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Variations in Senescence and Longevity Include the Possibility of Negligible Senescence

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The variations in senescence observed in different species span an enormous range of rates that may be described by mortality rate doubling times. This review considers examples of very slowly senescing conifers and fish from natural populations in which advanced age may not compromise reproductive functions. There is thus a basis for considering the possibility that some organisms may experience negligible degrees of senescence in certain environments. A tissue bank is urgently needed to provide specimens of long-lived organisms for study of possible anti-aging mechanisms that permit achievement of great ages.

RECENT information supports the possibility that the rates of senescence can be very slow or even negligible. In 1997, Jean Calment achieved a record life span of 122.4 years for humans, which approaches the record life spans of a few other vertebrates, as will be described. There is also good evidence for marked slowing of mortality rate accelerations at advanced ages in many human populations (1) as well as indications that increased survival to later ages may be accompanied by better health (2). These data diverge from the historical premise that each species has a characteristic maximum life span that is set by a hard-wired genetic program. However, these findings are also consistent with many examples from other species, which show alternate schedules of senescence according to the population and environment (3). This plasticity in aging give insights into how life spans have increased in recent history and how environmental factors may determine aging in the individual.

Life spans of sexually reproducing organisms vary over a million-fold range, from yeast to bristlecone pine (Figure 1), with the human record in the middle range of these life spans. One measure of the rate of senescence in a population is the time required for mortality rate doubling (MRD), which ranges at least 1000-fold (Table 1) (3,4). The total life span does not always correspond to the rate of senescence because the length of stages in development vary widely between species and even within populations. Extreme dissociation of development and senescence occurs in certain plants whose extensive juvenile phases last many decades, or even a century, before they mature, flower, and die after a rapidly manifested senescence (Figure 1, bamboo). Figure 1 shows rates of senescence on the horizontal axis that represent rates of senescence over a continuum calibrated between extremes of rapid and negligible senescence, which flank the more widely recognized intermediate forms of gradual senescence.

Rapid senescence may last for hours to days in association with extensive dying-off in the population, as epitomized by the Pacific salmon during their only reproductive season. The MRDs are in the range of days. In most examples, the entire population dies with more or less synchronous deterioration of functions. Laboratory yeast, nematodes, and flies may be considered in this category, because their short life spans are associated with short reproductive schedules. In general, rapid senescence leading to death after the first round of reproduction is uncommon in vertebrate life histories: it is observed in <1% of fish species (ref. 3, pp. 597–600) but not in reptiles, birds, or placental mammals (3,5). Most examples of rapid senescence leading to death after reproduction have clear hormonal triggers, which can be manipulated experimentally. Many examples are found in nematodes, fruit flies, salmon, and flowering plants (3,6).

Gradual senescence, the middle sector, is epitomized by humans and other mammals, in which senescence is not synchronized in the population by reproductive activity. Mammalian senescence has a general (canonical) pattern, upon which is superposed a number of genotype-specific diseases that distinguish individual humans and inbred animal strains (3). Thus, all mammals observed have some degree of age-related decline in reproduction: loss of compact bone, vascular endothelial proliferation and atherogenesis, and collagen oxidation. Brain amyloid (Aβ peptide), a hallmark of Alzheimer's disease, is accumulated by the majority of humans during aging, as well as by other mammals that live at least 10 years such as the dog (7) and the mouse lemur, a short-lived prosimian (8). However, laboratory rodents do not accumulate Aβ during aging unless made transgenic to overproduce Aβ. The timing of onset and progression of each of these aging changes varies widely between individuals, as illustrated by the consequences of estrogen deficits after menopause. Estrogen replacement therapy (ERT) is recognized for its efficacy in decreasing heart attacks and osteoporosis after menopause, but may also reduce the risk of Alzheimer's disease (9). (See below for more about estrogen and the evolution of life spans.)

