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Review

Resolving Darwin's Dilemma over Natural Selection, Individual Benefit and Aging-on the Natural Selection of Organismal Aging

Richard F. Walker

ProSoma, LLC, Clearwater, FL 33756, USA; drrwalker@gmail.com; Tel.: +1-727-422-6345
* Correspondence: drrwalker@gmail.com

Abstract: There is scientific consensus that organismal aging did not evolve by natural selection (NS) because it lacks individual benefit. Nonetheless it exists, leading to much speculation about its origins, and when the diminishing force of selection begins. Both concepts are based upon two misconceptions; that aging occurs in and of itself and is caused by the declining strength of NS during the reproductive lifespan. Although lacking individual benefit, aging evolved by NS as a tradeoff of survival for reproduction. Based upon regulatory dynamics that participate in this tradeoff, aging begins once reproductive success has been achieved through offspring nurturing. Thereafter, the strength of NS wanes to exponentially accelerate aging, leading to death. Assumptions of the theory are that: (1) a life-long, "holistic" regulatory mechanism whose genic expression is modified epigenetically, originates in ontogenesis; (2) the regulatory mechanism of the last developmental stage becomes redundantly expressed during "morphostasis", a non-aging, life interval of peak vitality to ensure completion of reproduction through nurturing, and (3) thereafter, loss of regulatory redundancy causes aging which reduces the strength of natural selection and allows accumulation of randomly occurring somatic damage.

Keywords: Trade-off of survival for reproduction; natural selection of aging; regulatory redundancy; aging's individual benefit; regulatory molecular biology; Darwin's dilemma; aging-reproduction trade-off; aging declines force of selection; master gene; holistic regulatory mechanism

1. Prologue

This paper describes more thoroughly, specific aspects of a previously introduced theory about the mechanism of aging in humans and other mammals [1]. It focuses on the roles of natural selection (NS), the developmental regulatory mechanism and "trade offs" in selection of organismal aging. These topics were inadequately discussed and/or inadvertently overlooked in the previous publication [1]. The current version resolves Darwin's dilemma by describing how positive selection participates in the initiation and progression of aging. As used previously, the word morphostasis defines the horizontal phase of the Makeham parameter displayed in a plot of the Gompertz law of mortality.

2. Background

Shortly after its publication, the validity of Charles Darwin's theory "*On the Origin of Species*" [2] was challenged over the role of NS in the evolution of aging. Criticism was based on the premise that aging lacks individual benefit, so that NS should prevent it from occurring. Critics argued that Darwin's Theory was inconsistent with the fact that humans and other animals age and die, claiming that aging was *prima facie* evidence that his description of NS mechanics was inadequate.

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Darwin remained confident that aging is "selected", writing that "*My theory says there must be some hidden compensating (individual, theory conforming) benefit so therefore there must be one.*" to which Goldsmith [3] opined that Darwin used his belief to predict a desired outcome rather than using an outcome as the basis for his theory, and that in general, he "*was perhaps 99 percent correct*". That aging cannot be selected is almost universally held today, despite the fact that there is no generally accepted explanation for how it evolved, except perhaps as described by Williams [4] and Medawar [5]. Their theories of aging are based upon the concept that NS wanes during the reproductive lifespan, thereby passively allowing maladaptive forms of pleiotropic genes to be expressed and deleterious mutations to randomly accumulate, respectively. Indeed, it is widely accepted that the "force of natural selection" declines, but with all due respect for the pioneering work of Medawar, Williams, Hamilton [4-6] and others, they were wrong, but not about its declining strength. Rather they incorrectly described the cause and timing of that effect, which is central to understanding how aging evolved in compliance with positive selection and individual benefit. Thus, this author feels that Darwin was correct. His opinion was not wrong, but simply incomplete for several reasons.

First, Darwin's intellectual focus was upon diversity, adaptation, variation, competition, overproduction, and speciation; generally regarded as characteristics of young organisms. It is doubtful that before publication of his famous work, he gave much thought to a relationship between NS and intrinsic mortality. Paradoxically, his theory extolled death as an engine of evolutionary progress. Paraphrased here is his proclamation that *"from the war of nature, famine and death, the most exalted object which we are capable of conceiving, namely, the production of higher animals directly follows."* Darwin observed the multitude of traits that existed in whole organisms, serving as the basis for determining their advantages or disadvantages for survival, reproduction, and continuance of species. His disinterest in aging as a selected trait, undoubtedly derived from his observation that free-living animals rarely if ever, age to the point of death since they are killed before dying naturally. Also, traits inherent in molecular and cellular processes were not discernable to him. In fact, senescence received relatively little attention until the early to middle 20th century when Comfort [7,8] published valuable reviews of the subject. Thus, viewing death as beneficial to the progress of evolution may have strengthened his confidence that while seemingly contradictory to his theory, there probably exists a hidden, compensating benefit of aging that explains it.

Second, the full nature of selection was not understood during Darwin's lifetime making relevant issues of NS either vague or incomplete in his original formulation. Subsequently, additional, core mechanics were elucidated and documented, causing the modern theory to be far more complicated and detailed, but better understood than when it was first proposed [9].

Finally, criticism of Darwin's theory was unjustified because evolutionary developmental biology (evo-devo) was yet to be comprehensively described. A primary obstacle to explaining how individual benefit is compatible with the onset and progression of aging is the contemporary assumption that it's evolution occurs independent of the developmental program (DP). Instead, they are interdependent functions. When attempting to explain its selection and evolution, aging is routinely considered in isolation due to the generally accepted concept that its cause lies hidden within its phenotype. It is folly to seek the cause of senescence within the aging phenotype because the process of morpholysis has already begun. Under those conditions, aging becomes the multifactorial product or effect of a cause that preceded its onset and progression. Similarly, as history has shown, it is impossible to explain how aging *per se*, which is devoid of individual benefit, could be selected pursuant to Darwin's theory. However, when aging is inextricably

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linked with a highly adaptive trait, it could then be selected as part of a trade-off. These considerations are essential for resolving Darwin's dilemma.

3. Natural selection, individual benefit and aging in contemporary theories

Aging theories consist of those that presume senescence evolved as a purposeful gene-driven program, those that view aging as the accumulation of random mutations following the waning strength of NS [10], and those that explain the developmental program as a product of biological evolution followed by aging, which occurs through interplay of mutation and selection [11]. While confluent, there is little support for the concept that development and aging are integrated through a common stage of life and that senescence derives directly from the DP.

Programmed theories assume that aging provides population but not individual benefit, so they are irrelevant to Darwin's dilemma. Stochastic damage theories explain that aging results from persistent waning of NS over time, which is circular reasoning because it is also plausible that aging erodes the strength of NS [12]. Most evolutionary theories have not identified a trait providing individual benefit that links development and aging giving them little power to resolve Darwin's dilemma. Only a recently published, novel theory involving a hypothetical master/holistic regulatory mechanism for guiding development and for maintaining organismal homeodynamics throughout life thereafter has that potential [1].

A brief discussion of NS is provided as a prelude to describing why and how it participates in the process of aging's selection for individual benefit, and how the same mechanism causes aging to appear programmatic.

4. Natural selection

According to Gould [13], Darwin emphasized the difference between his two great and separate accomplishments. The first was acknowledging evolution as *a fact* represented by change over time and descent from common ancestors. The second was presenting natural selection as a *theory* to explain specific events of evolution such as aging [14].

NS, is sometimes taken to mean that its actions are "all or nothing", whereby unfit individuals die, while the fit survive. Instead, it affects individual, mutation based, novel qualities/characteristics of an organism so that they are retained in its genome or rejected from it. Selection occurs in accordance with the degree to which trade-offs and/or specific novelties enhance reproduction, survival, or other essential elements of successful competition to live. Yet paradoxically, it also chooses aging, but not due to any of the multitude of factors that constitute its phenotype such as antagonistically expressed pleiotropic genes, accumulated deleterious mutations and so many others.

The opinion that "impressive diversity" characterizes aging, which is accepted by most if not all biogerontologists, leads to the erroneous assumption that the key to understanding "why and how" aging came to exist resides within the aging phenotype. It does not. The cause of aging is not multifactorial as commonly believed. It is the aging phenotype that is multifactorial. Its cause is selection of conditions or factors that allow it to begin and proceed. Historically, the cause of aging is accepted as the persistent decline in NS, which has been linked with decline of reproductive probability during aging. Thus, this effect could be interpreted as NS being passive in the emergence of aging, i.e.,

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permissive. However, as the name implies, NS actively chooses, or "selects" things to be included in the genome, it doesn't passively allow them to enter.

