ISSN 0006-2979, Biochemistry (Moscow), 2022, Vol. 87, Nos. 12-13, pp. 1512-1527 © The Author(s) 2022. This article is an open access publication.

REVIEW

Tracing Slow Phenoptosis to the Prenatal Stage in Social Vertebrates

David W. Leake

University of Hawaii at Manoa, Honolulu, HI 96822
e-mail: dwleake@aol.com

Received September 12, 2022
Revised November 8, 2022
Accepted November 16, 2022

Abstract—Vladimir Skulachev's coining of the term "phenoptosis" 25 years ago (Skulachev, V. P., *Biochemistry (Moscow)*, **62**, 1997) highlighted the theoretical possibility that aging is a programmed process to speed the exit of individuals posing some danger to their social group. While rapid "acute phenoptosis" might occur at any age (e.g., to prevent spread of deadly infections), "slow phenoptosis" is generally considered to occur later in life in the form of chronic age-related disorders. However, recent research indicates that risks for such chronic disorders can be greatly raised by early life adversity, especially during the prenatal stage. Much of this research uses indicators of *biological aging*, the speeding or slowing of natural physiological deterioration in response to environmental inputs, leading to divergence from *chronological age*. Studies using biological aging indicators commonly find it is accelerated not only in older individuals with chronic disorders, but also in very young individuals with health problems. This review will explain how *accelerated biological aging* equates to *slow phenoptosis*. Its occurrence even in the prenatal stage is theoretically supported by W. D. Hamilton's proposal that offsprings detecting they have dangerous mutations should then automatically speed their demise, in order to improve their inclusive fitness by giving their parents the chance to produce other fitter siblings.

DOI: 10.1134/S0006297922120094

Keywords: phenoptosis, biological aging, allometric scaling, mitochondria, epigenetic clocks, telomeres, free-riders

INTRODUCTION: THE CHALLENGE OF BIOLOGICAL AGING

Developmental research on humans and model animals has generally used a lifespan framework from infancy to senescence, but accumulating evidence from medical fields indicates that prenatal experiences strongly influence the course of development [1]. Much of the relevant research employs the concept of *biological aging*, which refers to how the rate of an animal's natural physiological deterioration can speed up or slow down in response to environmental inputs, leading to divergence from *chronological age*. Over just the past decade there has been a surge in research using new epigenetic clocks to estimate biological aging, raising challenges to many existing aging and life history theories. For example, telomeric and epigenetic indicators have shown that gestational distress can accelerate biological aging as measured at hatching or birth [2], contrary to the common assumption that aging starts around sexual maturity and then gradually accelerates. In addition, longitudinal studies have shown that, at any time across the lifecourse, toxic levels of stress can speed up biological aging, but with the possibility of being slowed down in response to better conditions [3].

The "proximate" mechanisms of biological aging are coming into better focus, especially through experimental research on model vertebrates including birds, rodents, and primates. When "ultimate" evolutionary roots are addressed, just about all theories fall into two categories [4]. One category is *developmental constraints* (or silver spoon): young organisms in harsh environments make adaptive trade-offs to survive but at the expense of poor health later in life. The other category is *predictive adaptive response*: young organisms adjust their developmental trade-offs based on cues about their likely future environment, which however leads to poor health outcomes due to mismatch if the future environment is different from that predicted. It is notable that both theory categories are based on individual level selection in which organisms are expected to strive above all for their own survival and sexual reproduction. Missing is consideration of the

possibility that some distressed offspring might altruistically speed their biological aging in the interests of *inclusive fitness*, by making way for kin with better fitness prospects to carry on their shared genes, as proposed by Hamilton [5].

This review will lead to the conclusion that accelerated biological aging can be equated to *phenoptosis*, as introduced by Vladimir Skulachev [6] to explain aging as a process that benefits the broader population, which is a common theme in programmed aging theories. The variable pace of biological aging seems beyond explanation by non-programmed aging theories, yet it makes sense if aging is understood as a program that can be speeded or slowed. As argued by Goldsmith [7], figuring out which is most valid, is important for medical research because the two approaches describe very different mechanisms responsible for age-related disorders.

Although "stress" in health news headlines typically implies something dangerous, stress response activation is essential for meeting life's challenges and can produce *hormesis*, the strengthening of bodily components in response to non-toxic stress. This review therefore follows stress research pioneer Selye [8] in distinguishing *distress*, where effects are potentially damaging, from *eustress* (hormesis), where physiological maintenance or even a boost in well-being is expected.

SAMURAI LAW OF BIOLOGY AND INCLUSIVE FITNESS

Altruistic basis of phenoptosis. According to Skulachev [9], the operation of his proposed Samurai Law of Biology: "...helps complicated living systems avoid the risk of ruin when a system of lower hierarchic position makes a significant mistake. Thus, mitoptosis purifies a cell from damaged and hence unwanted mitochondria; apoptosis purifies a tissue from unwanted cells; and phenoptosis purifies a community from unwanted individuals."

This law is rooted in the principle that "it is better to die than to be wrong" as reflected in the tradition of failing Japanese *samurai* warriors committing *hara-kiri*. As explained by Skulachev [10], Hamilton's [11, 12] inclusive fitness concept provides a theoretical justification of phenoptosis as altruistic self-sacrifice.

Bourke [13] used inclusive fitness and logic similar to the Samurai Law of Biology to explain why the six major evolutionary transitions brought ever-increasing biological complexity. Each transition led to a new level of sociality (e.g., eukaryotic cells, eusocial insects), which required new mechanisms to control renegade selfish components, or *free-riders*. Such mechanisms might reside in individual components (e.g., eusocial insect queens lay eggs but not workers), or be operative at higher hierarchic levels (e.g., detection and destruction of eggs laid by renegade eusocial insect workers). These and other considerations have led many evolutionary biologists to agree that the *maximization of inclusive fitness* represents a *universal design principle* for evolution (e.g., [14).

High infant mortalities as phenoptosis, the sooner-the-better. As reflected in U-shaped mortality curves such as in Fig. 1, animal infant mortality rates tend to be high. Hamilton [5] suggested a likely factor to be altruistic self-removal by offspring detecting they have high mutation loads, so their parents can then try to produce another offspring, which he termed *sibling replacement*. He stressed this self-removal should happen as soon as possible, preferably during gestation, to give parents the most possible time. He also proposed that parents might experience evolved motivations to hasten this, as suggested in the human case by infanticide being common in pre-modern times. Haig [15] used similar logic to explain

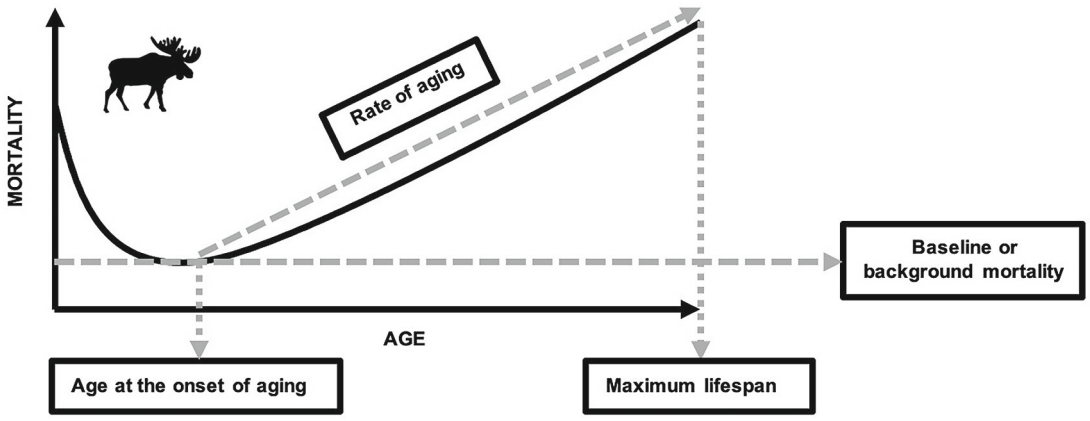

Fig. 1. Age-specific mortality curve for a typical mammalian species. Mortality decreases from birth to early adulthood, then stays relatively constant at a level generally called basal or background mortality and finally starts to increase until the maximum age observed in the population (maximum lifespan). The age when mortality starts to increase is defined as the age at the onset of aging and can vary substantially across species [but as explained in the text the "onset of aging" appears to actually be during gestation]. The rate of aging corresponds to the increase in the mortality rate with age (adapted from Lemaître, et al. [18], Fig. 1).

the evolution of maternal "screening processes" to identify fetuses with low fitness prospects and initiate their miscarriage, the sooner the better to enable earlier "reproductive compensation" (e.g., via sibling replacement). Based on evidence that aging can start during gestation, Kinzina et al. [16] proposed that mortality curves (such as Fig. 1) reflect both (i) early-life mortality due to selection against fetuses with high mutation loads or damage (e.g., from environmental toxins), and (ii) distinct aging-related mortality. Bruckner and Catalano [17] cited Hamilton [5] regarding sibling replacement in support of their similar "selection *in utero*" proposal.

Multilevel selection. Hamilton [19] came to promote multilevel selection, as distilled in the Price Equation, as a more general formulation of evolutionary processes than inclusive fitness. The Price Equation allows modeling of selective forces across multiple levels for any kind of inheritance process, not just genetic. Effects at different levels potentially oppose each other, especially individual level selfishness versus supra-individual levels where cooperation is required for groups to be competitive [20]. However, *non-programmed aging* proponents typically maintain that individual level selection is too strong to allow altruistic aging to evolve and be maintained (e.g., [21]). In response, Mitteldorf [22] explained that from a multilevel selection perspective, natural selection can indeed prevent individual level selection from hijacking altruistic aging mechanisms by embedding them along with redundant time-keeping clocks. Another common misunderstanding of programmed aging critics such as [21] is that the proposed genetic mechanisms "would kick in to abruptly increase death rate" at some chronological age, which they then claim must be wrong because aging is a gradual process. If they were more familiar with the phenoptosis literature, they would understand that *acute phenoptosis* can indeed be "abrupt" but can occur at any chronological age (e.g., to prevent spread of deadly infections), while "gradual" aging is equivalent to *slow phenoptosis*.