The most indolent forms of senescence are represented in Figure 1 as *negligible senescence*. There is now serious evidence of undiminished function in extremely long-lived

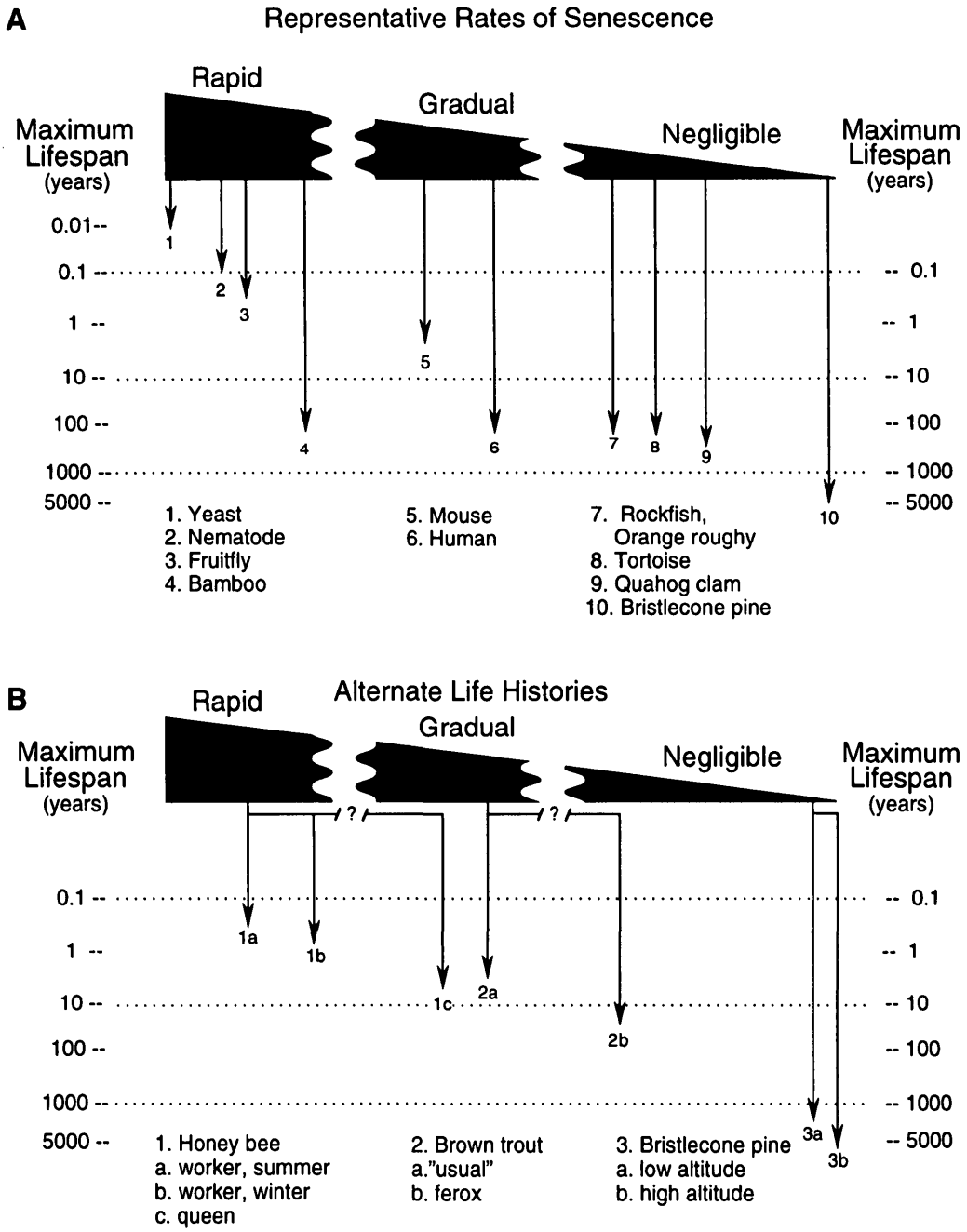

Figure 1. (**A**) A sample of species that differ widely in longevity (total life span from zygote to oldest adult in years) and the rate of senescence in adults (semiquantitative scale ranging from rapid to gradual to negligible senescence). Data on maximum life spans depending on husbandry conditions (temperature, nutrition) are shown. Sources of data are found in ref. 3, except as indicated. **Rapid senescence**: yeast (*Saccharomyces cerevisae*), 2–4 days during asexual budding; nematode (*Caenorhabditis elegans*), 30 days; fruitfly (*Drosophila melanogaster*), 60 days; Pacific salmon (*Onchorynchus*), 3–6 years. Vascular plants: thick-stemmed bamboo (*Phyllostachys bambusoides, Phyllostachys henonis*), 120 years; *Puya raimondii* (related to the pineapple), 150 years. **Gradual senescence**: mouse (*Mus musculus*), 4.2 years (1541 days); human (Jeanne Calment), 122.4 years. **Negligible senescence**: fish: rockfish (*Sebastes aleutianus*), 140 years; orange roughy (*Hoplostethus atlanticus*), 140 years (14,16); warty oreo (*Allocyttus verrucosus*), >130 years (17); sturgeon (*Acipenser fulvescens*), 152 years; tortoise (*Geochelone gigantea*), 150 years; Bivalve mollusc: ocean quahog (*Artica islandica*), 220 years; Great Basin bristlecone pine (*Pinus longaeva*), 4862 years, however, because ring-dating often underestimates, it is likely that the true ages are >5000 years (10). Inclusion of clonal, asexual reproducing species (e.g., clones of the creosote bush and other asexually reproducing species) would extend the upper range of postzygotic individual life spans to >10,000 years. Alternate rates of senescence: honeybee (*Apis mellifica*), 60 days summer worker; 300 days winter worker, with rapid senescence associated with change in occupation from hive to field bee; queens 5–7 years; queens in other social insects may live >30 years (21). Brown trout (*Salmo trutta*), 3–5 years for the usual small biotype; ferox (giant trout), >20 years (23,24). (**B**) Alternate life histories and longevities in the same species are shown by the horizontal branches. The (?) indicates uncertainty as to the classification for rate of senescence. The honeybee queen might prove to die from external causes, such as neglect in grooming or assassination by lower castes in the hive that monitor the depletion of her finite stores of sperm acquired during nuptial flights. The causes of death in Brown trout are unknown, but are not likely to be due to the type of rapid senescence in Pacific salmon. The ancient bristlecone pine appears to die from external hazards, e.g., fire, soil erosion, and boring insects or wounds that enable fungal rot (13). The oldest trees live at the highest elevations, whereas at lower altitudes, life spans rarely exceed 1500 years; at higher altitudes, there are few insects and less competition from other tree species.