5. Waning force of NS and aging

The functional relationship between regulatory dynamics, aging and the strength of NS was inaccurately described in my original publication [1]. Additional details are added and interpretive errors corrected herein.

Traditionally, the search for a general evolutionary theory to explain the origins of aging involves the relative strength of NS. The concept that NS has "strength", a word that can inadvertently be interpreted as having physical/tangible and judgmental characteristics as would a "material thing", undoubtedly derived from Medawar's [5] comments about the "*force of selection*".

That NS has relative strength regarding reproduction and aging is based to great extent on Williams [4] respected theory of pleiotropy, natural selection, and the evolution of senescence. At the time, there was an "*increasing awareness of the decline of selection pressures with increasing age*" throughout reproductive life, a principle that Williams claimed to be central to his theory, which was subsequently validated mathematically [6]. As a result, established theories now support the premise that an *inexorable* decline in the force of selection during adulthood is the cause of aging [5,6,15]. However, "correlation does not imply causation" [16].

Williams [4] defended his theory against criticism that it assumed what it purported to explain, i.e., declining vigor with increasing age, by denying that senescence existed before reproductive maturation, when reproductive probability (RP) reaches its peak. He argued that RP will decrease even in the absence of senescence because *"there would always be a cumulative probability of death. This would produce a decline in reproductive probability because the probability of reproduction at any age is a function of the probability of surviving to that age."* Since it is intuitively obvious that RP will decline over time, Williams nonetheless proposed that senescence begins at peak RP upon reproductive maturation of the soma. The reason for his decision regarding the onset of senescence at peak RP is not clear to this author except perhaps for the obvious fact that RP declines with advancing age, which he previously explained does not require senescence. He then causally related the obvious age-associated decrease in RP and the increasingly accepted notion that *"selection pressures decline with increasing age"*, to the emergence of an aging environment within which antagonistic expression of pleiotropic genes could occur.

To support his argument about declining NS, Williams modified Wright's [17] equation describing the natural selection of a gene with mixed effects on fitness, whereby its selection coefficient is the multiple of advantages or disadvantages associated with its separate effects. In his modification, the selective effects consisted of two factors; one being the direction and magnitude of each effect while the other being the proportion of the total reproductive probability influenced by the effect.

There are several problems with Williams' analysis that are based upon obvious circumstances used by the author to support his thesis. For example, he initially accepts that RP will decline due to causes other than senescence, e.g. increasing probability of death, then proposes that senescence and declining RP begin simultaneously at the point of reproductive maturation. He does not explain whether the age-independent decline in RP causes senescence or that it begins independently of RP and simply accelerates pre-existing reproductive decline by the additional factor of aging?

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And what of the waning strength of NS beginning at peak RP? Williams' analysis may link declining RP and aging with a diminishing force of NS, but it doesn't explain why it starts at peak reproductive probability (RP). Does waning NS cause senescence as is now generally accepted or does aging initiate and exacerbate the decline of NS? Williams just accepts that the force of NS declines to cause aging and supports that assumption with his second condition of Wright's modified equation, that total reproductive probability will obviously be lower in aged organisms than in young ones. Then, by multiplying it by the value of the direction and magnitude of each effect the selection coefficient will automatically reduce compared with results of multiplication by higher total reproductive probability values of youth. So, while NS admittedly declines during aging it is not clear whether it causes or is caused by aging.

Nonetheless, Williams theory anticipates weakened NS in aging environments thereby allowing detrimental effects of previously selected, pleiotropic genes to be expressed due to immunity from negative selection at older ages. Thus, he concluded that *"Natural selection may be said to be biased in favor of youth over old age whenever a conflict of interests arises,"* emphasizing that *"since senescence is an unfavorable character, the direct action of selection will always be opposed to it"*. This conclusion is consistent with criticism of Darwin's colleagues that aging cannot be a product of natural selection, an opinion with which I disagree!

Another problem with the concept that NS inexorably declines after peak reproductive probability, is the conflicting fact, confirmed by Williams that "life tables" show a very low rate of death occurring immediately following adolescence and completion of ontogenesis. To explain this inconsistency with his theory, he opined that "*in many primitive human societies the death of teen-age parents must have greatly reduced the survival prospects of any children they might have produced and that care of dependent offspring is as important to human reproduction as the production of gametes, thereby rationalizing the very slight rate of decline in reproductive probability in early adulthood which should result in a very low rate of senescence during the first decade of man's reproductive life*". However, during this period of non-aging, peak vitality was described in the previous version of Walker's theory [1] as the decade of morphostasis, which represents a continuation of the regulatory process from the last ontogenetic stage. During its expression, the regulatory mechanism of that final stage must become redundant since non-repeating stages of development are completed. Such redundancy must cause aging to begin at some point thereafter [18].

However, his comment unknowingly provides a clue to how aging can be selected pursuant to Darwin's theory. Recall that Walker [1] previously argued that aging doesn't start at peak reproductive probability and decline thereafter, but rather begins sometime afterward during the period of offspring nurturing. Aging is held in abeyance during the nurturing period by selection to ensure its successful completion. Aging begins thereafter due to loss of regulatory redundancy which is selected as will be discussed in the section on Trade-offs. Thus, aging begins in humans at about age 30, upon completion of morphostasis. Then NS declines because of aging, whereas aging doesn't result from declining strength of NS [12].

Thus, conjecture that NS spontaneously declines at peak reproductive probability during adolescence and proceeds to cause senescence [4,5] is inconsistent with the actual cause and time of human aging onset, which occurs more than a decade later. As previously described, [1] it is caused by damage/misrepair to the redundantly expressed, regulatory component of a holistic aging mechanism in humans and other mammals beginning during late morphostasis, the last part of the "non-aging" Makeham parameter of the Gompertz-Makeham law of mortality [19].

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Finally, because Williams proposes that progressing senescence creates an environment within which AP can occur, it provides *"the key to understanding the evolution of senescence"*. This is circular reasoning because he initially accepts that senescence begins at peak RP. If aging were to result from expression of deleterious pleiotropic genes, they would have had to accumulate during later life to then cause senescence during youth at peak RP. This is an illogical scenario.

6. Declining strength of natural selection is caused by aging, not vice versa

It is erroneous to assume that the waning strength of NS causes aging because selection is not actionable, and so, cannot initiate an effect. It is not purposeful nor a tangible physical or chemical entity. It is a spontaneous, unconscious action affecting a mutation or novel quality/characteristic of an organism based upon whether it/they will be retained in the genome or not. This definition stresses that the mechanism/process of NS involves two components. One is an action that produces an effect, such as a novel mutation or trait. The other is the probability of that effect being included in the genome to become heritable (Fig 1). Thus, NS is a probabilistic process whereby some traits with favorable qualities, but not all, are selected [20]. Inevitably, it is the probabilistic component of the process that Medawar [5] referred to as the "force of selection". It could be strong, weak or non-existent, based upon a continuous gradient of probabilities. For NS to have "strength", selection *must be preceded* (at a certain age) *by the emergence of a novel and specific characteristic or trait*. Only then, based upon the beneficial or detrimental value of that novelty to fitness of the organism is it *"selected"*. Without such "consideration" NS is devoid of "strength". This caveat stands in contrast to the classic theory [6] which lacks dynamical dimension [12], implicitly assuming [21] a persistent waning of NS over time that causes aging to begin and proceed. Instead, selection for the inevitable but later occurrence of aging happens during the *"transitional state between completion of ontogenesis and initiation of adulthood"* as part of a trade-off of survival for reproductive success before senescence begins. Identification of when and why aging occurs was discussed in the original theory [1] but the "tradeoff" which is central to resolving Darwin's dilemma was inadvertently overlooked. It will be discussed subsequently in greater detail. Based upon the evolutionary requirement for successful completion of reproduction, the transition from ontogenesis to morphostasis and beyond is essential for survival of the species despite its eventually initiating individual aging and progressively reducing the "strength" of NS. Thus, the declining effects NS is not the cause of aging, but conversely, aging causes it to happen (Fig 1.; [12].

