

# Calorie restriction, post-reproductive lifespan and programmed aging: a plea for rigour

Aubrey D.N.J. de Grey, Ph.D.

Methuselah Foundation

Email: aubrey@sens.org

## Abstract

All scientists are acutely aware of the profound challenge that they face when communicating scientific findings to non-scientists, especially when great uncertainty is involved and when the topic is of personal interest to the general public. Simplification of the issues – sometimes extending to a degree of oversimplification – is a sad but generally recognised necessity. It is not, however, a necessity when scientists communicate with each other, and when that happens the explanation may lie elsewhere: either in the speaker's vested interests or in overconfidence on the speaker's part in the extent to which he or she has grasped the topic under discussion. Both these explanations are serious allegations and must never be made without very good reason, not least because an alternative explanation is often the entirely legitimate preference for scientific "shorthand." However, when a general *tendency* towards oversimplification emerges within an expert community, not only in informal interactions but in learned publications, the field in question can suffer a loss of reputation for rigour, which may especially infect younger scientists joining that field (or contemplating joining it). I feel that this has occurred to a dangerous degree within biogerontology in respect of the way in which the effect of the environment on the rate of aging – whether that of an individual organism or of a lineage – is described. There are still important controversies in that area, to be sure, but I refer here strictly to issues concerning which a thorough consensus exists. In this essay I highlight some fundamental tenets of biogerontology that are frequently, and to my mind problematically, mis-stated by many in this field in their printed pronouncements. Greater precision on these points will, I believe, benefit biogerontology at many levels, avoiding confusion among biogerontologists, among other biologists, and among the general public.

## The role, or otherwise, of reproductive senescence in determining the rate of aging

It has been accepted for over half a century that the diminishing force of natural selection with age is the fundamental reason why aging has not been eliminated from the metazoan world over evolutionary time.<sup>1</sup> (Note that I refer here not to "the living world" – here, as throughout this essay, it is my goal to focus on areas where actual controversy is more-or-less absent, and to avoid topics that are the subject of active debate, such as the aging of various types of unicellular organism.) Natural selection requires procreation, so there is no doubt that a permanently sterile organism is, with the exception of possible social influences on its kin's reproductive success, evolutionarily identical to a dead organism. When we apply this principle to the evolution of lifespan, however, there is a potential for confusion. It is often – so often, in fact, that the naming of names would be gratuitous – stated that the loss of fertility at advanced age is the (or, at least, a principal) brake on evolution's impulse to postpone aging, since to do so would confer no benefit in terms of genes passed to future generations. This is so wrong that

acceptance of it can lead to all manner of collateral misunderstandings ranging across the whole of evolutionary biogerontology.

The error, of course, is in forgetting that evolution can modulate reproductive lifespan every bit as well as it can modulate total lifespan – indeed, that the latter positively depends on the former. The influence that environmental pressure (in the form of mortality from partly or wholly age-independent causes such as predation and hypothermia) exerts on the rate of aging over the course of generations is mediated by natural selection; it therefore operates directly on reproductive lifespan and only indirectly on total lifespan. In other words, the causality is the exact reverse of the interpretation I cite above. Aging affects reproductive functions and vital functions simultaneously, so evolution necessarily affects both simultaneously. The idea that evolution acts directly on total lifespan, but is impeded by an (unstated but implied) inability to affect reproductive lifespan, is totally and obviously incorrect – but it is the way the situation is all too often described, and hence all too often understood by the unsuspecting neophyte.

It is worth reflecting that this simple point does not rely on appeal to any particular biogerontological observation. The fact that hardly any species exhibit reproductive senescence at an age that an appreciable proportion of individuals attain in the wild reinforces the primacy of reproductive lifespan, but only reinforces it: such data are entirely dispensable to the argument just set out. Similarly, mechanistic considerations (the fact that reproduction is complex and resource-intensive, hence is naturally likely to fail before so many other systems fail that an organism dies) *can* be brought to bear to ramify the accepted theory of how longevity evolves, but need not be: in practice it may introduce complications and ostensible counterexamples that do more to confuse readers than to enlighten them.

