COMMENTS

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Aging: Predictions of a New Perspective on Old Data

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There may be very few, if any, topics that have more interest for scientists and lay public alike than slowing aging and extending life expectancy (LE). Many experimental methods have been studied, primarily in animal models. Significant and encouraging results have been achieved, most notably in mice, both with caloric restriction (1) and other methods (2–4). In a recent overview of aging, numerous aspects of interrelated physiological processes have been analyzed and integrated by Denham Harman, the originator of the free radical theory (2). In addition, as recently confirmed by Bliznakov (5), Harman has made other major contributions, including his warning regarding peroxidation (6) and the great danger of life-shortening mitochondrial aging (7). One of the purposes of his analysis was to elucidate the theory of factors influencing life span. Curves used in gerontology to exhibit effects on death rates, etc, have arisen from observations made on the populations of interest. The human survival curves studied by Harman were of primarily Euro-American nations and exhibited more than half of the deaths between ages 55 and 85 with only a few percent living to age 90 and a maximum observed life span of 122. It is of interest later that, for over 200 years, the general features of these curves have shown upward trends in LE because of a number of factors but little change in pattern of rapid aging and death above age 75 (see Fig. 1 in reference 2). In what follows, as the main thrust, we pursue a somewhat different approach developed by Ely (8–14):

Clearly, some animals simply reproduce and die and, thus, have very low ratios of LE to age of first estrus (AFE). We will be interested here in this dimensionless ratio that we define as R = (LE/AFE). If, as humans, we expect to rise as much as possible above this most primitive animal requirement to reproduce and die, our R must also rise as much as possible. Thus, starting with the ~4000 non-human mammals, we seek to select for study those that have a high R. We use the LE at AFE (instead of at birth) simply to avoid effects of large and variable mortalities at neonatal and early ages that prevail in many species. The theory suggests that in the relative safety of domesticated life, the R of protected mammals can and is likely to rise because (i) there is no longer a strong selection (by predators) against downward mutations of AFE; (ii) in the modern era, animal husbandry may deliberately enhance the downward drift of AFE in many species by selective breeding and nutritional advances; (iii) LE can rise because it is no longer strongly dependent upon agility, speed, strength, and/or other physical qualities, etc. Thus, scattered among the many normal mammals that have had long domestication by humans, we did find a number that constitute a group with values of R ~25 or more. However, for humans, using LE ≈ 88 years and AFE ≈ 11 yields a much lower value, R ~ 8. We proceed now to see what can be learned via the new theory from these data regarding the retardation of aging and the increase of LE by conventional means in humans (even including those alive today). It seems reasonable to expect that there is something different about the high R group mammals that might benefit humans. First, we consider whether the human R value might be found within the high R group.

Using Poisson statistics and R = 25 as an approximation for the high R group mean (m), we estimate the probability that R = 8 (r) could be in the same group:

$$P(r,m) = [e^{**}(-m)][m^{**}r]/r!;$$

$$P(8,25) = [e^{**}(-25)][25^{**}8]/8! = 0.00005 \text{ (i.e., } P < 0.0001).$$

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Thus, it appears extremely improbable that the human R value could be in the high R group. Is there a controllable variable that might be changed to make humans more like the high R group? Could this enable humans to shift by conventional means to the high-R mammal aging curves (much slower aging and higher LE)? If so how?

The Essential Nutrient Theory (ENT)

ENT, as we hereinafter call Ely's new theory, offers a surprisingly simple solution for the question just posed above. A clue is that our high-R mammals synthesize ascorbic acid in large amounts (circa 10 g/day per 70 kg of body weight) and never have scurvy until very late in life (i.e., >20 AFE). Our theory suggests a most common cause of death in humans has always been this fatal nutritional deficiency disease (with or without other disorders), especially in winter, high latitudes, migrations, wars, famines, etc. Nutrient optimization characterizes the success of high-R mammals in contrast with the nutritional failure represented by the low R of humans. This theory, developed from many animal studies (8–14), purports to show the greatest contribution to human life extension is mediated by optimizing internal levels of all essential nutrients. In human aging, in addition to visible surface signs such as osteoporosis and wrinkling of skin, all connective tissue throughout the body exhibits loss of both flexibility and elasticity. At eight times AFE, most humans (R = 8) are extremely aged in appearance because of chronic undiagnosed scurvy. This supports the concept that "aging is scurvy". In contrast, high R (>20) mammals such as the horse are youthful in appearance at eight times AFE and are not even middle-aged. Mammalian aging is characterized at the microscopic level by cross-linking and loss of solubility of collagen and elastin. The deterioration impedes the flow of oxygen and metabolites in organs and systems, causing progressive dysfunction throughout the body, accelerating loss of nonrenewable cells, etc, increasing susceptibility to all disease, and death itself. These same symptoms have long been observed in scurvy. The ease of its early reversal by ascorbic acid (AA) was demonstrated after AA isolation in 1927; this was literally a reversal of aging in the affected tissues. There are numerous physiological and biochemical processes, including aging, in which AA has a dominant role. One of these, called the pentose pathway or, alternatively, the hexose monophosphate shunt, performs a number of vital functions, including production of ribose and, as discussed in another paragraph below, these functions are strongly dependent upon AA.