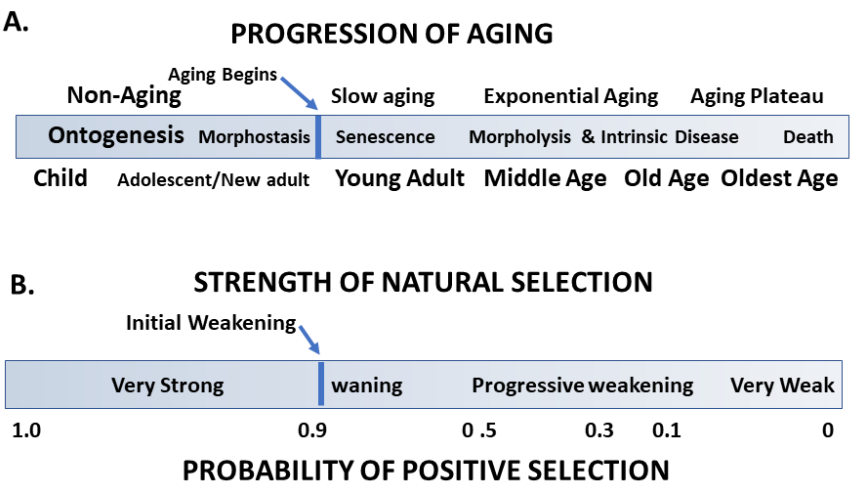

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Fig. 1 Natural selection and the progression of aging

Evolutionary theories of aging are based upon the Medawar's concept of a declining force of natural selection that passively allows aging to proceed. However, a more recent theory proposes that aging causes selection's waning strength, [12]. Walker [1] proposed that regulatory redundancy following completion of development causes aging. This idea provides a specific reason for the force of selection to decline when it does. As seen above, the strength of NS is very strong until aging begins when thereafter but not before, there is progressive decline with advancing age.

A. Vertical line indicates onset of aging toward the end of morphostasis
B. Vertical line indicates point at which natural selection begins to wane and progresses shortly after the onset of aging due to increasing loss of regulatory redundancy

Regarding Walker's comments that morphostasis is a non-aging interval following ontogenesis for completion of reproduction which is followed by initiation and exponential progression of aging, Giaimo and Traulsen [12] stated that, "*the absence of ageing is a transient or unstable state. The selection forces on fecundity and survival at reproductive ages may not always show a pattern of persistent decline during evolution. But, again, this is a transient or unstable phenomenon. When evolutionary* ***dynamics*** *reach a stable resting state and, therefore ageing has evolved, equilibrium selective forces must display a pattern of* ***persistent decline with age***".

Thus, aging in humans and other mammals doesn't begin until about the end of morphostasis, when reproductive success through offspring nurturing is completed. In humans completion of that evolutionary obligation of reproduction occurs at about age 30, which is well after peak reproductive probability that occurs during adolescence as recognized by Williams [4].

Paraphrasing Giaimo and Traulsen [12] while trajectories of fecundity and survival during adulthood are very diverse among species, aging is only one of its possible patterns. Caswell and Salguero-Gomez [22] argued that the inability of classical theory [6] to explain these observations may be due to two of its assumptions. These include, "*age-specific genetic effects that necessarily lead to declining selection with age and (ii) trade-offs between fecundity and survival across different ages"* are absent**.**

Giaimo and Traulsen [12] then concluded that when trade-offs are not considered, and "any sort of age-specific genetic effect is allowed, ageing remains the one and only stable outcome of evolution."

In Walker's modified theory, a trade-off of survival to ensure successful completion of reproduction by sustaining a transient, interval of morphostasis, explains the non-aging, post-ontogenetic period which is inconsistent with the classical concept of inexorable decline of NS during the reproductive period. In contrast, regulatory redundancy which was selected to complete nurturing and mammalican reproductive success as part of the "trade-off" must lead to its progressive loss of the inevitability of subserving the Gompertz pattern of mortality.

7. Types of natural selection

Two types of NS with opposite outcomes participate in shaping biological evolution. Positive selection promotes the spread of beneficial alleles or processes while negative selection purges fitness lowering, mutational or damage-based deleterious assaults upon

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the phenotype to hinder their spread [23]. Negative selection and positive selection cannot be separated, even though biologists often refer to one or the other depending upon their focus, eg. positive selection when an increase of rare variants that improve fitness occurs, or negative selection when harmful variants are removed [24].

Since a greater number of DNA alterations are harmful than beneficial, negative selection acts to maintain long-term stability by removing disruptive threats. This is one aspect by which selection participates in the mechanism related to Darwin's dilemma. Because of its role as a "protector" of stability, sustaining a viable condition in light of persistent onslaught of destabilizing factors, negative selection is also called "purifying" or "background". Because damage to the regulatory process resulting from deleterious mutations are removed by purifying selection thereby restoring the most reasonably optimal conditions, it is of great significance to the molecular mechanism of aging [1]. Such protection remains for as long as the damaging conditions persist to ensure as much as possible, that structural/functional optimization of the remaining regulatory mechanism is sustained. The caveat is that negative selection remains active only for as long as its outcome is not undermined by depletion of remaining components of the regulatory mechanism, which would eliminate the possibility for subsequent positive selection to reestablish normal function of the mechanism to the greatest extent possible. Thus, negative selection ensures against accumulation of deleterious factors that threaten stability and that any remaining components that become fixed, albeit temporarily (as in the case of the aging mechanism) are maintained within the limits of possibility imposed by unmanageable, extraneous factors. In many cases, and specifically for the aging mechanism, progression of negative selection is conditionally optimal because the very process that purifies the mechanism after damage, reduces the number of factors required for return to the original stable living state, which being adaptive is positively selected.

While negative and positive selection often have opposing effects, they also act in combination to produce different types of selection including stabilizing, directional and disruptive selection [25]. Each can produce very different *population* effects which are not directly relevant to the evolution of aging in individual organisms, so they are only mentioned for reference purposes. However, analogies using some, such as stabilizing selection [24]. which removes pseudogenes that arise through random mutations may be mentioned when applicable to dynamics of the aging regulatory mechanism. In this specific case, stabilizing selection keeps the degenerating regulatory process together by eliminating (negative selection) and keeping (positive selection) different components of the mechanism.

Finally, quantitative changes in the character of selection result from aging as it progresses, progressively shifting the balance from predominantly positive earlier in life to increasingly negative with advancing age. Thus, as previously mentioned, changes in the strength of NS result from aging;

they do not cause it [12].

8. Supporting evidence for late life effects of Darwinian selection

As will be discussed in detail during the section on resolving Darwin's dilemma, stabilizing selection maintains the redundant regulatory mechanism throughout the aging process, to ensure as much as possible, orderly passage through the phase of somatic deconstruction and thereby to realize full life potential. This would require that selection still be active during the "shadow period".

The effects of selection at later ages were observed in a large-scale genetic study of variants that impact health, disease and age-specific mortality [26]. The authors reviewed

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clinical data from electronic health records, survey data on demographic and behavioral factors, as well as environmental data from various sources that were linked with data from individuals having genetic predispositions and/or to environmental exposure that underlie age-related pathology. Evolutionary fitness was determined by identifying genetic variants that affect survival to a given age as a means to directly determine ongoing viability selection in humans.

Only a few common genomic variants with large effects on survival at older ages were identified suggesting that even those with late onset effects were weeded out or kept at low frequency by purifying selection. Effects of detrimental phenotypes were studied precisely because of their adverse health effects which occurred less often in people with longer lifespans, and, protective effects were associated with longer life span. The researchers proposed that natural selection eliminates mutations that cause disease or early death in favor of longer life. Then when beneficial genetic mutations occur, they are selected and passed on making their adaptive traits more common in the general population.

Thus, the authors concluded "*there is genetic evidence that Darwinian natural selection is happening in modern human populations.*" The report suggests that while negative (purifying) selection works against conditions/genetic variants that shorten life, positive selection favors those that increase the likelihood of achieving full, natural life potential, *but not* extending lifespan beyond the norm. The data demonstrate that *NS continues to be active late in life, which to some extent contradicts the generally accepted perception of its decline and eventual impotence upon completion of reproduction*. The point of this reference is that NS is active, even late in life which is relevant to the proposed mechanism by which aging occurs, since both negative and positive selection are required within it. This is important because positive selection is needed to sustain the regulatory mechanism until its redundancy is completely lost in one of the soma's serially linked functional segments, making death inevitable.

Thus, while the molecular process subserving aging is affected by positive and negative selection, they work jointly not increase lifespan, but rather to oppose intrinsic diseases. The "objective" of this effect is to ultimately achieve full duration of life potential by promoting healthier populations and ensuring species survival.

9. Inseparable effects of negative and positive selection.

Negative and positive selection are inseparable [24] but the degree to which they assert their respective influences changes with the dynamics of the process within which they are involved. This joint effect involving the role of positive selection during decay of the regulatory mechanism subserving aging (Walker 2022), identifies one of the two dynamics that resolve Darwin's dilemma. This combination that maintains to the extent possible, the integrity of the regulatory mechanism that participates in aging, could be considered a form of stabilizing selection.