Table 1. Life Spans and Mortality Rate Doubling (MRD) Times

Species	Life Span (years)	MRD (years)
Yeast (budding)	0.01	0.004
Fruitfly	0.3	0.03
Honeybee		
Worker		
Summer	0.2	0.02
Winter	0.9	0.03*
Queen	>5	>1
Nematode	0.15	0.03
Mouse	3	0.25
Herring gull	>40	3
Human	15–80	8
	>100	>16
Bristlecone pine	4862	?

Notes: Most of these data were quoted from refs. 3 and 4. The MRD of human centenarians must be at least twice as long as that observed before the mean life span, because mortality rates approach a maximum of 0.5/years after 105 years (1). There are too few survivors at highly advanced ages in human, fish, and conifer populations to calculate meaningful statistics on the MRD.

*After leaving hive in spring to become field worker.

conifers and reasonable evidence that reproduction is maintained in certain long-lived fish. The record is a Great Basin bristlecone pine at 4862 years in the high Nevada mountains (10). Of great interest is the absence of age changes in sexual reproduction of trees aged 700–4713 years, as judged in the laboratory by pollen germination, by seed weight, and by seedling growth rates (11). Parental age did not alter the frequency of abnormal germinants (putative mutations), nor did age alter the annual vegetative growth of shoots and cambium or their microstructure (12). It would be of interest to know the seed viability in trees of many genera that grow productively for a millennium or more (3). Death of these ancient trees seems to be due to external hazards including fire, soil erosion, and boring insects that enable fungal rot (10). The oldest trees live at the highest elevations, whereas at lower altitudes life spans rarely exceed 1500 years; at higher altitudes, these trees are not exposed to insects or competition from other trees.

As described to me by Ronald Lanner, the senior author of these conservatively interpreted papers (10–13), the seeding of bristlecone pine stands at higher elevations depends on Clark's nutcracker, a bird that stores (caches) seeds in these stark locations (10,13). Wind-dispersed seed, more typical of pines at lower altitudes, rarely reaches higher altitudes. Further, I suggest that the extreme life spans at higher altitudes are an adventitious outcome of the evolution of a seed-caching behavior, which thereby accessed a new niche for the bristlecone pine and increased its potential life span. One may consider that the recent expansion of human life spans (1) parallels that of bristlecones at high altitude, and may be due, in our case, to improvements of hygiene and nutrition that adventitiously favored greater life spans.