ALLOMETRIC SCALING OF METABOLISM AND LIFESPAN

Over a century of research indicates that (i) body mass scales with metabolism at a power law exponent of less than one across almost all life forms, and (ii) metabolic rates are a significant determinant of lifespans [23]. Universal scaling exponents of 3/4 and 2/3 have been proposed, but which is most valid, or whether exponents instead are quite variable, remains under contention. The important point is that a scaling exponent under one means that larger body size associates with slower metabolism and longer lifespan. These effects tend to be quite consistent within major taxons. For example, it has been observed that mammal species share the same approximate lifetime limit of about one-and-a-half billion heart beats (although humans now average about twice that due to the approximate doubling of average lifespans over just the past couple of centuries) [23].

Figure 2 shows the relationship between metabolic rate and body size when plotted using logarithmic scales, which indicates power law scaling when associations between factors approximate a straight line. The three animal categories have different average levels of metabolism, from highest in endotherms (warm-blooded animals) to lowest in planarians (the simplest animals to exhibit a body plan), yet their scaling lines are parallel. A similar figure in West and Brown [24] covered 27 orders of magnitude from respiratory complex to elephant.

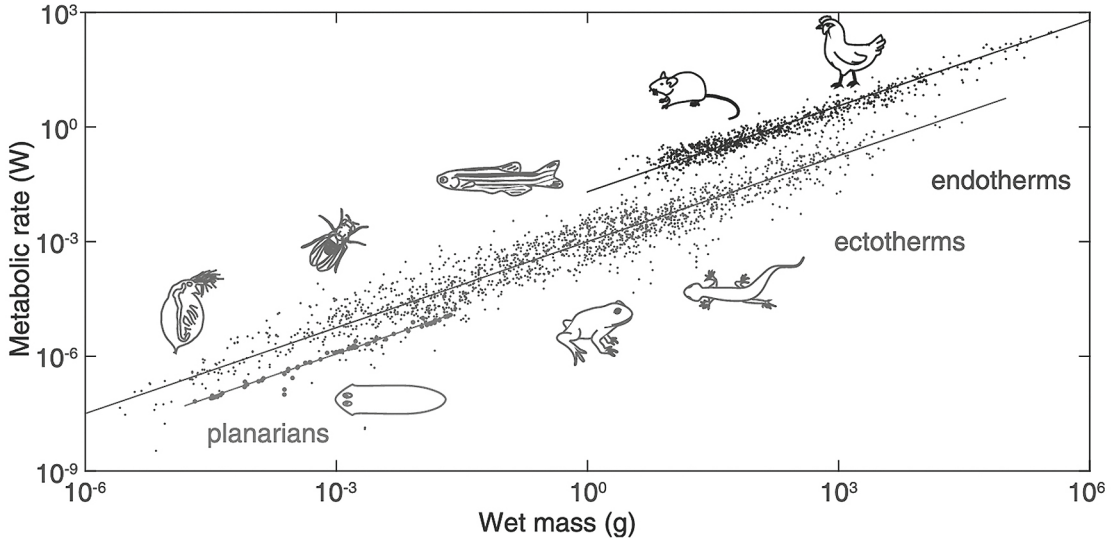

Fig. 2. Metabolic rate versus wet mass scaling in endotherms, ectotherms, and planarians. Dots correspond to individual measurements; the three solid lines trace the 3/4 scaling exponent ([26], Fig. 1D).

The scaling line slopes in both figures are about 3/4. This means that a multicellular species with twice the average weight of another species (and therefore twice the number of cells) will only require 2 to the power of 3/4 (or 1.682) times as much metabolic power, indicating more efficient energy use per cell. With regard to the relationship between body size and lifespan, a power law scaling exponent of 1/4 has been derived as a baseline, around which natural selection should optimize species-specific average lifespans [23]. Associations between higher metabolic rates and shorter lifespans have often been explained as due to the accompanying higher rates of wear-and-tear on the body, with a major component being oxidative stress from toxic reactive oxygen species (ROS) generated primarily by mitochondria [25].

Why lifespan should not be the primary focus. The aging field has long argued about the origins of species-specific lifespans without much attention to allometric scaling. That this concept is finally penetrating the siloes of aging theory is seen in a recent paper by prolific researchers on aging across species Lemaître et al. [18], entitled "Going Beyond Lifespan in Comparative Biology of Aging". The most significant reason was recognition of strong evidence for the allometric scaling of lifespan. They therefore proposed the research focus should shift towards *timing* (onset) of aging and subsequent *rate* of aging to explain variability *across species*. However, as reflected in Fig. 1 from Lemaître et al. [18], they failed to recognize the allometric scaling insight that metabolic wear-and-tear and aging go together and therefore *start at conception* [23]. Timing is critical because much *mathematical modeling* of aging theories has been based on assuming the later-in-life answer and would be thrown into serious doubt if aging actually starts at conception.

Did aging even "evolve"? Allometric scaling explanations of aging typically ascribe it to physiological wear-and-tear that unavoidably starts at conception in eukaryotes [23]. This challenges the common assumption that aging in eukaryotes must have evolved from non-aging ancestors, based on the apparent immortality of prokaryotes (assumed because they reproduce clonally) as well of a small number of eukaryotes such as *Hydra* and *Planaria*. However, these two taxons appear to have evolved protection from transposable elements as well as stem cell mechanisms enabling easy regeneration, which appear impossible for more complex animals [27]. Research on *Escherichia coli* casts doubt on assumptions that all bacteria are non-aging because, although their cell division is symmetrical, it was found that "mother" cells could be identified as inheriting the old end (pole) of the cell and to show signs of deterioration, while "daughter" cells inherited the new end and showed greater vigor but only lasting for three cell divisions before they too showed signs of deterioration [28].

Allometric scaling sets baseline for aging. A cogent explanation for why mammals share the same approximate lifetime limit of about 1.5 billion heartbeats [23] appears to be that this limit has been carried down since the last common mammalian ancestor, with average lifespans then determined by the average rate of heartbeats. Evolutionary adjustments around this baseline are to be expected through changes in biological aging rates. For example, mammals that hibernate have longer than expected lifespans for their body size, which research on yellow-bellied marmot rodents (*Marmota flaviventer*) found to be associated with the slowing of biological aging during hibernation [29]. Eusocial naked mole rats have far longer average lifespans than other similarly sized rodents, which appears related to their maintenance into later life of a universal mechanism that prevents generation of excess ROS in mitochondria (while similarly sized mice appear to be much shorter lived because this mechanism becomes inactivated later in their lives) [30].

MITOCHONDRIA AS ULTIMATE CONSTRAINT ON LIFESPAN

Eukaryotes are defined by two major differences from prokaryotes: (i) DNA within a cell nucleus, and (ii) mitochondria as energy generators with ROS as by-product. Skulachev's long mitochondria research history led him to an understanding of their many roles as the basis for the Samurai Law of Biology (see [31] summarizing his mitochondria research from the late 1950s). Mitochondria functions include conserving energy, dissipating energy as heat for thermoregulation, producing useful substances, decomposing harmful substances, and controlling various cellular processes. Skulachev helped illuminate how *apoptosis*, the cell suicide program, can be initiated by the suicide of mitochondria themselves when generating too much ROS, for which he introduced the term *mitoptosis* in a 1998 paper [32].

Mitochondrial DNA (mtDNA) lineages can't last forever. Skulachev [6] highlighted how mtDNA is liable to damage from mitochondrial ROS generation. Lane [25] proposed that such ceaseless mtDNA damage is the *ultimate constraint* on lifespan. Species-specific metabolic rates determine aging rates because faster metabolisms leak reactive electrons at faster rates than slower metabolisms. Lifespans are then limited to the inevitable point at which there is too much mtDNA damage to support life. The great diversity of eukaryotes stems from the potential to scale up mitochondria numbers as needed to power different cell types that are far larger than prokaryotes (which are limited in size due to lack of scalable energy generators such as mitochondria and chloroplasts).

Targeting mitochondria in anti-aging efforts. Research has failed to support the efficacy of antioxidant dietary supplements marketed to control ROS and fight aging [25]. An alternative approach is to target mitochondria

themselves with antioxidants to limit mtDNA damage. Skulachev [33] described SkQ compounds as having a rare ability among antioxidants, to accumulate in mitochondria (although he did not mention the "Sk" refers to "Skulachev" to indicate his role in their discovery [34]). The SkQ1 derivative has been found to have anti-aging effects in a variety of organisms, but hopes of lifespan extension are countered by findings that it prolongs median, but not maximum, lifespan in mice [35].

Mitochondria and the hallmarks of aging. Mitochondria are widely thought to be critical factors in aging, but whether they are the "ultimate" one remains an open question. The complexity that needs to be sorted out is reflected in *mitochondrial dysfunction* being just one of the nine Hallmarks of Aging proposed in 2013 [36]. All the hallmarks are thought to mutually influence each other and have been linked with biological aging.

WHAT IS BIOLOGICAL AGING?

As discussed by Bateson and Poirier [37], biological age can be considered "a common currency" that reflects variation in stress resilience, both between individuals and within individuals across time. They, however, took the traditional individual level explanatory perspective, while Shilovsky et al. [38] recently explained that biological aging should be considered as a central mechanism of phenoptosis in programmed aging. According to Skulachev [6], *slow phenoptosis* refers to the gradually accelerating pace of aging typical of chronic diseases. *Acute phenoptosis* occurs when signals of reaching a critical life stage activate a specific biochemical or behavioral "death" program, e.g., in some semelparous plants after their single flowering event and in Pacific salmon after spawning. Possible vertebrate examples include (i) high rates of rapid death (often within hours) in cases of sepsis and other deadly infectious conditions, which can be viewed as altruistic by preventing further spread of the responsible infectious agents, and (ii) the sudden switch from slow to fast phenoptosis when elderly individuals die of heart attacks or rapid failures of other organs.