Differentiating between negative and positive selection in complex functions is often a matter of perspective and interpretation. A specific demonstrable effect of the functional duality of negative and positive selection involving essentially the same gene is presented in the reports of Sun et al [27] and [28] Zhang, respectively. To better resolve Darwin's dilemma, their example of how perspective modulates interpretation of integrated NS functions in selection of seemingly opposite traits is briefly reviewed.

Sun et al [27] described the mechanism by which *Yersina pestis*, a lethal bacterial pathogen that causes plague, evolved in *Y. pseudotuberculosis*, a non-lethal, enteric bacterium.

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Y. pseudotuberculosis is not vector-borne but is transmitted by the oral–fecal route. It is unable to produce biofilms in fleas, the vector required for successful transmission of the bacterium to its hosts, rats and humans. *Y. pseudotuberculosis* cannot produce the biofilm in fleas because it's genome contains a negative regulator of the rcsA gene. However, when mutated, a pseudogene that contributed to the evolution of Y. *pestis* was created. The pseudogene's evolutionary effect was abolished when it was experimentally replaced by a functional *Y. pseudotuberculosis* rcsA allele. Thus, Sun et al (2008) concluded that mutation of *rcsA* to a pseudogene was maladaptive to the *Y. pseudotuberculosis* phenotype and thus, was purged by purifying/negative selection.

In contrast, Zhang [28] interpreted these findings as demonstrating that pseudogenization of *rcsA* was adaptive and driven by positive selection, contributing to the evolution of a new species, *Y pestis*.

These differing opinions demonstrate how negative and positive selection can affect the same process with different outcomes depending upon perspective and interpretation of their combined effects rather than of one or the other in isolation. The dual effect of selection on different parts of the developmental regulatory mechanism is directly relevant to control and programmatic progression of aging. By involving positive selection, it becomes part of resolving Darwin's dilemma. Purging of pseudogenes in the redundant regulatory mechanism by negative selection allows positive selection of the remaining number of redundant units, which ensure progression of aging through minimizing loss of redundancy.

In the case of lost redundancy within the regulatory mechanism involved in aging, the effects of each type of selection may not be equivalent, i.e. at one point positive selection may exert a stronger or more dominant effect than negative selection and vice versa, depending upon the number of remaining functional units of the total redundant mechanism and despite the fact that both forms of selection are occurring simultaneously.

10. Continuation of the DP into adulthood is often considered maladaptive

Hayflick [10] described the DP as "a cornerstone of modern biology within which a purposeful genetic program drives all biological processes that occur from conception to reproductive maturation". It is generally agreed that the DP eventually ends and some investigators feel that its continuation into adulthood is maladaptive. For example, deMaghalaes [29], Blagosklonny [30,31], and Singer [32,33] proposed several different ways that DP continuation into adulthood could cause aging.

deMagalhães [29] speculated that certain aspects of mammalian aging display predetermined morphogenetic patterns. These continue beyond completion of the DP due to oversight by a "shortsighted watchmaker," making "*aging in mammals … partly programmed*".

Blagosklonny [30] proposed that continuation of DP signal-transduction pathways involving mTOR causes cellular geroconversion and facilitates development of age-related pathologies. Thus, he proposed that aimless continuation of the DP involving the mTOR pathway provides a link between programmed growth of development and "quasi programmed" somatic damage and degeneration of aging [31]

Singer [32] proposed that aging is an *"integral part of the fabric of life"* because it begins at conception in concert with the DP. However, while describing the DP and aging as two parts of a whole transformational process, he claimed that the former is programmed whereas the latter is not. It is difficult to understand how aging could evolve

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within a program, *yet not be programmed*! The author simply argued that the DP is "plastic", constraining release of aging phenotypes/trajectories in youth until later in life by diminished strength of NS resulting from declining fertility. Despite being constrained, having aging begin in the zygote implies that it is selected. Singer supports aging as adaptive because it provides a means to "*regulate species population densities within the constraints imposed by the ecosystem organization*" [33]. This concept is similar to Mitteldorf's Demographic Theory [34] but is in conflict with his claim that aging is a product of group selection [35], whereas Singer's theory implies that it is part of the evolved developmental program. It is selected because in some way, it would seem to provide individual benefit. However, the author claimed it provides population, not individual benefit. Thus, like the other referenced theories, Singer's [32,33] does not resolve Darwin's dilemma since it doesn't support Darwin's opinion that there is a latent *individual benefit* in the aging process, nor does it satisfactorily describe why and how it could be realized.

A significant problem with these theories that propose continuation of some aspect of the DP causes aging, is that they fail to explain why NS doesn't prevent it. As the sentinel of individual benefit, NS should not allow aging to begin upon completion of ontogenesis, since it occurs in humans at about 20 years of age. However, the Gompertz law of mortality shows aging to begin in humans at about age 30, suggesting that the strength of NS doesn't begin to wane and aging begin until about a decade later. If so, why would the emergence and continuation of purported maladaptive events resulting from continued expression of the DP not be selected against about ten years before NS declines at the onset of aging? Also, the theories don't provide a mechanism for aging other than non-specific molecular and metabolic chaos. Basic to these aging theories is the question of whether evolution could be so imperfect as to allow developmental errors that risk completion of the reproductive effort, e.g. nurturing during morphostasis [1] to continue even though they are still subject to NS. And does aging really begin due to declining strength of Darwinian NS, or does the advent of aging initiate NS's quantitative decline [12]? None of the previously referenced theories support Darwin's opinion that there may be a latent individual benefit in the aging process, that intuitively must derive from the DP, nor do they describe why and how it could be realized.

11. Successful completion of reproduction requires continuation of the DP into adulthood

Contrary to traditional views, Walker [1] recently proposed that the DP and aging in mammals are functionally linked through an intermediate phase of life called "morphostasis". In humans, morphostasis is the post-ontogenetic, non-aging, vital period of life lasting for about a decade from about 20 to 30 years of age. It is visually evident in a plot of the Gompertz-Makeham law of mortality as the horizontal, concluding or "plateau" phase of the Makeham parameter. Unlike other theories, Walker's explains why and how molecular damage to a holistic regulatory mechanism originating in the DP and continuing thereafter, causes aging to begin and proceed following completion of morphostasis. This raises the question of why does aging emerge at that stage of life upon completion of reproduction? The answer resides in the dynamics of holistic regulatory mechanism expression following completion of the last ontogenetic stage. During the DP, regulatory gene expression changes as the epigenetic landscape is modified with each non-repeating stage of construction. These changes allow differential expression of the regulatory mechanism making it difficult for damage and errors to affect it at any stage. However, the lack of non-repeating stages during morphostasis and subsequent phases of life, makes the regulatory mechanism vulnerable to damage and to an increased risk for the emergence of aging. When stages of somatic construction are complete, regulatory oversight of the adult soma must become redundantly and appropriately expressed pursuant to the varying epigenetic conditions of the different body parts. Progressive

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stochastic damage erodes robust expression of these master regulatory mechanisms causing loss of redundancy that erodes functional and structural stability characteristic of senescence.

The operational focus of the theory is upon the dynamics of the hypothetical regulatory mechanism that continues beyond the DP to ensure completion of reproduction through offspring nurturing during morphostasis, but subsequently causes aging. Based upon the individual benefit of reproduction, DP continuity with the first post-ontogenetic stage of life is adaptive. However, in the initial version of his theory, Walker [1] did not explain that the aging mechanism is also selected at this stage of development. Thus, he did not resolve Darwin's dilemma. That oversight of the original mechanistic theory will be corrected to show that indeed, the mechanism subserving mammalian aging meets the criteria for selection, albeit through a hidden compensating individual benefit.