Other candidates for negligible senescence are certain deep-dwelling fish that live for at least 140 years, according to rigorous radioisotopic dating (14–17). Other supracentenarians occupy similar habitats: rockfish in the Northwest Pacific (15) and, in the southern hemisphere, the orange roughy (16) and warty oreo (17) (see Figure 1). Readers may have enjoyed the tasty orange roughy that is being harvested towards extinction (18). Study of these fish has barely begun. The few old rockfish examined had abundant, newly formed eggs and, lacking gross pathology, appeared in fine health (X. de Bruin, R. Gosden, C. Finch, and B.M. Leaman, unpublished data).

Yet other examples of very slow or possibly negligible senescence may be found in birds and reptiles, which, by field studies and credible anecdotal evidence, are in the upper range of human life spans (5,19). Some birds appear to age very slowly, with long MRDs (4). Moreover, birds have normal blood glucose of 250–350 mg/dl (in the range of uncorrected diabetics) and core temperatures of 39–41°C (3,5). By thermodynamics, the elevated glucose and temperature should cause extensive nonenzymatic oxidation of proteins. But there are almost no data on biochemical aging of birds. Because avian fibroblasts are more resistant to oxygen toxicity than those from mammals (20), birds may have evolved unique antioxidant mechanisms that allow great longevity despite their feverish metabolism.

There are few data on mortality rates at advanced ages in animals and plants, which, for animals, would require large captive populations (which do not exist) or difficult banding and recapture studies from natural populations. Nonetheless, the existence of a few individuals of great ages is consistent with very slow mortality rate accelerations, e.g., for conifers that live >1000 years, the MRDs could be >100 years long.

However, very long MRDs are not sufficient criteria for negligible senescence. For example, the acceleration of mortality in human populations slows after the average life span, so that by the age of 105, mortality rates may not increase higher than a maximum of about 50% per year, and may even show small net decreases in successive year groups (1). But this does not mean that human supracentenarians were rejuvenated by living so long. In fact, most centenarians are in a very fragile state. Thus, long MRDs may indicate a negligible state of senescence, but only when there has not been a preceding phase of accelerating mortality in adults and there has been no decline of reproduction or other vital functions. These criteria may be met in certain conifers and fish.

Compounding the diversity of life span by species are differences within populations, as illustrated above in the 3-fold differences of bristlecone life spans between lower and higher altitudes. Moreover, many social insects have castes with life spans differing by 100-fold or more (3,21). Queens of the honeybee live at least 5–7 years with intense seasonal egg laying, whereas worker life spans are 1–2 months (Figure 1B); these castes have identical genes, which are programmed differently during development. Although we lack data on tumors or other organ degeneration, intense seasonal egg production can continue for years, or for decades in some termites, suggesting possible negligible senescence. In some species, when sperm stores are eventually depleted, queens die by neglect from feeding and grooming by workers or are even assassinated (3,21). This would be an extreme case of rapid senescence superimposed on a baseline of negligible senescence. The short

life spans of worker bees are associated with foraging flights that expose them to predation and mechanical wear of irreplaceable wings. At a time determined by population density and by the foraging environment, there is an increase in juvenile hormone (JH) levels (6,22), which stimulates worker bees to foraging flights that, in turn, rapidly accelerate mortality (Table 1). If born in the later summer, workers overwinter as hive bees; the delay of foraging until the next spring also delays the acceleration of mortality. In many other species, other hormones also regulate aspects of both development and senescence (6).

Alternate patterns of senescence are also found in some fish in which some individuals become long-lived giant predators (3,23,24). In a well-studied case, brown trout populations often include individuals that prey upon other smaller fish when they reach a sufficient size. These "ferox trout" then continue to grow much larger, up to 100 cm, and live for at least 20 years, whereas their congeners, which feed on insects and other plankton, do not grow beyond 30 cm nor live beyond 3–5 years. Arctic charr, large-mouth bass, and perch show similar alternate life histories (3,23,24). Nothing is known about the causes of death in the short- or long-lived variants, but there is no hint of glucocorticoid driven death like that of Pacific salmon.