Maintenance of Youthful Flexibility and Elasticity

Maintenance of youthful flexibility and elasticity are necessary for (i) the heart and the arteries to provide maximum ejection fraction with minimum effort and back pressure; (ii) pulmonary efficiency; and (iii) leukocyte deformations in diapedesis and phagocytosis, etc. There is a large daily need of AA for the hydroxylation reactions necessary for synthesis of new connective tissue to maintain these youthful characteristics (15, p. 92). Ascorbic acid is often called "Vitamin C" (although it is not a vitamin); vitamins are only needed in minute amounts to achieve optimum health. According to ENT, almost every human on earth fails to satisfy the multi-gram daily AA need (and possibly others), primarily because of practical difficulties in dosing discussed later.

Hexose Monophosphate Shunt Rate

The hexose monophosphate shunt rate was discovered to be strongly proportional to intracellular AA concentration in 1971 (16). Ely was able to extend this finding theoretically to make predictions that were supported experimentally in aging, birth defects, cancer, infectious diseases, etc. (8–14, 17). These greatly broadened the scope of ENT, in addition to the central interest of AA in aging emphasized here. For example, in support of cell-mediated immune response, the hexose monophosphate shunt supplies: (i) ribose needed for mitosis in expanding a clone of lymphocytes; and (ii) hydrogen peroxide required for phagocytic activity. If AA is low, as is common in the aging, the shunt rate and cell-mediated immunity fall. Then, infectious diseases, cancer, and mortality from all causes rise. This failing cell-mediated immune response and proliferation of disease constitute another hallmark of aging (and provide more support for the concept "aging is scurvy").

Effects of Hyperglycemia

The dominant effects of hyperglycemia in human aging and many other disorders (as demonstrated by Ely and coworkers; 12, 13) have long been evident but widely ignored and misunderstood, impeding progress in the field. In the paragraph above, ENT demonstrated an expansion (caused by low AA) of susceptibility to numerous disorders in many groups, especially the elderly. A further expansion into much larger groups caused by hyperglycemia causing low intracellular AA (explained below) was predicted by ENT and conveyed to Pauling in 1972. This broadening of ENT explained to him that the successes of AA in clinical trials against colds and cancer were much less than expected because of the high blood glucose levels in developed nations (8–14, 17–22). This broadened threat to human health and longevity is mediated by the inability (in hyperglycemia) to raise intracellular AA because glucose competitively inhibits the insulin-mediated active transport of AA against the high gradient (AA in cells is ~50 times the plasma level in health (23, p.78)). Thus, according to ENT, a mechanism by which caloric restriction extends lifespan in animals is mediated via AA elevation (through lower blood sugar). A principal cause of human cardiovascular disease in affluent nations is hyperglycemia, which reduces AA to scorbutic levels in vascular intimal cells. Glycation of proteins is implicated in cross-linking and adverse aging changes in many tissues including the lens, etc. Glycation is antagonized by hypoglycemia and, in a dose-dependent manner, by increasing AA (slowing aging and improving immunity)

as explained by ENT. A strong world-wide correlation of cancer incidence with sugar consumption exists (24, 25). In the United States alone, an estimated 60 million people now living will present with clinical cancer in their lifetimes. ENT predicts this one-fourth of the population (!) may be identified approximately as the older half of the upper half by sugar consumption. Support for this prediction can be seen in the following three U.S. statistics: (i) we have 30 times more cancer above age 55 than below 35; (ii) the 2-hr value on glucose tolerance tests rises 10% per decade of age (10, 11); and (iii) until the 1900s, the low-sugar, whole-grain, unrefined diet produced 2-hr postprandial blood glucose values of 50–90 mg/dl (they are still seen where the primitive diet prevails (see Table 1 in reference 26) but were approximately half the glycemic levels typical of affluence today (11).