Why, then, is this mistake so widely propagated in the literature – and especially in biogerontologists' public explanations of why aging exists? I do not know, and indeed there is no basis for generalising, but it seems to me that a combination of influences can be blamed. Firstly there is the temptation to get the basic concept across before the reader's or listener's attention drifts. I feel that this is misplaced, because, let's face it, the whole strategy of invoking reproductive senescence is usually a digression in such contexts. Secondly there is genuine superficiality in the speaker's grasp of evolutionary gerontology; and here I stress that I am not casting aspersions on my colleagues' intellect, but rather bemoaning the fact that evolutionary biology in general (and, thus, evolutionary gerontology in particular) has acquired a wholly inappropriate reputation for being terribly scary and hard to master. While evolutionary biology is undoubtedly a thriving and challenging field of research, tenets that are basic to that field are as easily grasped by aficionados of other areas of biology as with any other cross-disciplinary example. Yet, there is a depressing tendency for experimentalists to shy away from more than the most introductory concepts in this area. This is broadly harmless in most cases, but unfortunately for biogerontologists – especially high-profile ones – it results in their being called upon to opine authoritatively on issues that they have more-or-less deliberately failed to study deeply enough to give accurate responses even to quite basic questions.

### **The existence, or otherwise, of genes that accelerate aging**

I mentioned, in opening the preceding section, that the reason why aging exists has been very widely agreed for over half a century. It is well known in the field that the reason why aging exists was also, and with equal confidence, agreed for the previous half-century, but that this

was a very different reason. A paragraph of background for the non-specialist is nonetheless in order.

The originator of modern evolutionary biogerontology, in most people's opinion, was the Nobel-laureate immunologist Peter Medawar.<sup>1</sup> (A case can be made that his thesis was presaged by J.B.S. Haldane,<sup>2</sup> but I digress.) In 1952, Medawar noted that aging must be a side-effect of evolution rather than a selected product of it, simply because selection can only operate on a phenotype that distinguishes the evolutionary fitness (number of progeny and of remoter issue) of the carriers of a given gene (or genetic pathway) from that of its non-carriers – and does so sufficiently often that the consequent selective pressure for retention of that gene outweighs the pressure of random germ-line mutations. So few organisms in nature live long enough to exhibit age-related decline that this simply cannot constitute a basis for the existence of aging. Medawar proposed that, instead, aging exists in nature for just the same reason that aging exists in man-made structures and machines: it is the default, and genes are required to combat it, just as mechanics and their ilk are required to combat the aging of man-made objects. Medawar's insight overthrew a dogma that had initially been espoused in the late 19<sup>th</sup> century by the equally eminent biologist August Weismann.<sup>3</sup> In Weismann's interpretation, aging exists for the long-term benefit of the species: it is beneficial because purging of individuals that were selected in a bygone era sharpens the knife of selection between young individuals in the context of the contemporary, and often substantially different, environment, on average resulting in a population better suited to its environment than if old individuals had hung on. Weismann thus proposed that aging was an active process, wrought by intrinsic machinery present within our cells and organs.

Before proceeding, I must again stress that my focus here is on those concepts that fall within the core biogerontological consensus, and that I intend to steer well clear of the penumbra of less universally accepted tenets. Thus, in this context I shall not explore the refinements of Medawar's original insight that were rapidly forthcoming, starting with Williams's concept of antagonistic pleiotropy<sup>4</sup> and extending through the contributions of Hamilton,<sup>5</sup> Kirkwood<sup>6</sup> and others, the more recent of which still await universal acceptance. Rather, I shall restrict myself here to the fundamental question of whether Medawar or Weismann was basically right: whether there are or are not genes for aging.

The concept that genes and genetic pathways without which aging would not occur are present in our genome has been raised repeatedly since Medawar, and is currently enjoying (if that is the word) a particularly intense resurgence.<sup>7-10</sup> Now, I would be the last to argue that any tenet of science, no matter how universally held, is beyond challenge; but any such challenge must – indeed, must as its starting-point – directly address the main argument that has been adduced in rebutting similar challenges in the past. My experience of recent proposals of “programmed aging” is that this has not been done.