How may all these different patterns of life history have evolved? Population biologists hypothesize that the statistical adult life spans result from selection for a reproductive schedule optimized to a particular habitat (25,26). Thus, predator pressure on adults may select for individuals that reproduce earlier and with larger initial numbers of offspring (25,27). As predicted, populations of guppies (25) and opossums (27) in locations with reduced predatory pressure show later maturation and longer reproductive schedules. Opossums on the mainland had more predator pressure than those on nearby islands. Consistent with theory, their life spans were 50% less, with parallel decreases of the MRD and of collagen cross-linking (27). In the laboratory, selection of outbred fruit flies for reproduction at early versus later ages yielded major shifts in life span within 10 generations (26). The efficacy of reverse selection on these same responses shows that some outbred populations maintain genetic variants that permit rapid responses to selection for different reproductive schedules. The very long life spans of fish also fit this model, with long prematurational phases of 10–30 years in deep sea habitats that have few predators besides commercial fishing. The ferox phenomenon, however, depends on a critical density of prey species that allows enhanced growth in these few individuals (24) and that indirectly yields longer life spans in parallel with extended reproduction.

Evolutionary biologists hypothesize that the force of natural selection inevitably decreases at later ages. Because in most natural populations mortality is generally so high that relatively few individuals reach advanced ages, young adults accomplish most of the reproduction (26,28,29). Thus, populations should randomly accumulate alleles with adverse effects that are delayed until after the major reproductive roles are completed. Williams (29) proposed the antagonistic pleiotropy hypothesis that genes may be selected for early advantage, whereas later dysfunctions may not be selected against if they arise after the statistical life span that suffices for reproduction to maintain the population. For example, hormones with important roles in development or adult function, but which also mediate later degenerative processes (e.g., JH in worker bees), support the concept of antagonistic pleiotropy (6).

If a habitat favors more extended reproductive schedules, then this would require evolution of slower age-related pathological processes, such as cancer, osteoporosis, or brain Aβ. For example, consider that the mouse lemur accumulates brain Aβ by 6–10 years (8), which is a year or more before puberty of chimpanzees and longer lived primates. The strong propensity for accumulating brain Aβ deposits during aging in mammals indicates a primitive trait that has persisted during the past 100 million years. The evolution of extended reproductive schedules, which are associated with more prolonged exposure to estrogens, may have slowed the accumulation of Aβ or reduced its impact on neuron viability. This hypothesis is consistent with the beneficial effects of estrogen replacement on blood lipids and Alzheimer's disease (9), but also with the neuroprotective effects of estradiol (30). The different rates of collagen cross-linking in island versus mainland opossums (27) also show the evolutionary lability of molecular aging. The huge range of life spans and schedules of senescence shows that life spans must expand and contract freely, and may do so frequently, during evolution in each phylum (3). This plasticity would be favored if the rates of senescence were determined by humoral agents, such as hormones and antioxidants, rather than by alterations in subcellular signaling mechanisms.

Although the evolutionary hypothesis of senescence predicts that the optimization of the reproductive schedule will select against genes with early adverse effects, the hypothesis does not inform about rates of senescence. Nonetheless, population biologists generally conclude from mathematical models that "senescence always creeps in," in Hamilton's trenchant phrase (28). This reasoning does not predict the apparent negligible senescence of long-lived conifers and fish that maintain reproduction at their most advanced ages. Moreover, it is puzzling that inbred invertebrates, like many other species, include relatively robust individuals that comprise subpopulations with reduced mortality rates at advanced ages (1). This diversity is consistent with genetic studies of humans, mice, flies, and worms, which concluded that the heritability of life span is minor, <35% of its variance (31). Although this implies a relatively greater importance of the environment than genes to outcomes of aging, we do not know the role of nonprogrammed developmental variations in cell numbers, for example, that may endow an individual with organ reserves that favor greater longevity.

In summary, the comparative biology of life histories shows the enormous plasticity of the schedule of senescence during evolution. The prospects for continued increase in human life expectancy are of course unknown, but examples from the natural world suggest that no firm limit is built into the human genome. The efforts to modify human aging via drugs, diet, and lifestyle interventions are entirely consistent with the observed plasticity in life histo-

ries of numerous other species. A tissue bank is urgently needed to provide specimens of long-lived organisms for study of possible anti-aging mechanisms that permit achievement of great ages. It is of great interest to obtain data on biochemical and cellular changes at advanced ages of diverse species, as well as on cell and molecular turnover. Time is running out on many very long-lived species that are being commercially overexploited or whose habitats are being destroyed. These rare populations are among our old Earth's greatest treasures and should be included in endangered species efforts (32). Even so, we may never know the extent of negligible senescence that may once have evolved in pristine natural populations.

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