Developmental programming. The concept of prenatal developmental programming gained prominence in the early 1990s based on the research showing prenatal malnutrition tends to modify metabolic systems in ways associated with metabolic and cardiovascular diseases later in life [39]. Research since then has identified increased risks for virtually every non-communicable chronic disease studied, in response to just about any kind of high distress experienced over the "first 1,000 days" (from conception through the first two years of life) [40]. Over time the basic model has evolved from being based on "one hit" of *genetic predisposition* at conception to "two hits" by adding *early postnatal* life adversity, and now "three hits" by adding *activation by later life adversity* [41]. This widely accepted model involves long-term changes in stress reactivity, temperament, metabolism, and immune functioning, which are associated with the early emergence of chronic disorders [42], which we can interpret as *slow phenoptosis*.

Cellular senescence and biological aging. Although *aging* and *senescence* are often used interchangeably, *senescence* is sometimes reserved for irreversible cell proliferation arrest. Such cells are called *senescence-associated secretory phenotype* (SASP) because they secrete proinflammatory protein factors with potentially toxic effects that accelerate biological aging. However, the SASP response is also essential for health, through such functions as tissue repair and clearance of cells that might turn cancerous due to DNA damage. SASP cells doing beneficial functions are typically then cleared and recycled. However, cell maintenance mechanisms become less efficient with age, leading to more and more damaged cells failing to self-destruct via apoptosis and instead persisting in a SASP state, which promotes senescence-inducing inflammation in surrounding cells even including healthy ones. Therefore, with increasing age, feed-forward cycles generating more and more SASP cells become more likely, possibly leading to a state of acute phenoptosis [43, 44].

Cell danger response (CDR) mediated by mitochondria. As explained by Naviaux [45, 46], the evolutionarily conserved CDR is triggered when mitochondria detect electron flow disturbances indicating cell stresses, infections, or damage. This three-stage healing process includes forming a "metabolic memory" of the inciting distress to facilitate future CDRs, an apparent mechanism for hormesis. However, some cells inevitably fail to complete the healing cycle and instead become SASP cells, which can be dangerous because just one in 350 normal cells is enough to degrade tissue function. Furthermore, operation of the CDR in response to environmental inputs is reflected in changing biological aging rates [46].

What is the ultimate purpose of biological aging? Although the connection between phenoptosis and biological aging seems clear, this is rarely recognized in aging and other stress-related literatures, which are instead dominated by assumptions that biological aging must serve individual survival and reproduction. Thus, the pioneering developmental programming research of the early 1990s was interpreted as showing that low nutrient levels signal the fetus to develop a *thrifty phenotype* to extract as much energy as possible from whatever food is available, in the interests of survival in the present as well as in the future when food is also likely to be scarce [39]. However, a review of human studies (limited to those using gold-standard longitudinal prospective methods) identified numerous unfavorable outcomes, but virtually no evidence that maternal stress during pregnancy might program offspring to improve either their immediate survival or long-term health [47].

The doubtful *live fast, die young* theory. Perhaps the most popular individual-level theory is that of *live fast, die young*, developed from the perspective of evolutionary psychology. It proposes that high distress in infancy and early childhood accelerates aging to speed reproduction to beat the odds against it in future environments expected to be harsh and dangerous, leading to the prediction that affected individuals should reach puberty and sexual debut earlier than average (but prenatal effects are only rarely considered) [48]. However, there is accumulating contrary evidence from primates, non-Western human populations, and historical data. Additional criticisms include failure to adequately account for genetic and other confounders, and misapplications of theories borrowed from evolutionary biology (according to evolutionary biologists themselves). These problems were highlighted in a special 2020 issue of *Evolution & Human Behavior* (Vol. 41, No. 6). A later commentary [49] even had a section headed "Don't Base a Theory Entirely on Something You Can't Measure" (referring to presumed energetic trade-offs into development-reproduction early in life, leaving less energy for maintenance later).

STRESS ACCOUNTING MECHANISMS TUNE BIOLOGICAL AGING RATES

Skulachev [9] theorized that programmed death phenomena are triggered when *internal monitoring systems* detect dangerous levels of damage or misfitness. Such stress accounting mechanisms are found in the *epigenetic regulation of gene expression* and *telomere attrition*, both of which are now widely used as primary indicators or clocks of biological aging at the *cellular level*. Both systems are often presented as *causal* of aging in response to distress, although evidence is mostly correlational. More recently the gut microbiome has also emerged as a likely causal source of aging [50].

Epigenetic causation appears related to deterioration of the *epigenome* (the entire set of gene expression regulators), sometimes called *epigenetic drift*, which can be accelerated by distress and reduces cellular efficiency. There are at least eight epigenetic categories, but best known is addition of methyl "marks" to genes which generally reduces their transcription [51]. Two recent reports support epigenetic drift as (i) primarily due to environmental impacts rather than genetics, and (ii) often traceable to the prenatal stage. They were based on longitudinal studies across the lifecourse (ages 0-92) along with a range of degrees of relationship, including many twins, and also assessing length of time in *shared environments* (assumed to induce similar epigenetic changes). One report described meta-analysis of *genome-wide average DNA methylation* rates for about 2300 people in seven such studies. It concluded that these genome-wide rates are "determined before birth" with their effects lasting across the lifecourse [52]. Another study calculated *epigenetic ages* using three clocks for about 4200 people in 10 longitudinal studies. Again, individual variability was traced to the prenatal period, because even twins tended to be born having significantly different epigenetic ages but which converged as they grew up [53]. Both reports described *genetic* factors as failing to reach significance in explaining individual variability, while *epigenetic changes* in response to environmental factors, especially those experienced *prenatally*, did produce significant impacts.

Telomere causation is related to the attrition of these protective chromosome caps, which naturally become a bit shorter with each cell division until the so-called Hayflick limit at which point cell division stops. However, high distress also causes telomere erosion, speeding the point when affected cells stop dividing and also making them more likely to avoid apoptosis or autophagy and to, therefore, persist in a toxic SASP state. That distress-shortened telomeres are causative of poor health and early death is suggested by observations that genetically short telomeres have similar negative effects [3].

Gut microbiome causation is found in deterioration of microbe species complexity, accelerated by distress leading to lower nutrient processing efficiency, higher pathogenic microbe levels, and disrupted brain circuits with increased risk for psychopathologies, especially depression [50]. The gut microbiome's importance to health indicates co-evolution with its invertebrate and vertebrate hosts, which Blaser and Webb [54] suggested has shaped human life history. Their *multilevel evolutionary model* showed the gut microbiome could have evolved to (i) foster its *own survival* by providing its host with a health-promoting composition of microbial species through reproductive age, but (ii) promote the long-term *persistence of its host population* by increasing the proportion of pathogenic species in post-reproductive senescent individuals, speeding their phenoptotic exit. This serves to optimize the population's balance of juvenile, reproductive, and senescent age classes.

Need for prospective longitudinal research. The important issue of causation requires *prospective longitudinal research*, but measures are typically taken only cross-sectionally, yielding only correlational evidence. For example, a 2018 meta-analysis of hundreds of associations between past adversities and current telomere length found that only 6.8% were longitudinal versus 93.2% cross-sectional [55]. Serious doubts about the value of cross-sectional epigenetics research are raised by longitudinal research in which significant associations were found based on prospective analysis, but none were found through cross-sectional analysis of the same data (e.g., [56]). The subsections below provide prospective research examples confirming that *distress at any time in life* can speed biological aging.

Prospective epigenetics research. Research using epigenome-wide association studies (EWAS) on umbilical cord blood and again on school age samples concluded that methylation of certain genes at birth is associated with later diagnosis of attention-deficit and hyperactivity disorder (ADHD) [57]. Another EWAS study compared umbilical cord blood samples with samples taken at age 7 and found that nearly all identified epigenetic changes could be traced to mother-reported adversities occurring before the age of three [58]. Epigenetic age measured in nearly 400 adolescents and again an average of about 8 years later found those reporting the most adversities showed over two additional epigenetic aging years compared to those with no adversities [56]. A review identified several studies on adults finding an association between hypertension and methylation of a gene that regulates cortisol in response to distress [59]. A study of US Iraq/Afghanistan war veterans found those suffering distress due to post-traumatic stress or alcohol use disorders showed significantly accelerated epigenetic aging over a period of about two years [60].

Prospective telomere research. Preterm infants in neonatal intensive care (known to increase oxidative stress and inflammation) showed significant telomere erosion from birth until discharge [61]. Children in a nationally representative UK birth cohort had a significant association between telomere erosion and exposure to two or more kinds of violence or abuse from age 5 to 10 [62]. A year-long study of physician interns at US hospitals (notorious for exceptionally long work hours) found significant telomere erosion rates on average six times greater than for university students in another study [63]. The rank order of telomere lengths in blood samples donated an average of 12 years apart by over 1000 adults barely changed, indicating inter-individual differences in telomere length are set early in life [64]. A study of healthy men and women aged 54 to 76 years found that those with signs of stress response axis dysregulation had significantly shorter telomeres three years later [65]. Eustress, by contrast, can at least partly reverse such distress effects in humans through activities such as physical exercise, positive social engagement, meditation, and mindfulness [3].

Prospective gut microbiome research. Such research is lacking but is becoming possible with new clocks based, e.g., on microbial species diversity; relative proportions of beneficial versus harmful taxons; measures reflecting microbiome functioning (e.g., Vitamin B12 biosynthesis); or microbiome-derived metabolites measured in blood, urine, or stool [66].

Variability of biological aging rates. Available prospective research is congruent with two themes of this review: (i) individuals of any age might speed or slow their biological aging in response to shifting stress levels, but (ii) the most sensitive periods are early in life, including the prenatal stage as further explored in the next section.

