Evolvability and Programmed Aging: A Reply to de Grey

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This letter is in response to the article *Plea for Rigour* by Aubrey de Grey.

Your article[1] criticizes me and my colleagues as having insufficient rigour in putting forth our arguments concerning the nature of aging and suggests that we are causing confusion and inhibiting research. We believe our approach is correct based on the preponderance of *current* scientific evidence and further that our activities are beneficial.

To briefly summarize the situation as seen from our point of view, there are *three* main schools of thought regarding the nature of aging in humans.

To people who are mainly knowledgeable about and concerned with human aging (most of the population including physicians, medical researchers, legislators, etc.) the overwhelming impression is that aging is the result of fundamental and unalterable deteriorative physical and chemical processes similar to those that cause aging in machinery or exterior paint. This concept leads naturally to the conclusion that anti-aging medicine is impossible and that anti-aging research is foolish and wasteful, a "chase after the fountain of youth." Journal articles are still published promoting generic degradation theories.

A second smaller group, much more knowledgeable about the life cycle characteristics of many non-human species, is very aware of the fact that life spans vary dramatically between even very similar species. The overwhelming impression here is that life span is as much a unique characteristic of a given species' design as any other design property. However, a core belief of this group is that the mechanics of evolution make it impossible for an organism to possess an evolved design feature that has an individually adverse net effect.

A number of different theories have been developed by this group to explain the multi-species observations while accommodating the core assumption. Some suggest[2] that the individually adverse effect of aging is negligible in the wild and that therefore species never evolved longer life spans or lost the capacity for a longer life. Other theorists[3] from this group criticized that idea and postulate that aging must have some compensating individually beneficial effect that is rigidly linked to the adverse aging effect thus creating a net individual benefit. ("Rigidly linked" means that it is impossible for organisms to evolve means for accomplishing the beneficial effect without incurring the adverse effect.) Efforts spanning many decades to find the supposed rigidly linked beneficial effect have so far failed. Without such demonstration, the argument is essentially circular: Our theory says it must be so therefore it is so. Many other

criticisms of both theory classes exist with, in our opinion, devastating cumulative effect. These theories also tend to be very pessimistic regarding anti-aging medicine. (Williams used the word "impossible" to describe prospects for medical intervention.)

A third group (ours) questions the core tenet of the second group and maintains that organisms can evolve design characteristics that have a net negative or neutral individual benefit if there is a compensating population benefit. Several different population benefits of a genetically limited or even regulated life span have been proposed. Some of us suggest that complex organisms including mammals have what are essentially suicide mechanisms designed to limit life span to a species-specific value, possibly a mechanism that can even adjust non-genetically to temporary or local conditions. In this view gradual aging in mammals is a subtler, more advanced life span control system than the biological suicide mechanisms seen in simpler species, and as such conveys additional benefit. Population benefit theories are not new and include group selection theories, the selfish gene theory, and various evolvability theories.

Population benefit theories of aging are generally more optimistic regarding medical intervention. If a complex suicide mechanism controls aging, its operation can probably be altered. Much of medicine is concerned with contravening or augmenting some aspect of normal or abnormal design.

Efforts to validate the population benefit concepts relative to the individual benefit concepts have involved work in several different areas:

1) Cataloging of observed conflicts with the individual benefit concept.

    a. Gradual senescence, (biological aging)
    b. Acute senescence, (biological suicide)
    c. Individually adverse human and animal behaviors including altruism and some mating behaviors
    d. Sexual reproduction
    e. Male puberty age in many species
    f. Many aspects of the inheritance system

2) Producing theories showing how *all* of these observed design features (including gradual aging selected for its deleterious effect) produce benefits (often multiple benefits) to populations and otherwise fit observations.

3) Analyzing inheritance mechanisms in order to refine understanding of how mutational changes propagate.

4) Exploring mechanisms for propagation of individually adverse designs.

5) Integrating observations that provide clues as to the detailed nature of aging (e.g. aging genes, progeria and Werner's syndrome, caloric restriction, species with negligible aging) into theories.

6) Exploring the possibility of new experiments specifically designed to provide additional detail on the nature of aging and distinguish between theories.

With regard to rigour, proponents of the theories that require individual benefit tend to ignore all the other discrepancies and typically deal only with gradual aging. This is easily rationalized. The other conflicts are outside the theorist's main area of expertise or interest. However, in my humble opinion, superior rigour should not be claimed if there are extensive unexplained discrepancies to one's core assumption.

I believe that your contention that our group is degrading research is also untrue. If all the people in group 3 disappeared the general situation would remain unchanged. Budding physicians, medical researchers, and people that fund research would still learn in Biology 101 that there are multiple different (group 2) theories of aging that attack each other, and still have inconsistencies, and that, freely translated, "biology doesn't know." All these people then happily go back to believing their intuitively obvious group 1 theories and the budget for aging research hovers somewhere well below the annual expenditures for chewing gum.

The situation borders on ludicrous. We have landed on the moon and sequenced the human genome but there is still no scientific agreement on even the nature of aging. The same arguments between the same three groups have been going on for nearly 150 years, a situation that has been allowed to continue only because of the almost universal perception that the subject is strictly academic.

So how do we avoid pushing the same rocks up the same hill for another 150 years? In my opinion what is needed is a "zero-base analysis" that re-evaluates *all* the assumptions in light of *all* the *current* scientific data. More particularly, there have been enormous advances in understanding the mechanics of inheritance since Darwin or even Medawar. These developments provide fascinating clues regarding the mechanisms whereby mutational changes are incorporated into an organism's design and suggest ways in which individually adverse design changes might propagate.

This letter is necessarily terse. My book[4] provides a much more comprehensive review of this subject.

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[1] deGrey, Aubrey, *Calorie restriction, post-reproductive lifespan and programmed aging: a plea for rigour*
[2] Medawar, 1952, and similar
[3] Williams, 1957; Kirkwood, Holliday, 1979, and similar
[4] Goldsmith, Theodore, The Evolution of Aging 2nd edition, October 2006, ISBN 0978870905