The basic concept of developmental regulatory mechanism that continues throughout life, derives from the early work of John Bonner [36] the developmental biologist who recognized the essential need for a regulatory mechanism within the DP. Although such a mechanism was not understood at the time, it's existence was obviously required to ensure that somatic construction proceeds as a continuous, uninterrupted assembly of properly positioned, anatomically and functionally correct structures representing an integrated whole. Previously, the properties of self-organization during embryogenesis were so inexplicable to the German biologist and neo-vitalist philosopher Hans Driesch (1867 – 1941) that he attributed it to *"entelechy"*, a mystical, vital biological force [37]. To avoid using potentially "supernatural" aspects of vitalism in his work, Bonner [36] rejected the term in favor of the more conservative, but still imprecise description of organismal regulation as the *dynamic interaction of ever changing constructive and limiting processes*. At the time DNA research was in its infancy, so he was unable to suggest a guiding mechanism based in molecular biology to direct those changing processes. Since then, much has been learned about molecular regulatory processes, but identification and description of a holistic mechanism has yet to be accomplished. Knowing that regulation at many levels is essential for integration of interdependent events throughout life, Walker [1] proposed that the developmental regulatory mechanism continues beyond ontogenesis into morphostasis and beyond. Unlike other authors, he viewed continuation of the DP (specifically the developmental regulatory mechanism in mammals) as adaptive because it ensures that a transient interval of non-aging vitality will occur during which newborn mammals may be nurtured to successfully complete the evolutionary obligation of reproduction. Thus, it is reasonable that such a mechanism exists not only during development and morphostasis but continues thereafter to exert control over lower order regulatory pathways essential for maintenance and repair of proper form and function of the adult soma.

Without accepting the premise that a holistic, developmental regulatory mechanism/process (*a master regulatory gene of some sort from the last ontogenetic stage*) continues its expression to sustain essential adult processes, there is no logical way to explain the emergence and programmatic appearing progression of aging from a non-aging programmed state as the result of positive selection. Any alternative explanation would require the evolution of a separate aging program, which has never been adequately described nor defended. Also, aging doesn't possess characteristics of a true program, so there would be no selective pressure for evolution of a separate aging program if the population benefit of aging were fulfilled by its occurrence in individual organisms.

If however, a lifelong functioning regulatory mechanism evolved to ensure development, successful reproduction, and somatic maintenance during adulthood, it could like all other processes be vulnerable with advancing age to stochastic damage that degrades

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its efficiency, thereby initiating and accelerating aging. The seemingly paradoxical relationship between reproduction and aging is a trade-off that explains how senescence can be a product of Darwinian selection. Those facts were not included in the initial report [1] and thus, did not explain how aging could be selected. That oversight of the original mechanistic theory will be corrected to show that indeed mammalian aging meets the criteria for selection, providing a hidden compensating individual benefit as predicted by Darwin.

12. Construct of the regulatory mechanism

Most aging theories focus upon characteristics of aging itself, hoping to determine its cause while failing to realize that they are futilely examining its consequences. Its multifactorial character should instantly provide evidence that the cause of aging preceds expression of its phenotype. The cause is progressive degradation of the master, holistic regulatory mechanism due to mis-repaired molecular damage [1]. Thus, unlike traditional stochastic damage theories of aging, which imply that aging is multifactorial, there is but a singular cause of senescence.

Considering the multitude of genes existing throughout an organism, and further that their appropriate expression is controlled by regulatory processes of ascending complexity, it is reasonable that a process of ultimate responsibility to integrate activity of the total organism would likely have evolved. Based upon insight gained from authors such as Yates [38,39] and experimental data of Hayano et al, [40], Walker [1] proposed that such a mechanism could consist of a common genetic "backbone" presumably existing in all cells of the body, or in regional groups capable of influencing related somatic regions whose expressions would be differentially and appropriately modified by the epigenetic landscape within which they reside.

Clearly, ontogenesis requires diversity of modified regulatory molecules due to construction of the various body parts. As previously suggested, these regulatory variants result from local epigenetic modification of gene expression to create initial conditions for each subsequent stage. In his discussion of regulatory control of morphogenesis, Yates [39] implied that the pattern-to-pattern sequencing of developmental stages is guided by a common regulatory mechanism initiated by "... ***genes*** *[which] act as dynamical constraints shaping* ***product formation*** *at each stage..[that]..****act as new constraints*** *on the next round of dynamics.* ***Epigenetic*** *influences carry great weight…"* [41].

It is important to understand that if the regulatory system affects phenotypic changes across the lifespan, and if we accept that the genome is the same throughout the body, then it must be the unique epigenetic environments of the various cells and tissues that affect differential expression of genes both temporally and appropriately for their geographic (spatial) locations. Thus, epigenetics makes the essential contribution that explains how a constant or fixed genotype could direct the various changes in phenotype that occur during the transition from development to advanced age, ie., how a synchronic informational genotype could functionally interact with a diachronic dynamic phenotype

The original theory assumed that during ontogenesis, regulation of each developmental stage begins with the product of the preceding stage that epigenetically constrains dynamics of the next stage by first directing expression of non-coding DNA (ncDNA) to which a major portion of transcriptional activity in mammalian cells is attributed. It was proposed that ncDNA participates in the process of developmental stage initiation because, it contains sequences that act as regulatory elements to determine when and where genes are activated or not and provides sites for transcription factors to bind and either activate or repress transcription. Additionally, regulatory elements of ncDNA include

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promoters, enhancers, silencers, insulators and also provide instructions for the formation of certain kinds of RNA.

Although ncDNA does not code for proteins, its transcription occurs throughout eukaryotic genomes, generating a wide array of ncRNAs [42] that account for a major portion of the transcriptional activity observed in cells. Some of these such as long ncRNAs (lncRNA) can regulate genes in both *cis* and *trans*, demonstrating their importance as regulatory molecules. _LncRNAs, also interact with protein complexes to modify chromatin structure [43]. One large class of ncRNAs includes those transcribed over the promoter regions of nearby protein coding genes. As the result of these important roles, ncRNA molecules have been considered by some to be genes [44] that play an important role in an epigenetic regulatory network thereby highlighting their prominent regulatory role [45].

The assumption that ncDNA is part of the initiating sequence for each regulatory cycles is also based upon the experimental evidence from Hayano et al [40] who reported creating a murine system within which endonuclease-induced DNA damage, i.e., non-mutagenic double stranded breaks (DSBs), could be precisely controlled at frequencies only a few-fold above spontaneously occurring, normal background levels. The DSBs that were created primarily in non-coding regions, altered the epigenome, resulting in a transgenic mouse model called, "Inducible Changes to the Epigenome" (ICE). Initiation and acceleration of organismal aging in young adult laboratory mice rapidly followed enzymatic damage to ncDNA and subsequent epigenomic alteration.

Both genetic and epigenetic factors set the initial conditions for the newly beginning regulatory sequence. This is an important role, since the regulatory behavior beyond ontogenesis during morphostasis and morpholysis observes laws of determinative chaos (DC) and thus, displays sensitive dependence upon initial conditions (SDIC). Subsequently, ncRNAs that are transcribed from the ncDNA to further affect gene expression, modify chromatin structure by interacting with protein complexes, to further establish and maintain specific epigenomic landscapes [42, 45-48]. Also, some sections of ncDNA transcribe ncRNA over promoter regions where they affect coding gene expression and play important roles in post-transcriptional regulation [42,49,50]. Thus, they initiate expression of protein coding genes as a secondary function of the initial events. Coding genes then direct production of essential proteins, explicitly specifying their primary structures. Thereafter, epigenetic factors existing as parts of the spatial and temporal environments create dynamical constraints on subsequent higher order protein structure, folding, targeting, scaffold attachment regions, origins of DNA replication, centromeres and telomeres. Since, coding genes are played upon to produce appropriate products for construction, they are not likely part of the initial conditions in the regulatory sequence for each developmental stage. Coding genes do have regulatory sequences but they are for controlling protein production not for maintaining a stable young adult soma nor for sustaining youth during morphostasis. Thus, it would seem that if coding genes are responsible for creating structure, i.e., protein, no individual one or combination could be a primary regulatory gene responsible for establishing the patterns that occur during the aging process.

13. Homeotic gene approximation of the hypothetical regulatory mechanism

Since the time of Bonner, much has been learned about molecular regulatory processes, but identification and description of a singular and holistic, super regulator has yet to be revealed. However, the existence of master regulators, which represent "*the gene at the top of the regulatory hierarchy, which should not be affected by the regulation of any other*

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genes" [51] have been described and may be an approximation of the pinnacle of a hypothetical holistic regulation hierarchy, particularly in regulatory pathways related to cell fate and differentiation. For that reason, master regulators will be briefly discussed.

If a single, holistic regulatory mechanism doesn't exist as proposed, perhaps homeobox and two related types of DNA sequences including homeotic and Hox genes that are found in the genome of eukaryotes may contribute to that role. The reason for this alternative is that while homeotic genes are recognized as universal regulators of body patterning during metazoan embryogenesis, they also transcend the boundary between development and adulthood where they not only serve as cellular positional markers, but more relevant in aging, they participate in renewal and regeneration of postnatal organs. Thus, during the post natal period, Hox-positive subpopulation of resident mesenchymal stromal cells may serve as a unique regenerative reserve. These cells coordinate creation and maintenance of the correct structure of the stroma through a tissue-specific combination of mechanisms. Thus, homeotic gene expression in adult stromal cells is not limited to storing positional information as during development, but also functions as master regulators of many processes affecting cell phenotype and, thus functional characteristics [52].