PRENATAL ORIGINS OF BIOLOGICAL AGING

Gestational distress. The prenatal stage in humans poses high challenges to collecting biological aging indicators, so research often uses *gestational distress* indicators of, e.g., deficient nutrition, toxins, oxidative stress, inflammation, and/or mother's psychological distress. Notably, higher gestational distress tends to be associated with shorter than average telomere lengths in umbilical cord blood [67]. On the other hand, *epigenetic clocks* trained with umbilical cord blood to estimate gestational age at birth have found both speeding and slowing, explainable by kind of distress. An inhospitable womb is likely to retard fetal growth and slow aging as reflected in *developmental immaturity* at birth, while factors like maternal overweight and pre-eclampsia appear to speed gestational aging, reflected in relatively high birth weights. However, both outcomes are predictive of poorer health later in life [68]. One factor appears to be that gestational distress can establish a "meta-plastic" state of greater sensitivity to environmental inputs after birth [69]. Affected infants are more likely to respond to distress with increased inflammation and dysregulation of the stress response system. This state is then likely to become *chronic* through its non-reversible shaping of developing immune, endocrine, and nervous systems, creating phenotypes already showing signs of immuno-senescence and systemic inflammation that are normally only observed later in life [41].

Regarding the *gut microbiome*, the placenta is a *sterile environment* so that infants require "seeding" at birth or soon thereafter. However, mothers are likely to have deficient microbiomes to pass on if they are socially distressed or had their microbiome disrupted by antibiotics, toxins, or diseases. Their newborns are often found to have deficient gut microbiomes and thus may be described as having non-genetic *birth defects* that interfere with healthy development. Of particular concern is the possible failure of the microbiome and immune system to develop mutual recognition and accommodation, without which long-term risks are raised for the many disorders associated with dysregulated inflammation [70].

Loss of epigenetic plasticity. Another way prenatal adversity can program later age-related disorders appears to be the accelerated loss of epigenetic plasticity, with earlier exposures having stronger long-term effects. There is "compelling evidence" that this impairs immune function and accelerates biological aging. Over the rest of the lifecourse, this lowered epigenetic plasticity is thought to make it more difficult for affected individuals to appropriately respond to both positive and negative experiences [71].

Prenatal distress effects reflect phenoptosis. Connection between the prenatal distress and the early arrival of age-related disorders is arguably a reflection of phenoptosis. Yet the literature is dominated by

non-altruistic explanations that negative health impacts result from (i) the mechanistic result of bodily systems being *overwhelmed by allostatic load*, and/or (ii) responsible mechanisms being activated to promote immediate survival and/or the *live fast*, *die young* reproduction strategy. Explanations in this second category are often theoretically supported by the Selection Shadow, which occurs later in life after individuals stop or reduce their sexual reproduction. Disorders that emerge during this period are thus presumed to escape natural selection, but major difficulties with this view will become evident in the following section.

INFLAMMATION AS A CENTRAL MEDIATOR OF PHENOPTOSIS

Chernyak et al. [72] proposed that the innate immune system's inflammatory response plays the role specified in their paper's title, as "executor of the programmed death of individual organisms for the benefit of the entire population" with mitochondria controlling the main signaling pathways. *Acute phenoptosis* typically involves a sudden "cytokine storm" of toxic proinflammatory factors, while *slow phenoptosis* is associated with *chronic inflammation* and its toxic impacts on bodily systems, notably the cardiovascular, pulmonary, digestive, and nervous. The gut microbiome has also been found to promote inflammation in response to distress, apparently via leakage of proinflammatory microbiome products, so the gut-brain axis has been referred to as the *gut microbiota–inflammation–brain axis* [52].

Inflammation as "executor" is already evident prenatally, being central to many of the selective mechanisms that weed out most human embryos before they can implant. When inflammation is abnormally high after implantation, as often occurs when mothers experience high distress, there are numerous possible negative effects on fetuses, including miscarriage, premature birth, low birth weight, and higher risks for later-life chronic disorders [73].

Does antagonistic pleiotropy explain toxic inflamm-aging? In support of programmed aging, Mitteldorf [44] argued that inflammation has been "co-opted in old age" to induce phenoptosis. However, the most prominent explanatory theory appears to be that of Franceschi et al. [74] who proposed the term *inflamm-aging* to highlight inflammation's causative role, but instead explained it through antagonistic pleiotropy. They described how systemic inflammation tends to rise in humans later in middle age, with those who are "robust" thanks to good genes and low distress levels able to enjoy "successful aging". By contrast, individuals who are "frail" due to genetic susceptibility and high distress levels are likely to suffer from higher inflammation levels leading to "unsuccessful aging". They proposed that such late-life destructive inflamm-aging persists because its negative effects fall in the Selection Shadow. However, Merz and Turner [41] summarized research showing that early life adversity is an accelerator of inflamm-aging and age-related diseases. Negative effects often begin appearing in childhood or adolescence, long before the Selection Shadow, and should therefore be subject to natural selection.

SOCIALITY AND THE SOCIAL REGULATION OF AGING

Sociality and the social brain. Sociality refers to individual organisms living in stable groups and expressing at least some cooperative behaviors, particularly reproduction. It is relatively rare across animal species, but is common in primates, with about 75% living in groups, 20% in pairs, and 5% solitary [75]. Humans and many other social vertebrates along with eusocial insects are prime examples of *obligative sociality*, unable to survive and reproduce outside a social group. Social vertebrates are distinguished by having what has been called the *social brain*, which in many species has apparently evolved to greater size to handle the extra cognitive demands of social life, especially through prefrontal cortex-limbic system feedback circuits [76]. All the interconnected bodily systems have also evolved to support social living, notably the stress response system, which is sensitive to social signals, especially those indicative of social status [77].

Social status hierarchies and social selection. Group living brings with it mutual social selection, a subtype of natural selection in which choices made by individuals about each other can influence their fitness and, hence, change gene frequencies [78]. Sentient social organisms appear to have means of comparing group mates with each other and with themselves as a basis for interacting with each other by, e.g., partnering with trusted cooperative individuals or avoiding those known to cheat. Individuals judged by group mates to be subordinate tend to (i) suffer *negative social selection* (e.g., rejected as social or sexual partners) and (ii) be dominated by others and therefore experience much *unpredictability* and *uncontrollability*, known to increase allostatic load [48]. Skulachev [79] raised these very factors as leading to phenoptosis, citing research showing correlations between mortality and psychological factors such as low emotional support and feeling unable to control one's own life. Naviaux [46] extended this insight back to infancy, noting that early-life psychological stresses activate many of the same metabolic and gene expression networks as the cellular defense response (CDR). The centrality of mitochondria to the CDR means that distresses induced by *negative social selection* lead to energy inefficiency and associated erosion of health, labeled "anachroadaptive mitocellular dysfunction" [45].

Role of stress in social status hierarchies. The evolution of social status and of stress response systems appear closely connected [80, 81]. Stress response systems are typically conceived as having evolved to optimize *individual* survival and reproduction, with negative ill health and biological aging assumed to simply be due to *allostatic loads* that overwhelm what the body can handle. However, there are formal modeling examples demonstrating that stress response systems in social species might *also* have evolved to induce phenoptosis. For example, Hadany et al. [82] demonstrated that stress response systems could have evolved, at least in part, because their long-term detrimental effects induce altruism in those individuals most affected by distress, which signals they have relatively low fitness compared to their group mates. They made the important point that benefits to the broader population do not require the death of such individuals. All that is needed is their restriction from the breeding pool, as reflected in much research in humans, rodents, and other species showing that highly distressed individuals tend to experience reduced fertility.

Social selection in defense of the genetic foundation of sociality. M. Skulachev et al. [83] recognized the high necessity of protection from harmful mutations and suggested this requires the "dictatorship of the genome" wherein higher-level components must be liable to sacrifice in its defense. Thus individuals "useful" for the community versus those "dangerous" receive different signals that contribute to their "decision" about their own aging, whether to accelerate or decelerate. In social status hierarchies, dominant individuals tend to experience more eustress, which signals being more "useful", while subordinate individuals tend to experience more distress, which signals being more "dangerous". The "danger" of subordinate individuals comes from the likelihood their *genetic makeups* are *inferior* to those of dominant individuals, by having relatively high mutation loads and/or genomes that are not well suited for the *current environment*.

As explained earlier, the sooner-the-better perspectives of Hamilton [5] and Haig [15] led to their predictions of prenatal mechanisms to detect and eliminate harmful mutations. In social species, we might expect such mechanisms to be enhanced by social selection, which tends to favor dominant individuals over subordinate ones. Pregnant females are likely to be particularly sensitive to distress during this vulnerable period, with humans in particular having high needs for social support providing such benefits as extra calories and alloparenting. Studies of prenatal effects therefore often include measures of maternal psychosocial distress, known to increase inflammation and raise risks for numerous negative outcomes, from miscarriage to low birth weight, particularly in mothers of relatively low status [73]. Such outcomes appear to represent not only selection against fetuses, but also against their parents, who likely suffer a decrease in fitness through offspring loss or bearing offspring damaged during gestation. This has been interpreted as "negative selection against parental deleterious alleles" [16].

The sooner-the-better perspective also indicates that individuals should start being judged and subjected to social selection right from birth. Thus Hamilton [5] suggested that human parents might achieve "sibling replacement" by providing less care to infants with signs of high mutation loads. A primate example of such early-life negative social selection is found in longitudinal research on free-ranging rhesus monkeys (*Macaca mulata*). Young males that disrupted others constantly (suggesting a genetic basis) were often ostracized by peers and attacked by adults, driving them from their natal troop prior to three years of age and almost certain death within a year after that due to social behavior deficits that kept them in a solitary state [84].

It is the *relative differences* between group members that are critical in social selection, with the same individual potentially being dominant at one point but then becoming subordinate, and even possibly dominant again later, as group composition and the competitive environment changes. These shifts are likely to induce changes in biological aging rates, as demonstrated by the prospective research on stress accounting mechanisms described above. Although dominant individuals in animal societies generally experience better health and longer lives, the most dominant males in some steeply hierarchical societies are likely to have shorter lives due to much fighting to keep their positions, but their control of sexual reproduction makes it worthwhile [81]. As dominant individuals become frail, signals of that in humans appear to induce phenoptosis, perhaps at acute levels. For example, ethnographic observations in traditional societies indicate frail elders who perceive themselves to be a burden on their kin then speed their demise through actions such as starving, exiting group into wilderness, or suicide [85].

