

Perspective

Adaptive Senectitude: The Prolongevity Effects of Aging

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In the past, it has been assumed that all the biological and medical changes that occur in old age are deleterious. It has therefore been concluded that treatment and prevention of such changes in old age should increase healthspan and delay death. However, accruing epidemiological and clinical trial evidence in older humans suggests that this is not the case. Some studies have shown that antioxidants and hormone supplements increase mortality, whereas high blood pressure, obesity, and metabolic syndrome are often associated with improved outcomes in very elderly people. Perhaps, some of these supposedly detrimental changes accompanying old age are in fact evolutionary adaptations to prolong life after reproduction in humans. Indeed, a form of reverse antagonistic pleiotropy or adaptive senectitude might be occurring. Some common biological and medical changes in old age might actually enhance longevity and represent novel targets for improving health in older people.

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THE biological processes that accompany aging are usually considered to be harmful, and most definitions of aging include negative terms such as “adverse,” “impaired,” “deterioration,” or “deleterious” (1). Yet interventions to reverse or prevent many of these biological processes have not delayed aging and, paradoxically, some reduce life span (2). Rather, it is becoming increasingly evident that some of these supposedly negative biological consequences of aging may actually be beneficial to health and longevity. Indeed, they may even represent evolutionary adaptations for increased longevity in humans. This hypothesis explains some of the many paradoxes of antiaging therapies and geriatric medicine and might lead to new therapeutic approaches for increasing healthspan and life span.

PARADOXES OF GERIATRIC THERAPEUTICS

Aging in humans is typically associated with increased oxidative stress (3), elevated blood pressure (4–5), increased prevalence of obesity (6–7) and metabolic syndrome (8), and a decline in circulating levels of sex and growth hormones (9–10). Because of our past acceptance that such biological aging changes are harmful, it has been assumed that reversing these changes should increase life expectancy. It is worth reevaluating whether this assumption has been borne out, now that we have accrued a considerable database of clinical trial and epidemiological evidence in older humans.

The free radical theory of aging was first postulated by Harman in 1956 (11). Because of the evidence of increased oxidative stress and oxidative injury with age (3), it was hoped that antioxidant supplements would delay aging. Unfortunately, extensive studies have not shown any longevity benefits with antioxidants, and for some, supplementation increased mortality (12). In a meta-analysis of antioxidant clinical trials, it was concluded that overall antioxidant supplements significantly increased mortality (relative risk [RR]: 1.05, 95% confidence interval: 1.02–1.08), including increased risk for the popular antiaging supplement, vitamin E (RR: 1.04, 95% confidence interval: 1.01–1.07) (12). Recently, a theory that is the exact opposite to the free radical theory has been published. This theory of Mitohormesis proposes that oxidative stress has beneficial hormetic effects for aging by activating pathways that improve mitochondrial function as well as those that increase endogenous antioxidant systems (13). Accordingly, oxidative stress in old age might increase longevity.

High blood pressure is common in old age, occurring in approximately 50%–60% of older people (4–5). It is well established that high blood pressure causes arterial disease and that antihypertensive therapy reduces the risk of vascular disease and reduces mortality (14). But some studies have shown that high blood pressure in very old people is associated with improved survival (15) and cognitive function (16–17). In addition, there have been signals in some clinical trials that antihypertensive therapy in very old people has either no effect (14) or even a negative impact on

mortality (18). Recently, the Hypertension in the Very Elderly Trial study concluded that antihypertensive therapy is effective in very old people (19), yet there are issues with this study (early stopping for apparent efficacy, lack of statistical significance for the predefined primary outcome of stroke, unusually low incidences of stroke and death despite recruitment mostly from China and Eastern Europe, and extremely low incidence of adverse drug reactions and serious adverse drug reactions) that we believe create some uncertainty about this conclusion.

What advantage could high blood pressure have in old age? Higher blood pressure in old age will increase blood flow and overcome any increased resistance caused by arteries that have become stenosed secondary to aging and exposure to vascular risk factors. Vascular aging with increased vascular resistance appears inevitable in older humans (20). Intensive blood pressure lowering in participants with established cerebrovascular disease reduces cerebral perfusion and risks progression of cerebral ischemia and cognitive impairment. Sufficiently high blood pressure appears to be crucial in maintaining adequate perfusion of deep subcortical areas of the brain in patients with cerebrovascular disease (17).

Another cardiovascular risk factor, obesity, has a paradoxical relationship with longevity in older people. Obesity and overweight are risk factors for many illnesses and increase in prevalence in old age. Between 30% and 50% of older people are overweight, and approximately 30% are obese (6–7). Yet some studies have shown that overweight and sometimes even obese older people have improved longevity and health, and the term “obesity paradox” has been coined to describe this relationship (6,21). The mortality rate in obese older participants compared with their normal weight peers has been reported to be reduced by 22% over 7.5 years (6), 50% over 4.9 years (7), and approximately 50%–56% over 6.9 years (22). Certainly, the recommended body mass index of 18.5–24.9 seems overly restrictive in older people (23). In addition, weight loss diets in older people may be detrimental to their health (24). It is plausible that extra body weight might provide additional energy stores required to help survive those serious illnesses that occur in older people. In fact, some studies have found that overweight and even obese older people have improved outcomes following serious illnesses, such as heart failure and hip fracture (25–26).