Like components of the hypothetical regulatory mechanism, homeotic genes do not participate in the structural and function outcomes of actions they regulate, but rather as transcription factors, direct proper dynamics of the events .

Global long-range regulations in secondary axes accompany Hox gene expression, while temporal activation of Hox genes involve changes in higher-order chromatin organization and step-wise transitions in its structure [53].

Especially relevant to the theory is that the common metazoan HOX genetic system is conserved in the reproductive tract, and is essential for appropriate tract development and for adult functions [54, 55].

Thus, like the hypothetical holistic regulatory system, the HOX system continues its expression following ontogenesis into adulthood to direct reproductive function of morphostasis. This particular characteristic is directly relevant to Walker's theory of DP-morphostasis continuity, wherein a developmental regulatory mechanism is required for successful completion of reproduction during the post-ontogenetic phase of offspring nurturing.

As in the female reproductive tract, Hox genes also function in *endocrine-driven developmental pathways in the adult hematopoietic system* and *in the adult hematopoietic system* as well [56].

Finally, like some mis-repaired, damaged components of the hypothetical, holistic regulatory system, which can trigger serious disease during aging, Hox genes that continue to be expressed in adult tissues when misregulated occur in certain human cancers,[57]. The purpose of this brief overview of some of the HOX system was to demonstrate that while the holistic regulatory system proposed in Walker's hypothesis is conjecture, there are actual master regulatory systems that in general, suggest the concept is valid.

14. Linking reproduction with aging

Returning to Darwin's dilemma; if the potential for aging evolved as an intrinsic element of the reproductive process beginning in adolescence (during the DP) and ending in young adulthood (during morphostsis), then the continuity of these life stages would be adaptive. This scenario would support Darwin's prediction that positive selection of aging occurs by a "*hidden, compensating individual benefit*" if it were shown that selection

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of the process that is required to complete reproduction (an adaptive trait with peak individual benefit) brings with it the *absolute certainty of aging and death*, which is devoid of individual benefit. Pursuant to those stipulations, *reproduction and aging/survival must be interdependent and thus, indivisible*. Besides mammals, this relationship is present in other species such as Pacific salmon, the marsupial mouse Antechinus, and some other semelparous animals that experience severe physiological decline, exhaustion, very rapid aging and death in preparation for, or as part of the reproductive ritual. Libertini [58] described this relationship between reproduction and obligatory aging as phenoptosis, a neologism for the death of an individual, independent of accidents or non-aging disease, but provoked by specific, genetically based mechanisms. Phenoptosis is presumed to have evolved as an adaptive program to purposefully cause death as the basis for its selection [59]. This conclusion is misleading because aging and death as described by Libertini [58] were associated with and obligatory upon reproduction, which is inarguably adaptive and positively selected. However, the evolution of such a program exclusively for aging disregards the fact that the mechanism or process ensuring reproduction, which is adaptive, brings with it a maladaptive trade-off and thus, is not selected in and of itself to ensure the occurrence of aging and death. Such a tradeoff of survival for reproduction is not specifically defined in phenoptosis theory leading to the conclusion that it neither supports aging as an evolved program, nor resolves Darwin's dilemma.

An admittedly important error in the initial version of Walker's theory is conjecture that "after individual benefit is realized, post-reproductive loss of NS may have evolved to ensure mortality and thereby, to bring population benefit through facilitation of evolvability. This possibility avoids the purposeful evolution of aging, a non-adaptive trait that violates Darwin's individual benefit mandate." Thus, by avoiding selection of aging, it did not resolve Darwin's dilemma.

15. Regulatory redundancy and aging: Specific cause for loss of regulatory redundancy

In the initial manuscript, Walker [1] recognized that redundancy ultimately leads to aging [18] and also that because the constructive modules of ontogenesis are non-repeating, the structure of the regulatory mechanism is modified appropriately for each developmental stage. Because of little if any redundancy of the regulatory process during the DP, its outcome is deterministic or predictable. However, upon completion of development when regulation is no longer required for assembly of the soma, it then is required to sustain homeodynamic organization/maintenance of the total organism throughout the course of its life. Continuance of the regulatory mechanism beyond development would forego the need to create a regulated program for maintenance in the adult, since it preexists in the DP. However, since the soma undergoes programmed change during ontogenesis, the dynamics of regulatory mechanism expression must correspondingly change when the constructive phase of the DP ends. Relevant to evolution, it is essential to recall that peak reproductive potential occurs during development, eg. adolescence, and that in early human societies, like mammals living in the wild, mating and birthing occur before or coincident with acquisition of adulthood. At this point, constructive transformation of the soma ceases, and the evolutionary obligation for successful reproduction requires nurturing of offspring until they become independent. As previously proposed this reproductive stage occurs during morphostasis, a life interval of non-aging and peak vitality recognized as the final portion of the Makeham parameter of the Gompertz-Makeham law of mortality. Such a period of non-aging has been previously proposed as being possible by Giaimo and Traulsen [12] who felt that such a period could exist as an unstable equilibrium within the dynamic evolution of lifespan. During this period, NS does not decline as proposed by others [4-6], and perhaps even increases.

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The only way for the DP to continue beyond the last developmental stage as adaptive for completing reproduction, is through redundancy of the holistic regulatory mechanism governing the last stage of ontogenesis which ultimately causes organismal aging and death (Fig 2).

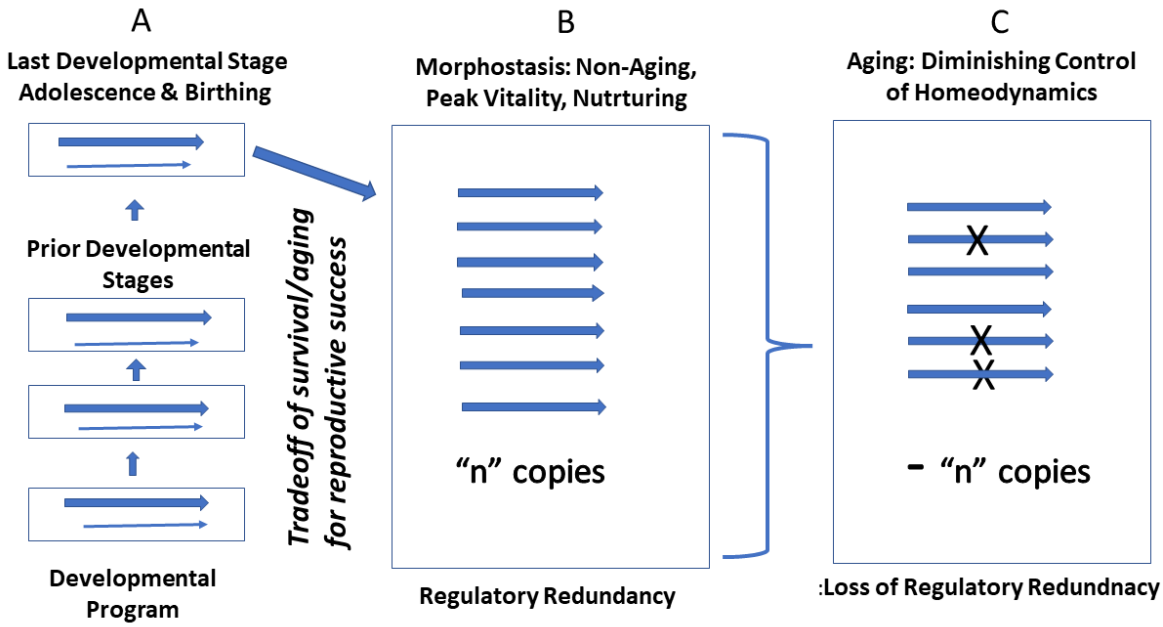

Fig. 2. Cause of aging is post-ontogenenic developmental regulatory redundancy

During ontogenesis somatic construction is guided by regulatory processes, one of which is proposed to be a "master" consisting of a genetic "backbone" whose expression, appropriate for each developmental stage is affected by the local epigenetic landscape. Since the constructive phases are non-repeating little if any regulatory redundancy is required to ensure successful completion of any phase [A]. However, upon completion of the DP, nurturing, the final act of reproduction in mammals occurs in new adults whose homeodynamics during morphostasis are ensured by redundancy of the regulatory processes present in each area of the adult soma [B]. Upon completion of nurturing, stochastic damage causes progressive loss of regulatory redundancy initiating and accelerating aging as well as reducing the force of natural selection [C]. Each box diagrammed above is presented for demonstration purposes to represents only one of the multitude of such somatic regions.