Social gradients of health. We can infer the existence of the above individual and social selection dynamics from their apparent reflection in social gradients of health, which have been observed in just about all social status hierarchies studied. A recent review of research on obligative social vertebrates found that the most socially connected and least distressed individuals tend to dominate and have better health and longer lives, while the least socially connected and most distressed individuals tend to have worse health and shorter lives [86]. What Marmot [87] called the *status syndrome* appears to be a major contributor to this pattern in humans, as individuals who perceive they are of subordinate status (by having less autonomy and deficient social integration compared to others) respond with health-harming chronic stress response activation.

Evolved basis of social status hierarchies and their social gradients. The status syndrome appears consistent with phenoptosis, but status hierarchies and social gradients are rarely seen as serving the dictatorship of the genome or other group adaptive purposes. Rather, they are often explained in mechanistic terms as resulting from even *small differences* in advantage *between individuals* becoming amplified, leading to cycles of increasing success or cycles of increasing maladaptation [88]. However, there are cogent arguments that such cycles have been evolutionarily shaped to advantage dominate individuals and disadvantage subordinate ones in reproduction (e.g., [89]). The sooner-the-better principle indicates this should involve acceleration of these cycles and, hence, their rates of divergence. Vertebrate research indeed indicates that becoming dominant activates a general *behavioral approach system*, which promotes positive affect and disinhibited social behavior (sometimes at aggressive levels), increasing the odds of mating. By contrast, becoming subordinate activates a *behavioral inhibition system* that promotes negative affect and inhibited social behavior, which likely reduces chances of mating [90].

Individual level explanations of such involuntary behavioral inhibition commonly assert it signals submission to superior opponents, to bring their threats or attacks to an end and allow losers to live on in hopes of reproductive success in the future, e.g., [91]. For humans, however, it is hard to see substantial *individual fitness* advantages of an involuntary defeat strategy. It appears difficult to reverse, being associated with feeling entrapped with little hope of escape, which in turn is associated with heightened risks for severe depression and other psychiatric disorders, extending to suicide. A meta-analysis covering about 10,000 people with depression, anxiety, PTSD, or suicidality confirmed perceptions of defeat and entrapment were strong (at least $r = 0.60$) across all disorders [92]. Suicide has been explained as serving inclusive fitness, which is supported by findings it is often associated with feelings of being so burdensome that one's death seems worth more than one's life to others [93].

Social management of free-riders. As per the Samurai Law of Biology, sociality at all organism levels requires effective free-rider management [13], for which the phenoptosis-inducing forces of negative social selection appear to be operative. Humans are characterized by moral systems that guide members of a society to identify signs of free-riding and impose appropriate controls. Moralistic group sanctioning has been described as a basic kind of cooperation found in every human society. Common control behaviors include shaming, bullying, shunning, ostracizing, and/or expelling, which all convey social rejection and can induce distressful social isolation [94]. The high potential to accelerate biological aging is seen in a meta-analysis of 70 longitudinal studies covering about 3.5 million people around the world. It found social isolation, living alone, and feeling lonely increase the chances of dying by about 30%, leading the World Health Organization to label *loneliness* as a major worldwide threat to health [76].

Social status hierarchies as reproductive channeling systems. In contrast to mechanistic explanations of social status hierarchies, the concepts of altruistic phenoptosis and sibling replacement suggest there must be group-level adaptive elements that help these social systems compete and persist within their ecological settings. Thus, the reproductive success of dominant and subordinate group members can be expected to diverge faster than indicated by a mechanistic process alone, thereby further promoting the reproduction of dominants and reducing that of subordinates [38]. Such *reproductive channeling* might promote the reproduction of relatively "good genes" while limiting the reproduction of harmful mutations at the population level. At the individual level, however, luck likely plays a significant role, with even apparently highly fit individuals possibly losing out due to chance injury or illness.

UPDATING NON-PROGRAMMED VERSUS PROGRAMMED AGING

This section highlights recent publications relevant to the controversy over whether aging is programmed or not. *Programmed theories* generally view aging as reflecting altruistic self-sacrifice, in the interests of inclusive fitness. There are three major categories of *non-programmed theories* which attribute aging to stochastic processes and, often, energetic trade-offs between processes or life stages. *Harmful mutation accumulation* (over either individual lifespans or the history of a lineage) is now generally rejected based on contrary research [95]. *Antagonistic pleiotropy* was described in the section on inflammation above along with doubts about its utility. *Disposable soma* will be addressed in the next subsection.

Fall of disposable soma based on energetic trade-offs. The popular disposable soma theory can be described as experiencing a "fall" because its developer, Thomas Kirkwood, *now rejects* its proposed metabolic energy trade-offs between current and future bodily maintenance. Thus, Omholt and Kirkwood [96] proposed a new non-trade-off life history model still consistent with Kirkwood's central assumption when he proposed disposable soma in 1977 – that energy allocation to somatic maintenance should be optimized to be just enough to keep an organism "in sound condition". The new proposal is that natural selection might achieve this through establishment of a genetic program to maintain allocation to somatic maintenance at a low level. Its adaptive purpose would be to reduce mortality risk because there would be less need for energy-seeking activities (e.g., foraging, hunting) and, hence, fewer contacts with sources of mortality.

While Skulachev appears to be the most cited scholar in support of programmed aging, Kirkwood is among the most cited in support of non-programmed aging and also among the most active critics of programmed aging. For example, Kowald and Kirkwood [95] identified major programmed aging theories, tested them with formal mathematical modeling and computer simulations, and concluded that all the theories were shown to be highly unlikely. Their dismissal of Skulachev's phenoptosis proposal (in just one paragraph) lacked rigor because it incorrectly described the logic and was based only on his short 1997 paper [6], failing to consider any of the many later papers of Skulachev and colleagues that expanded and further justified both acute and slow phenoptosis.

We might expect Kirkwood's change of mind on energetic trade-offs to be big news with substantial influence in the aging theory field. Indeed, Omholt and Kirwood [96] used their new disposable soma model to also cast doubt on the other major non-programmed aging theories, mutation accumulation and antagonistic pleiotropy. However, possible changes in the field will probably be quite slow, given that energetic trade-offs and non-programmed theories are so deeply entrenched in the literature, along with the very limited attention given so far to Omholt and Kirkwood [96]. According to a Google Scholar search in early November 2022 (about 17 months after its publication date), it had only five citations in peer-reviewed publications, none of which highlighted Kirkwood's reversal on the validity of non-programmed aging.

Rise of constraints to explain aging. Omholt and Kirkwood [96] explained that their downplaying of energetic trade-offs was partly inspired by Cohen et al. [97], entitled "Are Trade-Offs Really the Key Drivers of Ageing and Life Span?" These authors promoted the need to account for *constraints*, which are resistant to change by natural selection, explaining that aging-relevant constraints are pervasive but generally unacknowledged in the aging literature. For example, there is much contrary evidence against the common trade-off assumption that *sexual reproduction* induces energetic costs that are paid through *reduced lifespan* (as per disposable soma). Echoing [46], one constraints example they gave is how allostatic load due to chronic psychological distress in vertebrates is associated with failure to fully return to a physiological baseline. This induces dysregulation and positive feedback loops that accelerate biological aging, independently of trade-offs.

A PROVISIONAL MULTILEVEL MODEL OF AGING

This review's exploration of aging indicates that average lifespans at the *species level* reflect constraints imposed by the *allometric scaling of metabolism* and associated limits on how long metabolic processes can persist to sufficiently energize life. The aspect of aging most amenable to evolutionary shaping is therefore *rates of biological aging* of *individuals*, which can be expected to vary so as to promote *inclusive fitness*. The following model of aging is meant to account for these considerations: At the *species level*, average body size scales with average metabolic rate at a less-than-one exponent, so larger size associates with slower metabolism and hence lower metabolic "wear and tear" and longer average lifespan. At the *individual level* in *social vertebrates*, stress response systems are evolutionarily optimized to (i) accelerate the biological aging and limit the reproduction of identified free-riders as well as of subordinate individuals with relatively lower fitness prospects in the current environment, and (ii) boost the longevity and reproductive chances of those with higher fitness prospects, as signaled by higher social status and relatively greater distress resilience. This *reproductive channeling* (i) can begin prenatally (due to different gestational eustress–distress balances), and (ii) enhance the overall inclusive fitness of the family lineage and/or broader social group.

CONCLUSION

This review has explained how emerging research on early life adversity can be interpreted as showing that biological aging is a mechanism of phenoptosis that is already operative in the prenatal stage. It must be noted that every statement in this review is likely to be opposed in some way elsewhere in the literature. The research base, however, is currently unable to resolve many such conflicts particularly for humans due to difficulties in assessing the measure that matters most for both individual and inclusive fitness, the number of surviving offsprings. This is because the great majority of human societies have made the demographic transition to low fertility, with higher income individuals having the capacity to achieve high fertility if so desired, but instead tending to have fewer children on average than lower income individuals. Low fertility levels are also expected to reduce scope for inclusive fitness due to fewer numbers of interacting kin and tendencies for them to live away from each other, which in turn is associated with higher rates of distressing social isolation [98] (which we can assume tends to accelerate biological aging).

