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The complexity of aging: Are some aging processes more equal than others?

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In his pleasantly provocative opinion paper, Aubrey de Grey's argues that (a) independent age-related deteriorative processes evolve to reach approximately equal importance for the aging process as a whole, but (b) this equality can be broken by “protagonistic pleiotropies”, i.e. when a process is contributing to more than one competing death causes. In particular, the fact that nDNA mutations are extremely efficient in killing by inducing cancer implies that these mutations should be irrelevant for non-cancer aging.

In my opinion, (a) independent processes may not necessarily attain equal importance because of different inherent susceptibility of the corresponding genes or gene networks to evolutionary change. However, once this is taken in consideration, a refined evolutionary argument does imply that in protected environment, continuing lifespan extension will eventually make any age-progressive degenerative process a significant contributor to aging and (b) protagonistic pleiotropies may be ineffective in making degenerative processes irrelevant for aging if multiple protective pathways are available to neutralize them.

Consider evolution of longevity as a process with monotonically increasing life span. This paradigm seems appropriate for humans with their history of steady longevity increase, and reflects a general incentive to increase longevity: longer living individuals can bear more offspring. Longevity increases via attenuating various causes of death, including deaths associated with aging processes. The latter implies improving the corresponding anti-aging pathways. Selective pressure for an ameliorative pathway to improve is proportional to the corresponding death share. Therefore, as soon as the pathway improves, selective pressure decreases, and improvement slows down, while other pathways are pressured to catch up. Thus pathogenicity of different aging (and non-aging) deadly processes tends to equalize.

However, a mere pressure for equality does not mean attaining equality. In reality, different causes obviously command very different shares of deaths. In part this is probably because, in addition to selective pressure, the rate of genetic change depends on the availability of appropriate mutants. Mutants counteracting some deadly processes may be much harder to come by (or to fix in population, or to weave into existing gene network, etc.) than equally efficient mutants for other, “softer”, processes. These evolutionary “hard” processes resist improvement and thus cause more deaths than the “soft” ones. For example, far more mice are dying from owl predation than from sarcopenia, apparently because it is more difficult to create an owl-proof mouse than a sarcopenia-free mouse, and not because selective pressure to avoid owls is weak.

Note that the above logic differs from Aubrey's idea that pathways tend to become equally significant via “modest degrading” of *over-performing* ameliorating pathways. Indeed,

degrading of pathways may be easier than improving them: inactivating mutations are readily available. However, there is no evolutionary reason for those over-performing pathways to exist, except cases of decreasing longevity, which are not as interesting. In conclusion, although there exists evolutionary pressure for making different deadly processes equal, it does not guarantee that a single process can not be responsible for a great majority of deaths in a species and/or that death shares of different processes vary a lot.

What the above logic does imply is that no deadly process will be completely eradicated by evolution, because the improvement of the corresponding counteracting pathway(s) stops once the process becomes a barely significant cause of death within a typical reproductive lifespan. However, as human lifespan increases via attenuation of currently most significant causes of death, any of those suppressed processes and most notably those that are highly progressive with age, can become quite significant. And if life expectancy keeps increasing further (especially if it increases *greatly*, as in Aubrey's SENS scenario), more aging processes are expected to emerge as significant causes of death/morbidity, potentially progressively complicating further life extension. This seems to imply that just by picking a deteriorative process that is highly progressive with age, one can be reasonably assured of its eventual significance for human aging.

A potential catch, however, is that a deteriorative process that one suspects to cause a particular age-related problem, may be subject to Aubrey's “protagonistic pleiotropy” restriction. i.e. if it causes some *other problem*(s) (e.g. cancer), serious enough to force evolution to keep the process at a level well below “barely significant” for the initially suspected problem, so that even greatly extended lifespan won't make the process an appreciable source of death/morbidity.