The prevalence of the metabolic syndrome and its components such as insulin resistance increases in old age. About 40% of older people fulfill the criteria for metabolic syndrome (8). Much of modern medical practice focuses on treating the various components of the metabolic syndrome at all ages in order to prevent cardiovascular disease (8,27). However, the metabolic syndrome can be associated with improved longevity in older people, and the term “reverse metabolic syndrome” has been coined to describe this paradox (28). In one study, insulin resistance was associated with a substantial reduction of mortality in participants with a mean age of 85 years (28). Moreover, experimental

animals with various genetic defects in the insulin/insulin receptor pathways have enhanced longevity (9,29). Thus, it has been suggested that insulin resistance induces a state of intracellular caloric restriction, perhaps replicating some of the longevity effects of caloric restriction (13).

There are marked reductions in many hormones in old age, including testosterone, estrogen, and growth hormone (9–10). Supplementation with estrogens and testosterone does not increase longevity and may have the opposite effect through increased risk of cancer and thrombosis (30–31). Thus, the age-related decline in sex hormones might be a way to reducing risk of some cancers and thrombosis in old people. Growth hormone declines with age yet growth hormone supplementation does not have any beneficial effects on aging, and there are significant adverse effects (32). On the other hand, many humans and animals with reduced growth hormone activity secondary to genetic variability or hypophysectomy have increased life expectancy (33–34).

Obviously, there are confounding issues such as comorbidity and survivor bias to consider. Nevertheless, there appears to be at least some evidence that aspects of advancing age that were thought to be harmful might actually be beneficial in very old people and that our attempts to reverse these might be harmful.

EVOLUTIONARY MECHANISMS

If some of the biological changes that occur in old age are in fact longevity enhancing, then the obvious question arises: “Do such changes represent evolutionary adaptations that function to prolong life in humans?” Most previous evolutionary theories consider aging and its biological correlates to be unfortunate consequences of selection operating more strongly earlier than later in life. Peter Medawar’s mutation accumulation theory (35) proposed that evolution has little opportunity to act in old age. Hence, until the advent of modern medicine, extrinsic mortality weeded out most individuals before they got to advanced old age, allowing genes with late-acting deleterious consequences to accumulate in the genome. Williams (36) took this a step further in his theory of antagonistic pleiotropy, suggesting that selection favors genes that are useful at a young age, in particular for reproduction, even if they are harmful in old age. Sex hormones are the classic example of antagonistic pleiotropy where high levels of sex hormones enhance reproduction at an early age but reduce survival in old age through cancers and vascular disease. Thomas Kirkwood’s disposable soma theory and related life-history theories of aging (37–39) propose that there is only a certain amount of resources available to any organism, which can be invested either in reproduction (the germ line) or in longevity (the soma). John Speakman (40) has questioned whether such a trade-off between germ line and soma is inevitable because resources are often not limiting. Rather, he proposes that body mass is critical and that large size buffers against extrinsic mortality

and promotes investment in smaller numbers of well-resourced offspring and slower rates of aging. Which environments and evolutionary pressures favor large body size and associated life-history traits is of course another matter and relates in part to classical r-K selection theory (41–42).

However, none of these theories addresses whether selection might actively favor traits that extend life beyond the reproductive period—even if these same traits would have deleterious effects earlier in life, as appears to be the case in humans for hypertension, obesity, metabolic syndrome, insulin resistance, sex hormone, and growth hormone deficiency. In its extreme form, this would represent the antithesis of antagonistic pleiotropy, the evolution of traits that favor old age over relative youth. If we were to speculate one step further, might it be plausible that the opposing influences of antagonistic pleiotropy and selection for traits favored late in life may result in an intermediate lifestage—postreproduction but pre-old age—in which the deleterious consequences of both sets of traits combine? It is certainly suggestive that the effects of oxidative damage, high blood pressure, obesity, and metabolic syndrome have their greatest impact on disease risk when manifest during middle age.

That selection can favor traits that extend life beyond reproduction was first proposed by Bill Hamilton in 1966 (43) in his now famous grandmother hypothesis (44). Ronald Lee (45–46) has recently developed a model showing that transfers of resources from one generation to the next can lead to selection for an extended postreproductive period in social species, confirming that there are indeed theoretical grounds for predicting the evolution of traits that favor an extended life beyond reproduction.

CONCLUSIONS

We hypothesize that some or many of the biological processes and medical changes that occur in old age might be beneficial in terms of longevity. Such changes might even represent evolutionary benevolence toward older people, an adaptive senectitude. If we discard the belief that everything that accompanies old age is deleterious and harmful, then our therapeutic attitude to older people will change. We may choose not to treat some conditions that are common in old age even though they are risk factors for disease in younger adults. It is highly speculative, but perhaps there is potential to investigate the effects of enhancing rather than reversing some of those processes that we traditionally considered to cause aging and to be harmful in old age.

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