Figure 3 distills key points of this review and also illustrates how multilevel selection might lead to both individually adaptive and group beneficial responses to early life adversity, which, however, might be difficult to distinguish. It is inspired by a figure in Wesarg et al. [99] illustrating their mechanistic theoretical model of how early life adversity can launch a deleterious developmental cascade, which hinders development of self-regulation in early childhood, thereby raising risks for

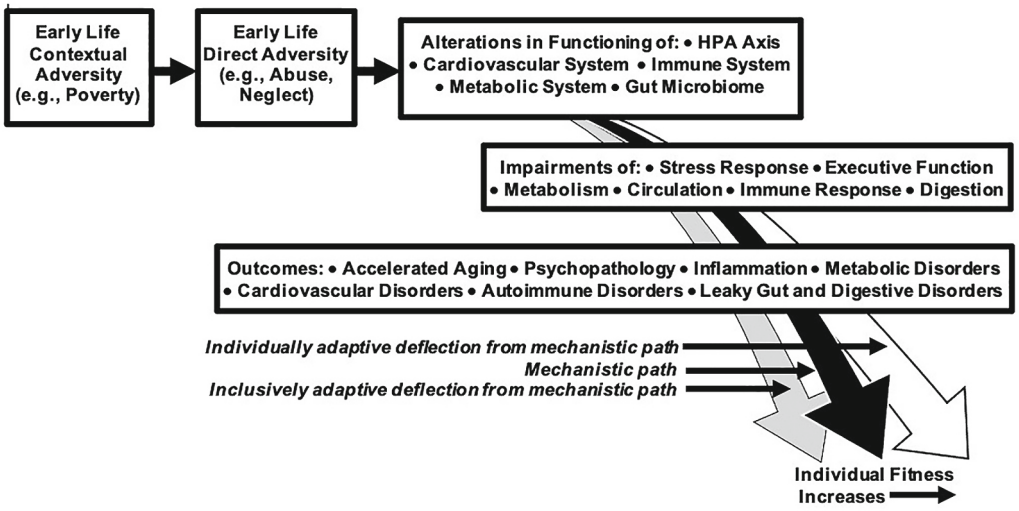

Fig. 3. Overview of how early life adversity might lead to downward cascades of accelerated aging, ill health, and lowered fitness, with slopes depending on whether adaptive deflections result from inclusive fitness or individual level selection.

psychopathology later in life. Figure 3 is generalized to encompass the similar downward cascades that are commonly described for other negative effects of early life adversity. The black arrow matches the figure in [99] by reflecting the assumed *mechanistic processes*. Two downward arrows are added to provide a *multilevel selection* perspective. The white arrow indicates how adaptations such as those proposed by *live fast*, *die young* might lessen the downward slope in the interests of *individual fitness*, while the gray arrow indicates how the downward slope might be increased in the interests of *inclusive fitness*. At the same time, however, the figure reflects the empirical difficulties of distinguishing between mechanistic and adaptive alternatives, because if countervailing individual-versus-inclusive adaptations are present then data analysis might fail to detect the existence of one or both.

Meanwhile phenoptosis is demonstrating its applicability to an expanding range of phenomena. For example, one of the most recent uses of "phenoptosis" (citing [79]) was to help to explain how hormesis and inflammation are rooted in thermodynamic and quantum principles and serve to control aging across the webs of life [100].

Ethics declarations. Author declares no conflicts of interest. This article does not contain any studies with human participants or animals performed by the author.

REFERENCES

1. Camerota, M., and Willoughby, M. T. (2021) Applying interdisciplinary frameworks to study prenatal influences on child development, *Child Dev. Perspect.*, **15**, 24-30, doi: 10.1111/cdep.12395.
2. Entringer, S., de Punder, K., Buss, C., and Wadhwa, P. D. (2018) The fetal programming of telomere biology hypothesis: an update, *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, **373**, 20170151, doi: 10.1098/rstb.2017.0151.
3. Epel, E. S., and Prather, A. A. (2018) Stress, telomeres, and psychopathology: toward a deeper understanding of a triad of early aging, *Annu. Rev. Clin. Psychol.*, **14**, 371-397, doi: 10.1146/annurev-clinpsy-032816-045054.
4. Malani, A., Rosenbaum, S., Alberts, S. C., and Archie, E. A. (2022) *Seeing the Future: A Better Way to Model and Test for Adaptive Developmental Plasticity*, National Bureau of Economic Research, Cambridge, MA.
5. Hamilton, W. D. (1966) The moulding of senescence by natural selection, *J. Theor. Biol.*, **12**, 12-45, doi: 10.1016/0022-5193(66)90184-6.
6. Skulachev, V. P. (1997) Aging is a specific biological function rather than the result of a disorder in complex living systems: biochemical evidence in support of Weismann's hypothesis, *Biochemistry (Moscow)*, **62**, 1191-1195.
7. Goldsmith, T. C. (2014) Modern evolutionary mechanics and resolving the programmed/non-programmed aging

controversy, *Biochemistry (Moscow)*, **79**, 1049-1055, doi: 10.1134/S000629791410006X.
8. Selye, H. (1976) *Stress in Health and Disease*, Butterworths, Boston.
9. Skulachev, V. P. (2002) Programmed death phenomena: from organelle to organism, *Ann. N. Y. Acad. Sci.*, **959**, 214-237, doi: 10.1111/j.1749-6632.2002.tb02095.x.
10. Skulachev, V. P. (2012) What is "phenoptosis" and how to fight it? *Biochemistry (Moscow)*, **77**, 689-706, doi: 10.1134/S0006297912070012.
11. Hamilton, W. D. (1964) The genetical evolution of social behaviour, *J. Theor. Biol.*, **7**, 1-16, doi: 10.1016/0022-5193(64)90038-4.
12. Hamilton, W. D. (1964) The genetical evolution of social behaviour II, *J. Theor. Biol.*, **7**, 17-52, doi: 10.1016/0022-5193(64)90039-6.
13. Bourke, A. F. G. (2011) *Principles of Social Evolution*, Oxford University Press, Oxford, doi: 10.1093/acprof:oso/9780199231157.002.0003.
14. Levin, S. R., and Grafen, A. (2019) Inclusive fitness is an indispensable approximation for understanding organismal design, *Evolution*, **73**, 1066-1076, doi: 10.1111/evo.13739.
15. Haig, D. (2010) Transfers and transitions: Parent–offspring conflict, genomic imprinting, and the evolution of human life history, *Proc. Natl. Acad. Sci. USA*, **107**, 1731-1735, doi: 10.1073/pnas.0904111106.
16. Kinzina, E. D., Podolskiy, D. I., Dmitriev, S. E., and Gladyshev, V. N. (2019) Patterns of aging biomarkers, mortality, and damaging mutations illuminate the beginning of aging and causes of early-life mortality, *Cell Rep.*, **29**, 4276-4284, doi: 10.1016/j.celrep.2019.11.091.
17. Bruckner, T., and Catalano, R. (2018) Selection *in utero* and population health: theory and typology of research, *SSM-Popul. Health*, **5**, 101-113, doi: 10.1016/j.ssmph.2018.05.010.
18. Lemaître, J. F., Garratt, M., and Gaillard, J. M. (2020) Going beyond lifespan in comparative biology of aging, *Adv. Geriatr. Med. Res.*, **2**, e200011, doi: 10.20900/agmr20200011.
19. Hamilton, W. D. (1975) in *ASA Studies 4: Biological Anthropology* (Fox, R., ed.) Malaby Press, London, pp. 133-153.
20. Wilson, D. S., and Wilson, E. O. (2007) Rethinking the theoretical foundation of sociobiology, *Q. Rev. Biol.*, **82**, 327-348, doi: 10.1086/522809.
21. Vijg, J., and Kennedy, B. K. (2016) The essence of aging, *Gerontology*, **62**, 381-385, doi: 10.1159/00043934.
22. Mitteldorf, J. J. (2013) How does the body know how old it is? Introducing the epigenetic clock hypothesis, *Biochemistry (Moscow)*, **78**, 1048-1053, doi: 10.1134/S0006297913090113.
23. West, G. B. (2017) *Scale: The Universal Laws of Growth, Innovation, Sustainability, and the Pace of Life in Organisms, Cities, Economies, and Companies* (Kindle, ed.) Penguin, NY.
24. West, G. B., and Brown, J. H. (2005) The origin of allometric scaling laws in biology from genomes to ecosystems: towards a quantitative unifying theory of biological structure and organization, *J. Exp. Biol.*, **208**, 1575-1592, doi: 10.1242/jeb.01589.
25. Lane, N. (2018) *Power, Sex, Suicide: Mitochondria and the Meaning of Life* (2nd ed.) Oxford University Press, Oxford.
26. Thommen, A., Werner, S., Frank, O., Philipp, J., Knittelfelder, O., Quek, Y., Fahmy, K., Shevchenko, A., Friedrich, B. M., Jülicher, F., and Rink, J. C. (2019) Body size-dependent energy storage causes Kleiber's law scaling of the metabolic rate in planarians, *eLife*, **8**, e38187, doi: 10.7554/eLife.38187.
27. Holtze, S., Gorshkova, E., Braude, S., Cellerino, A., Dammann, P., Hildebrandt, T. B., Hoeflich, A., Hoffmann, S., Koch, P., Terzibasi Tozzini, E., Skulachev, M., Skulachev, V. P., and Sahm, A. (2021) Alternative animal models of aging research, *Front. Mol. Biosci.*, **8**, 660959, doi: 10.3389/fmolb.2021.660959.
28. Singer, M. A. (2016) The origins of aging: evidence that aging is an adaptive phenotype, *Curr. Aging Sci.*, **9**, 95-115, doi: 10.2174/1874609809666160211124947.
29. Pinho, G. M., Martin, J. G., Farrell, C., Haghani, A., Zoller, J. A., Zhang, J., Snir, S., Pellegrini, M., Wayne, R. K., Blumstein, D. T., and Horvath, S. (2022) Hibernation slows epigenetic ageing in yellow-bellied marmots, *Nat. Ecol. Evol.*, **6**, 418-426, doi: 10.1038/s41559-022-01679-1.
30. Vyssokikh, M. Y., Holtze, S., Averina, O. A., Lyamzaev, K. G., Panteleeva, A. A., Marey, M. V., Zinovkin, R. A., Severin, F. F., Skulachev, M. V., Fasel, N., Hildebrandt, T. B., and Skulachev, V. P. (2020) Mild depolarization of the inner mitochondrial membrane is a crucial component of an antiaging program, *Proc. Natl. Acad. Sci. USA*, **117**, 6491-6501, doi: 10.1073/pnas.1916414117.
31. Skulachev, V. P. (2009) Functions of mitochondria: from intracellular power stations to mediators of a senescence program, *Cell. Mol. Life Sci.*, **66**, 1785-1793, doi: 10.1007/s00018-009-9183-6.
32. Skulachev, V. P. (1998) Uncoupling: new approaches to an old problem of bioenergetics, *Biochim. Biophys. Acta Bioenerg.*, **1363**, 100-124, doi: 10.1016/S0005-2728(97)00091-1.
33. Skulachev, V. P. (2007) A biochemical approach to the problem of aging: "Megaproject" on membrane-penetrating ions. The first results and prospects, *Biochemistry (Moscow)*, **72**, 1385-1396, doi: 10.1134/S0006297907120139.
34. Armstrong, J. S. (2008) Mitochondria-directed therapeutics, *Antioxid. Redox Signal.*, **10**, 575-578, doi: 10.1089/ars.2007.1929.
35. Zinovkin, R. A., Skulachev, M. V., and Skulachev, V. P. (2016) Mitochondrial genome and longevity, *Biochemistry (Moscow)*, **81**, 1401-1405, doi: 10.1134/S0006297916120014.
36. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., and Kroemer, G. (2013) The hallmarks of aging, *Cell*, **153**, 1194-1217, doi: 10.1016/j.cell.2013.05.039.

