespan. I suggest that we need to consider the hypoxic and hypercapnic environment of these burrowing animals, which is reflected in hemoglobin gene changes that alter oxygen dissociation and pH sensitivity. The low

body temperature ($<35^{\circ}\text{C}$) should also be considered as a factor in allometric comparisons, which could bring them closer to the central trends [1, p. 152]. We may anticipate future detailed demographic analysis and information on gametogenesis, age-related pathology, telomere length, DNA oxidative damage, and cell resistance to stress which are needed to characterize the nature of aging in the naked mole-rat. Pending critical details on demographic parameters, reproductive aging, and pathology of aging, I conclude that the naked mole-rat appears to age very slowly for a rodent of its size, but does not yet meet criteria for negligible senescence.

Human centenarians merit a place in this discussion as possible cases of extremely slow aging. These individuals are remarkable as statistical outliers of the modal age of death, which is 75–85 years in health-rich populations. However, centenarians comprise a tiny fraction of human 20th century populations, 0.01–0.02%, and fewer than 20 have exceeded the age of 115 [37, 38]. They may be regarded as survivors of specific clinical conditions, some of which arose decades before [39–41]. Corresponding to their chronic disease load, most supracentenarians are physically frail and depend on considerable assistance. The number of centenarians is growing exponentially relative to other age groups [41], which is providing a deeper database for analyzing mortality rates at later ages. In the Gavrilovs' recent analysis of highest quality regional data from the US Social Security Administration Death Master File [42], the Gompertz mortality rate trajectory continues beyond 105. These findings suggest that mortality rate plateaus are much shorter than initially indicated by Vaupel et al. [43] who concluded from data of a decade ago that mortality rates remained approximately constant after age 105 up to a 'mortality rate plateau' of about 60%/year. The Gavrilovs' analysis also mirrors aging laboratory rodents, which Malcolm Pike and I showed to lack definitive mortality plateaus [6]. However, future centenarians could have quite different phenotypes in response to medical advances in the 20th century. I anticipate that the next decade of observations will show shifts in the chronic disease profiles of those born after 1900 who had the advantages of childhood inoculation and better nutrition, as well as drug treatments for hypertension and other vascular risk factors. While many expected the record human lifespan of Jeanne Calment at 122 years [37] to be superseded soon after she died in 1997, it has not fallen despite the centenarian avalanche noted above.

I conclude from the extensive pathology of most centenarians and the continuing increase in mortality that

human centenarians may have slower aging and mortality schedules, but they do not meet the three criteria for negligible senescence. Nonetheless, some genotypes may conditionally protect against extreme disability at advanced ages. The hunt is on to identify genes that allow survival to advanced ages with minimal dysfunctions. Among several interesting candidates is an allele of cholesterol ester transport protein, which is associated with good cognitive function at advanced ages [40]. There may be important gene candidates from other animal species with very long lifespans such as whales, which merit higher priority for genomic sequencing than recently given [44].

Emerging Developments in Slowing Aging

'Negligible senescence' has been taken far beyond from my scholarly concept [1] by proponents of human prolongevity. Aubrey de Grey has developed a research program 'SENS' (Strategies for Engineered Negligible Senescence) to identify 'incremental refinement that could prevent death from old age (at any age) within a time frame of decades, leading to four-digit lifespans of many people alive today' [45]. A conference organized by de Grey in June of 2008 featured recent advances in cell and molecular repair and replacement for the immunological elimination of cancer cells, which he considered 'a major step in addressing the credibility problem' [46]. SENS or not, these and other approaches in regenerative medicine will be developed for clinical applications in specific diseases, and may be expected to incrementally increase life expectancy at later ages.

Alternatively to the SENS strategy of gero-engineering for specific lesions, Michael Rose suggests a more generalizable approach seated in evolutionary theory, 'SENSE' (Strategies of Engineering Negligible Senescence Evolutionarily), which considers the underlying mechanisms in extremely slow aging of many species and in the germ cell lineages [12]. The rapid increase in lifespan in flies

artificially selected for later reproduction [10, 12] could identify gene pleiotropies that promote robust longevity. I anticipate that the full genomic analysis of these longer-lived flies will identify new regulatory mechanisms in aging and targets for interventions. It is deeply frustrating that still so little is known about the details of aging in long-lived fish, turtles, birds, and bats and other vertebrates and invertebrates not mentioned here.

I would also emphasize the environment (hygiene, public health, nutrition, purity of food and water), which has major influences on life expectancy [47], also noted briefly by Rose [12]. In a further development of the human population differences noted earlier [1, pp. 15–21], Eileen Crimmins and I showed that historical improvements in Sweden that lowered infant mortality were linked to increased life expectancy at all adult ages in the 18th and 19th century [47, pp. 134–135; 48, 49]. Because most chronic diseases are associated with inflammation [47–50], we hypothesized that historical reductions in the inflammatory load mediated the increase in life expectancy. The hypothesized link of lowered inflammatory load with the historical increase in lifespan suggests the possibility of further improvements through drugs, diet, but also air quality [1, pp. 409–410]. In lab rodents, caloric restriction attenuates a remarkable range of aging diseases and changes, in apparent coordination with the reduction of inflammatory processes [47, pp. 184–221]. There may be shared regulatory modules of caloric restriction with genomic changes that also mediated the increased human longevity from great ape ancestors, as human ancestors shifted to an increasingly meat-rich diet, yet doubled the life expectancy [47, pp. 376–407]. The implementation of gero-engineering approaches (SENS and SENSE) alone or in combination with drugs and diet may slow aging further, but limits in the approach to negligible senescence may be imposed by our increasingly dirty environments. Still, the IMR continues to decline in Sweden [50] and a few other privileged populations, which could allow greater potential lifespans if the Gompertz acceleration can also be slowed. Time will tell!

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