Review of: "On the Origin of Aging by Means of Natural Selection"

Josh Mitteldorf

Potential competing interests: I have written extensively with competing theories on these same topics. You have permission to sign my name to this review and unblind myself as reviewer to the author.

I apologize that the due date has come and I have not yet gotten to the end of this manuscript. If Dr Walker wishes to address the issues I've raised in a resubmission, I promise to read and comment on the remainder of the ms.

General Comments:

The thesis of this paper is that there is an inertia in the developmental program that carries on after development is complete and ultimately results in all the detrimental effects of aging. (Mikhail Blagosklonny has championed this perspective in the past, and he should be referenced more thoroughly.) This argument is a modernization of Williams's "antagonistic pleiotropy" theory. Williams imagined the genome to be static and unchanging through the course of a lifetime. Williams did not know in 1957 what we know now — that not just genetics but also epigenetics is subject to natural selection; that gene expression is tightly regulated, and that genes are routinely turned on in exactly the times and places where they are needed.

My principal objection, which I would like to see the author address, is that gene expression seems to be so well controlled by internal sensing of time and place that it stretches credibility to imagine that the body turns on genes during development and then can't turn them off again when they are no longer beneficial to the organism. This is usually explained in terms of a "selection shadow", but Dr Walker argues against the selection shadow, and I think he's right about this.

Another general comment on the scope of this ms: It is a mistake to consider human aging outside the context of other animals. It is unreasonable to think that humans evolved aging via a different mechanism from all other species, so we can certainly learn about evolution of human aging by looking at the animal kingdom in general. In particular, if a mechanism applies to humans but not to other mammals that age similarly, it is not a good candidate explanation for how human aging evolved. In particular, human children have an extensive period parental dependence, which plays an essential role in Dr Walker's theory. Does he want us to think that other animals which have much shorter periods of parental dependence (or none at all) have evolved aging on an entirely different basis from humans?

Bottom line: The ms is potentially worthy of publication, with ideas worth considering. However, it is rambling and prolix, hard to read because it's not clear how the various points he's trying to make relate to one another. The wide-ranging

introduction reads more like a screed than a scientific review. Before re-submission, I suggest that the ms be not just shortened but tightened, with clear definitions of terms like “reproductive fitness” and “force of natural selection” – terms for which he seems to have non-standard definitions. The ms also needs clear statements of a scaled-back list of points that he can substantiate.

My own work has been deeply critical not just of the standard theories of aging but of the methodology and assumptions of the “new synthesis” known as “neo-Darwinism” or “population genetics” or, less formally, the “selfish gene model”. I’ve tried to make it clear which premises of the theory I accept and which I refute. I suggest that Dr Walker would do his readers a service if he followed this practice as well — which postulates of the classic theory does he accept and which does he reject, and why?

In summary: I am inclined to be sympathetic to Dr Walker’s thesis because he and I are both critics of the mainstream theory. If I have a lot of trouble understanding Dr Walker’s thesis, I assume that his target audience of mainstream evolutionary biologists will discard the ms as unreadable.

Stylistic problems

The ms is hard to read. I can’t say that Dr Walker’s example is more egregious than the majority of academic authors’, but I suggest that the writing style does not support his thesis in a way that he would wish.

Diction examples:

“After age 30, there occurs a linear decline…” To mathematicians, the word “linear” has an exact meaning, which I don’t believe is Dr Walker’s intention in this statement. I think the word he wants is “monotonic”.

“Once parental physical development is completed and progeny sufficiently nurtured to make them independent, reproductive fitness is achieved.” This is an example of a sentence that suggests the author is using words in a way that departs from standard definitions. Individual “reproductive fitness” has a mathematical definition (=r) and it is a property of an entire life history. It does not change moment-to-moment in an individual’s life. (In my own writings, I have argued that this definition of reproductive fitness is not an accurate representation of the target of natural selection in the real world.)

“These changes correspond to the progression of aging, which can temporarily cease to allow reproductive fitness to be achieved.” By “cease to allow” does he mean “prevent”? By “progression of aging” does he mean anything other than “aging”? By “correspond” does he mean “that’s what aging is”? And the bigger question: What does he mean by “achieving reproductive fitness”? Does he simply mean “impaired fertility”?

“Survival and aging are not the same.” *Res ipsa loquitur*

“The molecular regulatory mechanism linking development to reproductive fitness will be described, and physico-chemical factors that degrade it as a cause of aging will also be discussed.” What is the referent of the word “it”? The literal meaning of the sentence suggests that physico-chemical factors degrade a cause of aging. I suspect that’s not what Dr Walker intended.

“Development and aging are continuous functions that are linked by an emergent property that facilitates fitness while subsequently causing aging to emerge and proceed from a non-aging stage of life.” The meaning of the word “emergent” is unclear in this context. “Facilitates” is not the right choice of word here — “contributes to fitness”? If we take the sentence literally, the subject is “Development and aging” and the predicate is “causing aging to emerge”. Even the conjunction “while” is inappropriate.