37. Bateson, M., and Poirier, C. (2019) Can biomarkers of biological age be used to assess cumulative lifetime experience? *Anim. Welf*, **28**, 41-56, doi: 10.7120/09627286.28.1.041.
38. Shilovsky, G. A., Putyatina, T. S., and Markov, A. V. (2021) Altruism and phenoptosis as programs supported by evolution, *Biochemistry (Moscow)*, **86**, 1540-1552, doi: 10.1134/S0006297921120038.
39. Hales, C. N., and Barker, D. J. (1992) Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis, *Diabetologia*, **35**, 595-601, doi: 10.1007/BF00400248.
40. Hanson, M. A., Poston, L., and Gluckman, P. D. (2019) DOHaD – The challenge of translating the science to policy, *J. Dev. Orig. Health Dis.*, **10**, 263-267, doi: 10.1017/S2040174419000205.
41. Merz, M. P., and Turner, J. D. (2021) Is early life adversity a trigger towards inflammageing? *Exp. Gerontol.*, **150**, 111377, doi: 10.1016/j.exger.2021.111377.
42. Ambeskovic, M., Ilnytskyy, Y., Kiss, D., Currie, C., Montina, T., Kovalchuk, I., and Metz, G. (2020) Ancestral stress programs sex-specific biological aging trajectories and non-communicable disease risk, *Aging (Albany NY)*, **12**, 3828, doi: 10.18632/aging.102848.
43. Gasek, N. S., Kuchel, G. A., Kirkland, J. L., and Xu, M. (2021) Strategies for targeting senescent cells in human disease, *Nat. Aging*, **1**, 870-879, doi: 10.1038/s43587-021-00121-8.
44. Mitteldorf, J. (2017) *Aging Is a Group-Selected Adaptation: Theory, Evidence, and Medical Implications,* CRC Press, Boca Raton, FL, doi: 10.1201/9781315371214.
45. Naviaux, R. K. (2014) Metabolic features of the cell danger response, *Mitochondrion*, **16**, 7-17, doi: 10.1016/j.mito.2013.08.006.
46. Naviaux, R. K. (2019) Incomplete healing as a cause of aging: the role of mitochondria and the cell danger response, *Biology*, **8**, 27, doi: 10.3390/biology8020027.
47. Van den Bergh, B. R., van den Heuvel, M. I., Lahti, M., Braeken, M., de Rooij, S. R., Entringer, S., Hoyer, D., Roseboom, T., Räikkönen, K., King, S., and Schwab, M. (2020) Prenatal developmental origins of behavior and mental health: the influence of maternal stress in pregnancy, *Neurosci. Biobehav. Rev.*, **117**, 26-64, doi: 10.1016/j.neubiorev.2017.07.003.
48. Ellis, B. J., and Del Giudice, M. (2019) Developmental adaptation to stress: An evolutionary perspective, *Annu. Rev. Psychol.*, **70**, 111-139, doi: 10.1146/annurev-psych-122216-011732.
49. Jones, J. H., and Promislow, D. E. (2021) Commentary on the life history special issue: The behavioral sciences need to engage more deeply in life history theory, *Evol. Hum. Behav.*, **42**, 284-286, doi: 10.1016/j.evolhumbehav.2021.03.001.
50. Jazwinski, S. M., and Kim, S. (2019) Examination of the dimensions of biological age, *Front. Genet.*, **10**, 263, doi: 10.3389/fgene.2019.00263.
51. Tikhodeyev, O. N. (2018) The mechanisms of epigenetic inheritance: how diverse are they? *Biol. Rev.*, **93**, 1987-2005, doi: 10.1111/brv.12429.
52. Li, S., Wong, E. M., Dugué, P. A., McRae, A. F., Kim, E., Joo, J. H. E., Nguyen, T. L., Stone, J., Dite, G. S., Armstrong, N. J., Mather, K. A., Thalamuthu, A., Wright, M. J., Ames, D., Milne, R. L., Craig, J. M., Saffery, R., Montgomery, G. W., Song, Y. M., Sung, J., Spector, T. D., Sachdev, P. S., Giles, G. G., Southey, M. C., and Hopper, J. L. (2018) Genome-wide average DNA methylation is determined in utero, *Int. J. Epidemiol.*, **47**, 908-916, doi: 10.1093/ije/dyy028.
53. Li, S., Nguyen, T. L., Wong, E. M., Dugué, P. A., Dite, G. S., Armstrong, N. J., Craig, J. M., Mather, K. A., Sachdev, P. S., Saffery, R., Sung, J., Tan, Q., Thalamuthu, A., Milne, R. L., Giles, G. G., Southey, M. C., and Hopper, J. L. (2020) Genetic and environmental causes of variation in epigenetic aging across the lifespan, *Clin. Epigenetics*, **12**, 158, doi: 10.1186/s13148-020-00950-1.
54. Blaser, M. J., and Webb, G. (2014) Host demise as a beneficial function of indigenous microbiota in human hosts, *MBio*, **5**, e02262-14, doi: 10.1128/mBio.02262-14.
55. Pepper, G. V., Bateson, M., and Nettle, D. (2018) Telomeres as integrative markers of exposure to stress and adversity: a systematic review and meta-analysis, *R. Soc. Open Sci.*, **5**, 180744, doi: 10.1098/rsos.180744.
56. Copeland, W. E., Shanahan, L., McGinnis, E. W., Aberg, K. A., and van den Oord, E. J. (2022) Early adversities accelerate epigenetic aging into adulthood: A 10-year, within-subject analysis, *J. Child Psychol. Psychiatry*, **63**, 1308-1315, doi: 10.1111/jcpp.13575.
57. Neumann, A., Walton, E., Alemany, S., Cecil, C., González, J. R., Jima, D. D., Lahti, J., Tuominen, S. T., Barker, E. D., Binder, E., Caramaschi, D., Carracedo, Á., Czamara, D., Evandt, J., Felix, J. F., Fuemmeler, B. F., Gutzkow, K. B., Hoyo, C., Julvez, J., Kajantie, E., Laivuori, H., Maguire, R., Maitre, L., Murphy, S. K., Murcia, M., Villa, P. M., Sharp, G., Sunyer, J., Raikkönen, K., Bakermans-Kranenburg, M., IJzendoorn, M. V., Guxens, M., Relton, C. L., and Tiemeier, H. (2020) Association between DNA methylation and ADHD symptoms from birth to school age: a prospective meta-analysis, *Transl. Psychiatry*, **10**, 398, doi: 10.1038/s41398-020-01058-z.
58. Dunn, E. C., Soare, T. W., Zhu, Y., Simpkin, A. J., Suderman, M. J., Klengel, T., Smith, A. D. A. C., Ressler, K. J., and Relton, C. L. (2019) Sensitive periods for the effect of childhood adversity on DNA methylation: results from a prospective, longitudinal study, *Biol. Psychiatry*, **85**, 838-849, doi: 10.1016/j.biopsych.2018.12.023.
59. Argentieri, M. A., Nagarajan, S., Seddighzadeh, B., Baccarelli, A. A., and Shields, A. E. (2017) Epigenetic pathways in human disease: the impact of DNA methylation on stress-related pathogenesis and current challenges in biomarker development, *EBioMedicine*, **18**, 327-350, doi: 10.1016/j.ebiom.2017.03.044.
60. Wolf, E. J., Maniates, H., Nugent, N., Maihofer, A., Armstrong, D., Ratanatharathorn, A., Ashley-Koch, A. E., Garrett, M., Kimbrel, N. A., Lori, A., Va Mid-Atlantic MIRECC Workgroup, Aiello, A. E., Baker, D. G., Beck-

ham, J. C., Boks, M. P., Galea, S., Geuze, E., Hauser, M. A., Kessler, R. C., Koenen, K. C., Miller, M. W., Ressler, K. J., Risbrough, V., Rutten, B. P. F., Stein, M. B., Ursano, R. J., Vermetten, E., Vinkers, C. H., Uddin, M., Smith, A. K., Nievergelt, C. M., and Logue, M. W. (2018) Traumatic stress and accelerated DNA methylation age: a meta-analysis, *Psychoneuroendocrinology*, **92**, 123-134, doi: 10.1016/j.psyneuen.2017.12.007.