Because the non-repeating stages of the DP end, and with it the associated, phase-related changes in regulatory program characteristics, regulation during morphostasis and beyond must adopt a different dynamic to sustain order within the more stable, new adult organism. To do so, the regulatory mechanism becomes redundantly expressed throughout the body. Gavrilov & Gavrilova [18] proposed that application of Reliability theory [60] would provide a valuable approach to explaining how such redundancy subserves exponentially increasing death rates during aging as described by the the Gompertz law of mortality.

Unlike biological organisms, components of manufactured devices can be "*quality controlled*" for reliability, thereby requiring little redundancy. In contrast, biosystems cannot be pre-tested, and because they contain more damaged or dysfunctional elements

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than technical devices, require a high degree of redundancy to ensure reliability. Nonetheless, Reliability theory predicts that systems, "*even those containing non-aging elements*" will deteriorate and fail more often "*if they are redundant in irreplaceable elements*". Thus, in biological organisms that initially contain but lose redundant regulatory elements, aging proceeds as a "*direct consequence of system redundancy*" [18]. However, redundancy can temporarily persist without causing aging during the nurturing phase due to selection, successful repair of damage, and/or failing to exceed the minimum threshold of loss to initiate aging. Any of these alternatives would sustain the stable period of morphostasis previously described, which is eventually lost due to DNA damage/misrepair.

In demography, failure rate is equivalent to the force of mortality, which increases in systems that deteriorate more rapidly with advancing age. This effect is demonstrated in the Gompertz-Makeham law of mortality, which describes failure rates of non-aging as well as aging systems [61,62]. The non-aging component or the Makeham parameter describes failure rates due to extrinsic causes through development and the first adult stage of morphostasis, i.e., which in humans describes the decade from completion of the DP until the emergence of aging or morpholysis. When during latter morphostasis, damage to the regulatory mechanism reduces the number of redundant elements and loss of regulatory redundancy exceeds the threshold for initiating organismal failure, then aging begins. Damage results from DNA double stranded breaks (DSBs), a lethal form of damage that is often mis-repaired, and increases in frequency over time. DSBs were proposed to be the singular cause of aging [63], whereas Hayano et al [40] reported that when a modest number of DSB's were experimentally produced by enzymatic cutting of ncDNA in mice, they experienced significantly accelerated, but "normally" progressing aging.

DNA double stranded breaks (DSBs), cause changes in gene structure of the regulatory mechanisms' finite number of redundant non-expendable components that are distributed throughout the body. These pseudogenes are purged by negative selection causing redundancy to be progressively lost and aging to begins and accelerate. Thereafter, the Gompertz function describes the exponential failure rate of the aging component resulting from progressive loss of regulatory redundancy. It increasingly disrupts physical and functional homeodynamics, causing and increasing age-related somatic degeneration and intrinsic disease.

Based upon this and other evidence, Walker proposed that spontaneously occurring, mis-repaired DSB's within the post-ontogenetically expressed, holistic regulatory mechanism accelerates during aging in mammals and other animals that nurture their young. These quantitatively reduce holistic regulatory redundancy and thereby increase mortality rates from young adulthood throughout the remainder of life unto old age, when in the oldest of old individuals, redundancy exhaustion, aging deceleration and mortality plateaus occur. As the result of progressive, accumulated damage, he speculated that regulatory behavior shifted over time from deterministic to chaotic, characteristic of aging's progression.

Thus, as previously described, the molecular mechanism subserving aging as described by the Gompertz Makeham law of mortality is relevant to humans and perhaps some other non-mammals that nurture their young. Based upon that rationale, formulation of a general theory of aging having the same trade-off stipulations is probably not applicable to all residents of the animal kingdom.

16. Programmed vs appearing programmatic in the context of aging

When describing the characteristics of biological sequences, program means that they are constrained by certain rules representing a set of structured activities or events leading

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to a specific conclusion. The most obvious example of this definition in biology is the developmental program (DP). During ontogenesis, it is a dynamic process of non-repeating, integrated constructive stages that transform the conceptus into a young adult [64]. A program such as the DP is orderly, displaying causally determinative behavior involving molecular instructions that lead to predictable outcomes.

A common remark about aging's progression is that it appears programmatic. This observation provides another clue to the origin of aging suggesting that it's programmatic appearance represents the degradation of a program such as the dp from which it is derived . This definition functionally differentiates program which is deterministic and orderly throughout its course, from programmatic which implies that the action, re: aging, cannot be taken literally as being program driven nor that its progression is strictly programmed. Unlike the DP, aging does not proceed in a strictly predictable fashion since genetic damage due to mis-repaired DSBs is random and cumulative causing expressions and rates of aging to not follow a strict pattern as during ontogenesis. However, because aging is not all or none, and since causal events are relatively few and occurring randomly, it initially displays behavior resembling causal determinism, which to some extent is predictable. However, based upon damage-induced changes in initial conditions of the regulatory mechanism in concert with loss of its redundancy during its progression, determinative chaos behavior emerges, continues and accelerates unto unpredictably chaotic behavior.

Specific construct of the aging process from its somewhat orderly inception to the unpredictable nature of its conclusion has never been described within the context of any programmed aging theory. This lack of specificity derives in part from the ambiguous description, i.e., programmatic appearance, which is devoid of predictable changes such as those that are characteristic of the non-repeating stages of ontogenesis. Instead, it refers to a loose pattern of functional failure in different parts of the body, accompanied by emergence of intrinsic disease and associated with progressive degeneration of local homeostasis maintaining processes. This sequence of change in structure and function of the body during aging is that which would be expected from gradual decay of a holistic DP regulatory process due to progressive loss of redundancy.

Since aging follows and is directly linked with the DP through morphostasis, its programmatic appearance represents stochastic, progressive damage to the holistic regulatory mechanism that causes aging trajectories to display programmatic features, but not exactly the same in each individual. The resulting inability to restore all redundant components of the holistic developmental regulatory process that continues beyond completion of ontogenesis causes progressive disorganization and deconstruction of the soma. Thus, rather than being a unique, evolved entity, aging is a process that appears programmatic because the mechanism for directing homeodynamic stability progressively loses its essential, redundant elements. Accordingly, aging does not require the evolution of a novel program even though during early stages of morpholysis the soma temporarily displays predictable consequences of aging as the result of its transitional relationship with the DP, specifically from morphostasis. Subsequently it becomes increasingly unpredictable and chaotic as aging proceeds and regulatory oversight increasingly decays. These behavioral differences between somatic construction and deconstruction support the argument that the aging process emerges from the progressively decaying developmental regulatory process that evolved to regulate somatic construction and subsequent morphostasis. Thus, theories that identify the origin of aging as degeneration of developmental program continuance more logically recognize that process as the reason for aging's programmatic appearance i.e., possessing some characteristics of a program but not similar to the precise stages of ontogenesis nor meeting its specific definition of a program.

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This causes aging to appear *programmatic*, meaning related or appearing to possess some characteristic(s) of a program. But it is neither a "partial" program [29], a quasi-form program [30] nor originating as a program at conception that loses its program characteristics due to plasticity [32]. Since the developmental regulatory mechanism is an integral part of somatic construction and maintenance, then its decay during adulthood represents not only the cause of aging, but also explains aging's programmatic appearance.

So for that and other reasons previously mentioned, the concept of programmed aging seems untenable, whereas non-programmed theories are more logical and potentially testable.

Thus, the progression of aging appears programmatic due to differential, random loss of regulatory redundancy among various parts of the soma. In contrast, stochastic, randomly occurring somatic mutations or antagonistic expression of pleiotropic genes cannot do so, unless perhaps if they were operational parts of the DP regulatory process.

17. Resolving Darwin's Dilemma: Trade offs and the positive selection of aging

"The evolution of different life history strategies and thus different ageing patterns essentially depend on the nature of the underlying trade-offs between **survival and reproduction**. To fully comprehend ageing, we need to understand these trade-offs" [65]. Furthermore, It is impossible to explain Darwinian selection of aging in mammals without it resulting from a tradeoff of survival for reproductive success.