“aging begins upon attainment of reproductive fitness” ⇒ “aging begins at sexual maturity”. “Reproductive fitness” is used by evolutionary academics to describe a property of the life history, not of an individual at a given moment in time.

“The temporal relationships of reproduction and aging associated with the developmental process derive from primitive societies that evolved when human lifespan rarely exceeded 30 years.” It wasn’t the societies that evolved but the temporal relationship. “Human lifespan rarely exceeded 30 years” needs a footnote. A quick check suggests to me that at least ¼ of the population lived to 45.

This is just a small sample of the many times in which Dr Walker’s writing is less clear than this reader would wish.

What does the ms set out to prove? In Walker’s own words:

1. Aging is inextricably linked with reproductive curve.
2. NS does not inexorably decline as the result of waning fecundity throughout the reproductive lifespan, but rather changes in strength at various stages of life.
3. ***These changes correspond to the progression of aging, which can temporarily cease to allow reproductive fitness to be achieved.*** [not clear to me what this sentence means]
4. Aging is not multifactorial but has a single cause.
5. ***Development and aging are continuous functions that are linked by an emergent property that facilitates fitness while subsequently causing aging to emerge and proceed from a non-aging stage of life. [not clear what this means]***
6. ***The molecular regulatory mechanism linking development to reproductive fitness will be described, and physico-chemical factors that degrade it as a cause of aging will also be discussed.*** [This sentence is particularly opaque]
7. Finally, (1) DNA damage, specifically double-stranded breaks (DSB’s) linked to apoptosis, and (2) cellular aging will be described as contributing causes to ***decay of the ontogenetic emergent property*** [bad phrasing] which is the primary, single cause of aging in humans and other mammals that nurture their progeny unto independence.

To what extent does he convince us of these 7 claims?

(2)

“Giaimo and Truelsen [2] proposed that selection forces may at times be stronger later in life than earlier.” This statement seems to contradict everything I thought I knew. We should be offered at least (1) a definition of the “force of natural selection” and (2) a summary of their argument.

Though I have long thought it logically impossible that the force of natural selection might increase with age, I am grateful to Dr Walker for jogging my thinking on this point. What I understand as “the force of NS” is the Malthusian coefficient ***r*** calculated for the remaining lifespan. It is indeed true that, by this definition, the force of NS increases monotonically until the age of first reproduction. This is because the discounting factor in ***r*** is smaller the closer we get to reproduction. For animals and (especially) plants that have a steeply increasing reproductive curve, this may also be true later in life.

In humans, the mortality curve starts to climb around age 5 and reproductive maturity isn’t achieved until about age 12. Is this a counter-example to the well-accepted claim of Medawar that aging cannot in principle begin before puberty? If this is the point that Walker is trying to make he could be clearer about it.

[caption of fig 5] “Assuming that the force of NS is inversely correlated with mortality risk” do you mean “correlated with” or “proportional to”? In either case, why should we think that this is true? It is true within the context of the Medawar theory which Walker says he doesn’t believe.

“a plot of The Gompertz-Makeham law shows that there are three segments of the Makeham function that indicate increasing, decreasing and non-changing intervals of NS strength.”

Quibble: “*United States Life Tables, 2003”*The relevant mortality curve for Walker’s argument is the one from the era in which humans were evolving, not the very different curve in a post-industrial environment.

“aging causes NS to decline, not vice versa” By my Malthusian definition above, the mortality curve is an ingredient in ***r***, and ***r*** determines the force of NS at each moment in the life history. This is an interesting circularity. It means that Medawar’s theory predicts ***r*** to be evolved as curve that is self-consistent.

Mathematical side note: I spent an hour with a spreadsheet (since the equations are not integrable analytically) and discovered that this condition is not satisfied for simple, common cases. Based on this preliminary calculation, I believe the quantitative version of Medawar’s hypothesis is provably wrong. I'd be interested to collaborate with Dr Walker if he wishes to address this point in a future version of the ms.

(4)

Dr Walker’s thesis is that the diverse phenotypes of aging can all be explained by a single cause. This is a broad and provocative statement, that could only be supported by listing the diverse phenotypes and tracing each one to the proposed cause (extension of the developmental program past its “sell-by” date). I don't see this

(7)

Dr Walker asserts that DNA damage and telomere shortening (cellular senescence) are ultimately derived from termination of the developmental program. I haven't followed his argument to this effect, and I must admit that I am prejudiced against this statement at the outset.

“The current theory proposes that aging is not caused by random accumulation of DNA damage in contrast to Medawar’s

hypothesis.” Medawar's theory is understood today as “mutation accumulation”, though he never used that phrase. What the phrase means is that detrimental mutations appear in the germ line over evolutionary time. It is a common misconception that “mutation accumulation” refers to somatic mutation during the lifetime of a single organism.

I apologize that I didn't get further in this review. – JJM