What, then, is this main argument – the keystone of the mainstream evolutionary gerontology paradigm? It is merely an offshoot of the logic I summarised in the previous section concerning reproductive senescence: that selection can only occur when there is a difference of phenotype, leading to a difference in reproductive success. Since gradual decline in performance with age happens by default, genes mediating such a decline would not actually be doing anything; hence they would mutate to oblivion.

The traditional counterexample to the above, which is too often dismissed for the wrong reason, is the clearly genetically based phenomenon of semelparity.<sup>11</sup> Semelparity – the rapid metabolic meltdown that ends the lives of a variety of organisms, the best-known of which is salmon – is most certainly mediated by genes, which therefore must be selected for retention. Many

commentators have tended to acknowledge that this is a counterexample to the rule that aging is not programmed, and to adopt the position that, well, that's OK, biological phenomena often have counterexamples and the utility of the general trend is not thereby diminished. But, in fact, it is by no means a counterexample, precisely because the very rapidity of semelparity is (presumably) what makes it valuable to such species. Rapid degeneration does not happen by default, so it must necessarily be mediated by genes in order to occur at all. For present purposes, it is in fact counterproductive to consider semelparity as a type of aging at all.

Contemporary revisitations of the concept that aging is programmed (i.e., that there are genes for it) vary widely in their details, being founded on a range of experimental and observational data. I shall not attempt here to critique any particular such case, because my point here is what they have in common – or, to be more precise, what they lack in common.

It is customary for undergraduate students in theoretical physics to be posed “relativity paradoxes” – situations in which the tenets of relativity are used as the basis for *reductio ad absurdum*, thereby ostensibly showing that the theory of relativity is incorrect. The task set the undergraduate is to identify the flaw in the logic presented, thereby “rescuing” the theory: the converse outcome – that the class, the lecturer and eventually the wider world abandons the theory – is not considered a plausible outcome. Similarly, the reason why the US patent office explicitly refuses applications for patents on perpetual motion machines is because on the one hand it has absolute confidence that such machines are impossible, while on the other hand it appreciates that the details of a specific design for such a (proposed) machine may obscure its unimplementability so thoroughly that an unacceptable expenditure of staff time would be required to identify the error.

It seems to me that there is one overwhelming reason why purported demonstrations that aging is programmed continue to emerge, and even to be published in the more respectable specialist journals: namely, that many in the field – including, apparently, those invited to evaluate such manuscripts' suitability for publication – are alarmingly prone to give such a manuscript the benefit of the doubt even when (as is typical) it does not even attempt to address the fundamental logic outlined above, the fact that genes can only survive across many generations if they actually do something. Unless a proposal that aging is programmed places front and centre a concrete description of how the organism in which “pro-aging” genes purportedly exist would be different if it lacked such genes, it is quite simply a waste of time to evaluate the proposal further.

This requirement is so straightforward that one must ask why it is so often overlooked. My only guess is that many biogerontologists tend temporarily to forget that it is not trivial – that is, that in the absence of pro-aging genes the organism would not simply be non-aging. I am decidedly reluctant to accept this guess, however, since the fact that aging is the default condition of a metazoan is so thoroughly instilled in the biogerontological consensus that it seems incredible that any expert would forget it. Yet, try as I may I can find no alternative for the incessant appearance in the literature of articles that propose the existence of genes for aging while making no attempt to address this core issue; following Holmes, I am thus forced by elimination of the impossible to accept the otherwise highly improbable as true.