61. Belfort, M. B., Qureshi, F., Litt, J., Enlow, M. B., De Vivo, I., Gregory, K., and Tiemeier, H. (2021) Telomere length shortening in hospitalized preterm infants: a pilot study, *PLoS One*, **16**, e0243468, doi: 10.1371/journal.pone.0243468.
62. Shalev, I., Moffitt, T. E., Sugden, K., Williams, B., Houts, R. M., Danese, A., Mill, J., Arseneault, L., and Caspi, A. (2013) Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study, *Mol. Psychiatry*, **18**, 576-581, doi: 10.1038/mp.2012.32.
63. Ridout, K. K., Ridout, S. J., Guille, C., Mata, D. A., Akil, H., and Sen, S. (2019) Physician-training stress and accelerated cellular aging, *Biol. Psychiatry*, **86**, 725-730, doi: 10.1016/j.biopsych.2019.04.030.
64. Benetos, A., Kark, J. D., Susser, E., Kimura, M., Sinnreich, R., Chen, W., Steenstrup, T., Christensen, K., Herbig, U., von Bornemann Hjelmborg, J., Srinivasan, S. R., Berenson, G. S., Labat, C., and Aviv, A. (2013) Tracking and fixed ranking of leukocyte telomere length across the adult life course, *Aging Cell*, **12**, 615-621, doi: 10.1111/acel.12086.
65. Steptoe, A., Hamer, M., Lin, J., Blackburn, E. H., and Erusalimsky, J. D. (2017) The longitudinal relationship between cortisol responses to mental stress and leukocyte telomere attrition, *J. Clin. Endocrinol. Metab.*, **102**, 962-996, doi: 10.1210/jc.2016-3035.
66. Ratiner, K., Abdeen, S. K., Goldenberg, K., and Elinav, E. (2022) Utilization of host and microbiome features in determination of biological aging, *Microorganisms*, **10**, 668, doi: 10.3390/microorganisms10030668.
67. Enlow, M. B., Sideridis, G., Bollati, V., Hoxha, M., Hacker, M. R., and Wright, R. J. (2019) Maternal cortisol output in pregnancy and newborn telomere length: evidence for sex-specific effects, *Psychoneuroendocrinology*, **102**, 225-235, doi: 10.1016/j.psyneuen.2018.12.222.
68. Palma-Gudiel, H., Fañanás, L., Horvath, S., and Zannas, A. S. (2020) Psychosocial stress and epigenetic aging, *Int. Rev. Neurobiol.*, **150**, 107-128, doi: 10.1016/bs.irn.2019.10.020.
69. O'Donnell, K. J., and Meaney, M. J. (2017) Fetal origins of mental health: the developmental origins of health and disease hypothesis, *Am. J. Psychiatry*, **174**, 319-328, doi: 10.1176/appi.ajp.2016.16020138.
70. Dietert, R. R. (2017) The microbiome-immune-host defense barrier complex (microimmunosome) and developmental programming of noncommunicable diseases, *Reprod. Toxicol.*, **68**, 49-58, doi: 10.1016/j.reprotox.2016.04.026.
71. Krause, B. J., Artigas, R., Sciolla, A. F., and Hamilton, J. (2020) Epigenetic mechanisms activated by childhood adversity, *Epigenomics*, **12**, 1239-1255, doi: 10.2217/epi-2020-0042.
72. Chernyak, B. V., Lyamzaev, K. G., and Mulkidjanian, A. Y. (2021) Innate immunity as an executor of the programmed death of individual organisms for the benefit of the entire population, *Int. J. Mol. Sci.*, **22**, 13480, doi: 10.3390/ijms222413480.
73. Mac Giollabhui, N., Breen, E. C., Murphy, S. K., Maxwell, S. D., Cohn, B. A., Krigbaum, N. Y., Cirillo, P. M., Perez, C., Alloy, L. B., Drabick, D. A. G., and Ellman, L. M. (2019) Maternal inflammation during pregnancy and offspring psychiatric symptoms in childhood: timing and sex matter, *J. Psychiatr. Res.*, **111**, 96-103, doi: 10.1016/j.jpsychires.2019.01.009.
74. Franceschi, C., Bonafe, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., and De Benedictis, G. (2000) Inflamm-aging: an evolutionary perspective on immunosenescence, *Ann. N. Y. Acad. Sci.*, **908**, 244-254, doi: 10.1111/j.1749-6632.2000.tb06651.x.
75. Silk, J. B., and Kappeler, P. M. (2017) Sociality in primates, in *Comparative Social Evolution* (Rubenstein, D., and Abbot, P., eds) Cambridge University Press, Cambridge, pp. 253-283, doi: 10.1017/9781107338319.010.
76. Bzdok, D., and Dunbar, R. I. (2020) The neurobiology of social distance, *Trends Cogn. Sci.*, **24**, 717-733, doi: 10.1016/j.tics.2020.05.016.
77. McEwen, B. S. (2016) In pursuit of resilience: stress, epigenetics, and brain plasticity, *Ann. N. Y. Acad. Sci.*, **1373**, 56-64, doi: 10.1111/nyas.13020.
78. Nesse, R. M. (2009) Social selection and the origins of culture, in *Evolution, Culture, and the Human Mind* (Schaller, M., Heine, S. J., Norenzayan, A., Yamagishi, T., and Kameda, T., eds) Lawrence Erlbaum, Philadelphia, pp. 137-150.
79. Skulachev, V. P. (1999) Mitochondrial physiology and pathology; concepts of programmed death of organelles, cells and organisms, *Mol. Aspects Med.*, **20**, 139-184, doi: 10.1016/S0098-2997(99)00008-4.
80. Korzan, W. J., and Summers, C. (2021) Evolution of stress responses refine mechanisms of social rank, *Neurobiol. Stress*, **14**, 100328, doi: 10.1016/j.ynstr.2021.100328.
81. Sapolsky, R. (2021) Glucocorticoids, the evolution of the stress-response, and the primate predicament, *Neurobiol. Stress*, **14**, 100320, doi: 10.1016/j.ynstr.2021.100320.
82. Hadany, L., Beker, T., Eshel, I., and Feldman, M. W. (2006) Why is stress so deadly? An evolutionary perspective, *Proc. R. Soc. Lond. B Biol. Sci.*, **273**, 881-885, doi: 10.1098/rspb.2005.3384.
83. Skulachev, M., Severin, F., and Skulachev, V. (2015) Aging as an evolvability-increasing program which can be switched off by organism to mobilize additional resources for survival, *Curr. Aging Sci.*, **8**, 95-109, doi: 10.2174/1874609808666150422122401.
84. Suomi, S. J. (2005) How gene-environment interactions shape the development of impulsive aggression in rhesus

monkeys, in *Developmental Psychobiology of Aggression* (Stoff, D. M., and Susman, E. J., eds) Cambridge University Press, NY, pp. 252-268, doi: 10.1017/CBO9780511499883.012.

85. Kahn, J. (2012) *Angst: Origins of Anxiety and Depression*, Oxford University Press, NY.
86. Snyder-Mackler, N., Burger, J. R., Gaydosh, L., Belsky, D. W., Noppert, G. A., Campos, F. A., Bartolomucci, A., Yang, Y. C., Aiello, A. E., O'Rand, A., Harris, K. M., Shively, C. A., and Tung, J. (2020) Social determinants of health and survival in humans and other animals, *Science*, **368**, eaax9553, doi: 10.1126/science.aax9553.
87. Marmot, M. G. (2006) Status syndrome: a challenge to medicine, *J. Am. Med. Assoc.*, **295**, 1304-1130, doi: 10.1001/jama.295.11.1304.
88. Sloman, L., and Gilbert, P. (eds) (2000) *Subordination and Defeat: An Evolutionary Approach to Mood Disorders and Their Therapy*, Lawrence Erlbaum, Mahwah, NJ, doi: 10.4324/9781410605207.
89. Akçay, E., and Van Cleve, J. (2016) There is no fitness but fitness, and the lineage is its bearer, *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, **371**, 20150085, doi: 10.1098/rstb.2015.0085.
90. Johnson, S. L., Leedom, L. J., and Muhtadie, L. (2012) The dominance behavioral system and psychopathology: evidence from self-report, observational, and biological studies, *Psychol. Bull.*, **138**, 692-743, doi: 10.1037/a0027503.
91. Price, J. S., Gardner Jr., R., Wilson, D. R., Sloman, L., Rohde, P., and Erickson, M. (2007) Territory, rank and mental health: the history of an idea, *Evol. Psychol.*, **5**, 531-554, doi: 10.1177/147470490700500305.
92. Siddaway, A. P., Taylor, P. J., Wood, A. M., and Schulz, J. (2015) A meta-analysis of perceptions of defeat and entrapment in depression, anxiety problems, posttraumatic stress disorder, and suicidality, *J. Affect. Disord.*, **184**, 149-159, doi: 10.1016/j.jad.2015.05.046.
93. Chu, C., Buchman-Schmitt, J. M., Stanley, I. H., Hom, M. A., Tucker, R. P., Hagan, C. R., Rogers, M. L., Podlogar, M. C., Chiurliza, B., Ringer, F. B., Michaels, M. S., Patros, C. H. G., and Joiner, T. E. (2017) The interpersonal theory of suicide: a systematic review and meta-analysis of a decade of cross-national research, *Psychol. Bull.*, **143**, 1313-1345, doi: 10.1037/bul0000123.
94. Boehm, C. (2014) The moral consequences of social selection, *Behaviour*, **151**, 167-183, doi: 10.1163/1568539X-00003143.
95. Kowald, A., and Kirkwood, T. B. (2016) Can aging be programmed? A critical literature review, *Aging Cell*, **15**, 986-998, doi: 10.1111/acel.12510.
96. Omholt, S. W., and Kirkwood, T. B. (2021) Aging as a consequence of selection to reduce the environmental risk of dying, *Proc. Natl. Acad. Sci. USA*, **118**, e2102088118, doi: 10.1073/pnas.2102088118.
97. Cohen, A. A., Coste, C. F., Li, X. Y., Bourg, S., and Pavard, S. (2020) Are trade-offs really the key drivers of ageing and life span? *Funct. Ecol.*, **34**, 153-166, doi: 10.1111/1365-2435.13444.
98. Milot, E., and Stearns, S. C. (2020) Selection on humans in cities, in *Urban Evolutionary Biology* (Szulkin, M., Munshi-South, J., and Charmantier, A., eds) Oxford University Press, Oxford, pp. 268-289, doi: 10.1093/oso/9780198836841.003.0017.
99. Wesarg, C., Van Den Akker, A. L., Oei, N. Y., Hoeve, M., and Wiers, R. W. (2020) Identifying pathways from early adversity to psychopathology: a review on dysregulated HPA axis functioning and impaired self-regulation in early childhood, *Eur. J. Dev. Psychol.*, **17**, 808-827, doi: 10.1080/17405629.2020.1748594.
100. Nunn, A. V. W., Guy, G. W., and Bell, J. D. (2022) Thermodynamics and inflammation: insights into quantum biology and ageing, *Quantum Rep.*, **4**, 47-74, doi: 10.3390/quantum4010005.