We argue that protagonistic pleiotropies are not necessarily as efficient in rendering deteriorative processes irrelevant for their “reasonably expected” endpoints. Indeed, usually there are more remedies (protective pathways) to the *other problem* than just attenuating the process in question. Then, according to our logic, evolution should balance the improvement of all the available protective pathways according to their “softness”, and there is no guarantee that attenuating the process in question will be the easiest target for improvement. Considering the DNA mutations/cancer example, we note that, in addition to the DNA maintenance pathway, there are many other anti-cancer pathways. Which path have evolution followed? An improvement of DNA maintenance quality cannot be arbitrary small, because it is driven by discrete genetic changes involving a complex system of multiple repair/detoxification pathways. Thus, theoretically, an individual may always be better off choosing to create/improve an alternative anti-cancer pathway (e.g. increase apoptosis) than to invest into DNA maintenance. Thus cancer may in fact impose little selective pressure on DNA maintenance. If so, DNA maintenance quality may be determined by (and thus be critical for) other processes, e.g., non-cancer aging or protecting the germ line. The truth probably lies somewhere in the middle, with nDNA mutations contributing to both cancer *and* non-cancer aging.

The above logical exercise does not prove anything, but it hopefully shows that pure logic is insufficient, and other approaches are needed to estimate the relative contributions of nDNA mutations to cancer and non-cancer forms of aging. One potential alternative approach is to use a sort of perturbation theory to analyze instances of documented increase of nDNA mutations. In such cases, the resulting *excesses* of cancer and non-cancer deaths should be *proportional* to the non-perturbed shares of *mutation-associated* cancer-related and non-cancer-related deaths, respectively. In this paradigm, Aubrey's protagonistic pleiotropy hypothesis predicts that an increase in mutational levels results in an increase of cancer deaths *only*.

This prediction indeed seems to be correct in the case of hereditary non-polyposis colorectal cancer, HNPCC, a disease associated with increased microsatellite instability. This disorder is an almost pure increase of cancers, implying that, according to the perturbation approach, microsatellite instability is unlikely to be involved in aging, at least in aging of tissues affected in HNPCC. However, other nDNA maintenance-related diseases that are probably associated with increased mutational levels result in mixed cancer-non-cancer symptoms. Some of the premature aging syndromes mentioned in Jan Hoeijmakers' opinion are a good example.

Perturbation analysis can also be done on human populations subject to radiation exposure. In atomic bomb survivors, mutations are indeed increased: lymphocyte chromosomal aberrations increase linearly with radiation dose up to 30% (~10× background) (Kodama et al., 2001). In this population, *both* cancer and non-cancer exposure-related excess mortalities increase linearly with the dose, with cancer mortality increasing three-fold faster than non-cancer deaths (Preston et al., 2003). In a more dramatic example, at the Semipalatinsk nuclear test site, non-cancer deaths actually *outnumbered* cancer deaths by *several fold* (Bauer et al., 2005). Although relative cancer/non-cancer risks in the two cases are different (probably due to different types of exposure), both show a significant number of non-cancer deaths. Thus nDNA damage apparently does not cause cancers *only*, in disaccord with the prediction of the protagonistic pleiotropy hypothesis.

Interpretation of radiation exposure or DNA maintenance-related disease data deserves great caution, however. Deaths/symptoms may be caused not by nDNA *mutations* but by non-mutant events such as double-stranded DNA breaks, and resulting stem cell depletion, though the prevalence of heart disease and stroke among a-bomb survivors is not easily explained by stem cell depletion. Furthermore, radiation-induced and DNA maintenance disease-associated mutations may not correctly represent real-life distribution of mutations both by tissue type and type of mutations.

A-bomb survivors offer another way of testing whether nDNA mutations are involved in aging. These relatively healthy people with high nDNA mutational level may help to estimate tolerable mutational loads in nDNA. Indeed, a large 10-fold increase of lymphocyte chromosomal aberrations (Kodama et al., 2001) is associated with only a modest excessive non-cancer death risk of 0.5 (Preston et al., 2003). Thus, lymphocyte chromosomal abnormalities are probably irrelevant to natural aging (indeed, since they are relatively benign even at high levels in radiation victims, they most likely are benign at much lower levels in old people). It would be of interest to determine if abnormalities are also abundant in other tissues. If so, then this would argue *against* the involvement of chromosomal aberrations in non-cancer aging in the respective tissues.

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