### **Programmed modulation of aging**

The topics addressed so far in this essay are, in my view, examples of highly undesirable confusion that can and must be addressed as a matter of urgency in the interests of biogerontology's stature in the wider biological community, and so in the interests of the

quality of (to highlight just one important aspect) the students whom it attracts. However, I have left the most serious such case to last – and, lest I appear to be adopting too self-righteous a tone in this essay, I will confess without equivocation that I have myself been somewhat guilty in the past of the error that I now describe.<sup>12</sup> It concerns the treatment, both in the academic literature and in biogerontologists' pronouncements in the mainstream media, of the response that a wide range of organisms mount when wholly or partially deprived of nutrients, or when otherwise manipulated so as to bring about gene expression changes resembling the response to nutrient deprivation.

The discovery of *age-1*<sup>13</sup> and *daf-2*<sup>14</sup> was the defining basis for the emergence of biogerontology from the doldrums that it had for so long occupied, conferring upon it its rightful status as a major biological discipline. Whether its low reputation thitherto was truly justified remains controversial, not least because the main reason why so many biologists suddenly began to take it seriously was not so much that they saw the error of their prior ways but rather that aging had suddenly become accessible to the methods that those biologists were accustomed to employing in other areas. The assumption that a field in which those methods cannot (yet) be applied is somehow a second-class field is, in many people's eyes, unproven to say the least.

Be that as it may, biogerontologists rapidly responded to their new-found acceptability at the high table of biology by highlighting the importance of these discoveries within biogerontology as a whole, as they continue to do. It goes without saying that the arguments which experts in a given field use most frequently and energetically in educating their peers from other areas are those in which precision is of the highest priority, as regards both the quality of those peers' assimilation of key concepts and the confidence with which those peers conclude that the experts really know what they are talking about. I feel that the forms of words chosen by many of my colleagues in this area too often fall short of this ideal.

The detailed causal basis of the evolutionary pressure that preserves genes for “hunkering down” in response to shortage of nutrients is still the subject of intensive research, not least because competing hypotheses appear to make radically divergent predictions concerning how much human aging would be slowed by such means (or by pharmacologically tricking the body into a similar response). However, as in previous sections, the point I wish to make here does not rest on the adoption of one or another of these competing schools of thought. Rather, it arises from aspects of the essentially universally shared – but often downplayed – understanding of this phenomenon.

Specifically: there is no support whatever within evolutionary gerontology for the view that the extension of lifespan in response to nutrient deprivation constitutes a refutation of the Medawarian paradigm. The fact that certain genes are down-regulated in these circumstances, and correspondingly that artificial down-regulation of those genes (such as by the hypomorphic mutations discovered by the Johnson and Kenyon groups) results in a phenotype sharing some of the same features (including, of course, life extension), does not make those genes “genes for aging.” Rather, this is universally appreciated to be a case of antagonistic pleiotropy, the adventitious shortening of lifespan by the action of pathways that confer benefit during the earlier phases of life on which natural selection operates so much more powerfully than it does on late life. The precise nature of that antagonistic pleiotropy is unclear, in the sense that a variety of plausible alternatives have been proposed and may apply in certain cases; but that is irrelevant. What matters is that the existence of an effect of an early-life (or genetic) intervention on late-life metabolic and physiological performance has for 50 years been understood *not* to imply any direct evolutionary selection for that late-life consequence.

Lest the above comments appear too abstract, let me describe one example in a little more detail – while repeating that this example is given purely for illustration, rather than being a plank of my argument. One attractive hypothesis for why nutrient deprivation of so wide a range of species results in extension of their maximum lifespan is that, in the wild, famine relieves the organism of the urgency to reach fertility at as early an age as possible. When food is plentiful, individuals will contribute the most to the next generation if they reach fertility very young, since that maximises their chance of procreating before succumbing to age-independent mortality (such as predation). In a famine, by contrast, procreation itself may be impaired and, perhaps more importantly, survival of one's offspring to maturity is likely to be even more severely compromised. (This is just as relevant because the failure to produce grandchildren is ultimately no different in evolutionary terms than the failure to produce children.) Thus, the severely but sub-fatally starved organism is better off taking the time to grow more “carefully,” applying its various molecular and cellular quality control procedures more thoroughly than is possible when growth is breakneck, and thus achieving adulthood in a more pristine state. Since age-related mortality is simply the culmination of a progressive decline from the organism's peak condition at the end of development, it stands to reason that a higher-quality peak state will take longer to decline to the point at which the organism suffers terminal failure. Hence, life extension in response to early-life nutrient deprivation is purely a side-effect of the altered priorities early in life; or, to put it another way, the “pro-aging genes” whose down-regulation extends life are in fact merely “pro-growth” or “pro-early-fertility” genes. The actual benefit accruing to the species from the fact that, in famines of an appropriate duration and intensity, some organisms that grew slowly and carefully will survive and procreate successfully when they would not have done so otherwise is as negligible as Medawar pointed it out to be in the general case (i.e., irrespective of nutrient availability).