Biological aging can occur consistent with principles of reliability theory [18] primarily due to Darwinian selection of a redundantly expressed, damage-vulnerable regulatory mechanism and secondarily by selecting unpurged, remaining adaptive elements of the development/aging regulatory process that continues throughout adulthood to sustain life, not to end it. The mechanism that evolved to complete reproduction by linking the DP to the post-ontogenetic interval by selection of a failure-prone process (redundancy) thereby causing aging is a paradox, but constitutes an essential tradeoff of survival for reproduction. Coincidentally, it also provides population benefit.

The aging process involves two trade-offs. One happens during the transition from the DP into young adulthood and the other during the aging process itself. The first trade-off provides the key to resolving Darwin's dilemma because it reveals the "hidden, compensating benefit" that justifies and explains positive selection of aging. As previously discussed, successful completion of reproduction requires nurturing of offspring. This final reproductive event occurs in humans during the decade immediately following ontogenesis, i.e., between the ages of 20 to 30 years. As the epitome of individual benefit, completion of reproduction would be positively selected. However, to have reproduction succeed, a functionally integrated soma must transcend the regulatory division between the DP and morphostasis.

Recall that to sustain continuity and order between development and adulthood, the multitude of interrelated somatic processes must be regulated to keep them functionally organized as an integrated whole, not a loose association of separate parts. It has been long recognized that the DP consists of many non-repeating stages that are regulated by a process employing the product of each preceding stage in setting the initial conditions for the subsequent stage. This continuity of regulation continues until adulthood is reached, which in humans occurs at about age 20 years. For regulation to continue during adulthood when non-repeating stages of development are completed, the product of

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the last developmental stage must set the initial conditions for subsequent regulatory expression. Then to continue oversight suitable for maintenance of the the young adult phenotype, the regulatory mechanism must become redundantly expressed, which as previously explained guarantees that aging will eventually follow. Since redundancy of post-ontogenetic regulatory expression is essential for transitioning from development to adulthood, successful reproduction is inextricably linked with aging. Paradoxically, life and death become interdependent during this transition, resolving to a great extent Darwin's dilemma. This tradeoff alone demonstrates selection of aging provides a hidden individual benefit, i.e., reproductive success, thus supporting Darwins prediction.

A second, more subtle tradeoff occurs during morpholysis, when aging due to DSB/misrepair damage to the redundant regulatory mechanism is resisted by negative and positive selection. Recall that stochastic damage to the genic component of the regulatory mechanism creates pseudogenes. Walker [1] originally proposed that they would change initial conditions of the regulatory mechanism at the affected site, eroding its behavior from causally determinative to various degrees of chaotic, as the numbers of units become increasingly damaged. While this indeed would be expected to happen, and perhaps does at the later stages of life, initially damaged elements of any regulatory unit would more likely be purged by negative selection. Correspondingly, the remaining functional regulatory unit(s) in that cohort would be positively selected to sustain integrity of the regulatory mechanism. These complementary effects of negative and positive selection upon the eroding aging mechanism that oppose uncontrolled loss of master regulatory redundancy, paradoxically serves to achieve for as much as possible, the potential of life's full duration. However, while seemingly opposing aging, loss of redundancy is facilitated by positive selection of the remaining components of the aging mechanism, thus giving it individual benefit.

Both of these examples demonstrate that through tradeoff of survival for reproduction, aging has hidden, compensating and theory conforming individual benefit that accounts for its positive selection, thereby resolving Darwin's dilemma. Indeed, Darwin was correct in supporting his Theory regarding natural selecton of aging!

Finally, no benefit derives from the evolution of an "aging program" that is complementary to the DP since such benefit is fulfilled by its evolution in individual organisms as described herein. Thus, aging itself is simultaneously maladaptive and adaptive in individuals and populations, respectively. Although maladaptive for individuals, its evolution is justified by tradeoff for the individual benefit of reproduction and also because of its population benefit by the same process. Since the aging mechanism that is adaptive in individuals, is also adaptive for populations, the need for an esoteric mechanism of group selection for aging is negated.

These two tradeoffs that are essential for resolving Darwin's dilemma were inadvertently overlooked in the original version of "A mechanistic theory of development-aging continuity in humans and other mammals " [1] .

18. Conclusion:

The evolution of aging is missing from Darwin's classic book, "On the origin of species by means of natural selection", which it is focused upon survival and preservation of life in viable, reproductively competent organisms. A search of the literature reveals that he had greater interest and concern in the controversy over the creation of life, than in the process of its termination [66].

Accordingly, the applicability of Darwin's theory to aging's origins was questioned because of his claim that a trait must provide "individual benefit" as a requirement for

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natural selection. This constraint led to the generally accepted belief that *"Aging diminishes fitness, …*[so that it]*…could never evolve as an adaptive program* affecting individuals!" [35]. But the error in this opinion is that it views aging in isolation, without trade-offs. Viewing trade-off of survival as an essential element for successful reproduction makes the evolution of aging possible pursuant to Darwin's theory of natural selection.

According to Goldsmith [3] "Darwin's dilemma" has been a major constraint to every subsequent attempt to devise a scientific explanation for aging for nearly 150 years. Scientists have been forced to choose between believing that aging was an adaptation, a deliberate part of organism design, despite orthodox mechanics theory, and believing that it was not an adaptation …" This dichotomy has lead to a number of imaginative and opposing theories involving evolved programs and stochastic damage, respectively. However, there has been scientific consensus that aging is non-adaptive for individual organisms and adaptive for populations.

Thus, if a simple explanation for the evolution and individual benefit of aging were found, it would simultaneously resolve Darwin's dilemma, and eliminate the need to explain population benefit of aging in controversial methods such as "*group selection on a scale that goes beyond the theory of multilevel selection*" [35]. That simple process was described herein.

Previously, the difficulty in explaining the evolution of aging, derived from aging being taken as the starting point for research. To seek the cause of aging in old organisms *is* futile, because the process has already begun, thereby obscuring its origins. Logically, a cause will precede its effect. As an example, using human beings who begin to age at about 30 years old, or the end of the first decade of young adulthood, then its cause must occur before that age. From an evolutionary perspective, two important events occur during this time of life. First, the decade begins at upon completion of ontogenesis. Second, progeny who were born during parental adolescence are nurtured. Thus, reproduction begins and is completed during the period transcending development to morphostasis, preceding the onset of aging. The only possible way for this functional linkage to occur while maintaining integrity of the parental soma is through oversight by a developmental regulatory mechanism whose expression becomes redundant once the non-repeating stages of the DP end. Since regulatory redundancy leads to aging, its selection must involve a "tradeoff" of survival for reproduction. Since reproduction is of highest priority in evolution, this "tradeoff" for aging and certain death of individuals is positively selected and unquestionably reasonable. Thus, this is the first resolution of Darwin's dilemma.

The second resolution involves positive selection of remaining components of the aging regulatory mechanism as its damaged parts are purged by negative selection. Paradoxically, positive selection of the futile effort to salvage the regressive aging regulatory mechanism sustains order for as long as possible, consistent with the characteristic mortality rate defined by the Gompertz function.

Thus, Darwin was correct in his prediction that there is a theory conforming benefit of aging. In animals that nurture their young until independence, it is hidden within the "tradeoff" of survival for successful reproduction. Thus, the theory conforming hidden benefits of aging is two fold. They are assurance of successful reproduction through a time of offspring nurturing explicitly dependent upon a mechanism the must cause organismal aging, and selection of remaining redundant elements of the aging mechanism.

Finally, aging cannot be prevented because of the inevitable effect of DSB damage to initial conditions of the regulatory mechanism or more likely, loss of redundancy due to DSBs. Unless the genetic "backbone" actually exists and can be identified and stabilized against attack by DSBs or through creation of an improved repair mechanism (both of which seem fairly unlikely) the desire of programmed aging advocates to find the program will also be disappointed by epigenetic alteration of the regulatory sequence

throughout the body and the random occurrence of DSBs throughout it which makes the programmed concept of aging too simplistic.

The fountain of youth sought by dreamers of a simple key to understanding aging as the product of a program the intervention into which will lead to immortality, will find that indeed identifying the genetic component of the regulatory key to be relatively simple, but like the fabled German WWII wartime cipher machine, Enigma, interpretation of its overwhelming number of possible combinations due to cell and tissue specific epigenetic landscapes that shroud and protect it from explicit analysis will make it extremely more difficult if possible at all. On a more positive note, there might emerge among us, inciteful beings such as Alan Turing and his colleagues at other Bletchley Parks, [67] to develop innovative computer technology and programs at comparable Universities of Manchester to crack the operational code of the holistic developmental regulatory mechanism such as that which mystified the early embryologist John Bonner, and also Hans Driesch who hopelessly attributed it to vitalism and entelechy.

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