Am I making a mountain out of a mole hill here? Is the distinction between famine-induced programmed aging and aging resulting from famine-induced antagonistic pleiotropy a mere esotericism? Far from it, because here we are not in fact talking about aging itself, but the *acceleration* of aging. If the removal (or the appropriate degree of down-regulation) of such genes were believed to be a route to the total elimination of aging, one might reasonably be able to claim that it really doesn't much matter whether that would result in some deleterious early-life adjunct, because its biomedical recapitulation might very plausibly avoid that adjunct. But when we acknowledge that any such intervention would merely retard, rather than eliminate, the aging process we must be altogether more careful. Paradoxically, the suggestion that aging is programmed (and that the program is somehow tweaked by nutrient deprivation) actually *weakens* non-specialists' confidence that it can be appreciably postponed (let alone defeated) with foreseeable technology, even though that suggestion might simplistically be thought to support that conclusion.

To see this, consider what makes so many people inherently reluctant to accept that aging will ever fall fully within the purview of medical intervention. This attitude is plainly illogical, because it flatly contradicts the fact that the body is a machine (albeit an enormously complex one for which we do not have the plans), and thus that, like all machines, it ongoingly accumulates initially harmless but eventually function-compromising damage as an intrinsic side-effect of its normal operation. It is also illogical because of the absence of any basis for why aging should differ from conditions that medicine can indeed combat – or, for that matter, from conditions that medicine cannot yet combat very well but that it is generally expected to be able to combat in due course. In a nutshell, the non-specialist's view of aging is that it is basically magic: that there is some kind of elusive time bomb built into us, which will kill us

more-or-less on schedule even despite any success we might have in postponing the “symptoms” of aging.

Various aspects of the rhetoric all too often preferred by biogerontologists in their interactions with the public actively reinforce this mystical view of aging, and I find it incomprehensible that so many of my colleagues are oblivious to the effect that they are having in this regard. I refer in particular to two themes: the assertion that aging is not a disease,<sup>15</sup> and the assertion that a realistic (and desirable) goal of biogerontology is to postpone age-related debilitation and disease without similarly postponing death.<sup>16-17</sup> Both of these assertions elevate aging to a position of apparent inviolability, effectively denying that the principles we apply to the preservation of function of man-made machines can even in principle be applied to the human body.

The suggestion that aging is the result of genetic agency is a clear example of the same thing: the naïve listener will be strongly inclined to take away the message that aging is something never to be tackled by mere mortals. The biogerontologist may not expect this reaction, since the suggestion that just tweaking a few genes might greatly postpone aging surely makes life extension sound rather easy. But when we bear in mind the immense bias present among the general public<sup>18</sup> in favour of what I have termed the “pro-aging trance” – the resolute refusal of those who have made their peace with aging to rejoin the fight – it is easy to see that the natural reaction will in fact be pessimistic, along the lines of “Ah, well, that means we need to age, so any attempt to mess about with aging is sure to end in tears.” It is only by thoroughly demystifying aging – by systematically demolishing all opportunities to regard it as a phenomenon without counterparts in those realms in which human intervention is familiar – that we can banish the fatalism that so powerfully opposes our efforts to scale up research aimed at seriously postponing our oldest and most murderous remaining foe. Oversimplified characterisations of the mechanistic basis of aging can severely impede this critical task.

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