Implementation of ENT

Thus, implementation of ENT gives rise naturally to use of controlled hypoglycemia concurrent with AA. An unrefined diet, moderate caloric restriction (by titration to constant fat-fold) and physical activity provide glycemic control that maximizes intracellular AA (and cell-mediated immunity) but avoids the adverse effects of excessive hypoglycemia. The normal daily requirements for AA in most species of mammals have been shown by Stone (27, p. 53) and Pauling (15, p. 99) to be well-approximated by 50 mg/kg body weight. When in stress, these needs are far higher (~100 fold!; 23, p.109). In the 4000 mammals that can synthesize AA (i.e., we often call normal mammals), their variations in need are automatically met over a wide range of conditions because of the adaptability and efficiency of a global endocrine synchrony. Unfortunately, the human as a nonsynthesizing mammal does not have this synchrony but is burdened with the same daily AA requirements. Thus, humans have the lifelong need (not an option!) to supplement this essential nutrient. In nonsupplementing humans, one gram is a commonly observed body content and, without stress, this AA is catabolized and lost at about 30 mg/day. If no AA is obtained by such a human after the body pool falls below one gram, death usually occurs in ~30 days. Circa 1930 AD, AA was first made available by commercial synthesis. Before this, the prevailing condition for humans was to exist in ignorance (and peril) of scurvy on the accidental AA content of their diets. Historically, even to the present time, this has been a principal cause of aging and death. However, the amount required for humans is unavoidably greater than the normal mammal need. In humans, simply providing the daily need of ~50 mg/kg body weight as one or a small number of doses (oral or other) on a fixed schedule will not replicate the sufficiency seen in normal mammals. Such dosing will result in a major part (or most) of the AA being lost by excessive spilling in the urine. This spilling would likely be far above the continuous spilling that occurs in normal mammals. Even when not in stress, normal (AA synthesizing) mammals such as the dog have plasma AA levels higher than the renal threshold and void AA in the urine ~1 g/day. The high R value of 25 in synthesizing animals is posed herein as a goal possibly achievable in humans by an unrefined diet and suitable supplementation of AA, other essential nutrients, and a variety of agents including phytochemicals, etc.

Ubiquinone (coenzyme Q10), as well as AA, has been shown to counter the effects of aging on the immune system (3, 28). The decline of endogenous synthesis of ubiquinone in mammals with age can result in mitochondrial aging (7) and irreversible shortening of life. Bliznakov has shown that supplementation of ubiquinone significantly extends life in the mouse (3). Animals with optimal ubiquinone, via synthesis and supplementation, are more agile, have a more youthful appearance, and are more resistant to diseases such as cancer and viral infections (3). Thus, ENT predicts that optimal AA and ubiquinone not only lengthen life but also prolong the years of high-quality functioning.

Details of AA dosing (involving increased need for vitamin E, various ascorbates, routes, sustained release, etc) and ubiquinone are not yet optimized but still in flux (28–31). As an example, heightened clearance due to elevated AA (as hepatic electron donor), complicates dosing of and intoxication by xenobiotics. As a second example, in advanced age, and in life extension, AA elevation is necessary for maintenance or restoration of the parenchymal mass of the thymus and, hence, cell mediated immunity (32, 33). For dietary guidance on general principles and food specifics, many excellent texts exist (i.e., 34–36). The all-important renewal of structural proteins in life extension, according to ENT, includes the AA/lysine therapy originated by Pauling for heart disease (37, 38); regarding lysine oxidizability caveat, see p. 10 in Harman (2). Finally, we have in preparation for this journal an article on life extension principles, including dietary modification using oxygen radical absorbance capacity (ORAC).

Conclusions

ENT involves a valid direct application of animal data to human populations, which usually is not possible. It predicts that humans now alive can shift themselves, by conventional means, to an entirely different family of survival curves than those discussed by Harman in his detailed studies. In fact, ENT suggests that (i) humans on the new survival curves can be healthy and active in the same age span (from 50 years to over 100) in which they rapidly age and die in the world today; and (ii) human maximum lifespans greater than 150 years are consistent with the animal data. Despite the extreme differences between the two families of survival curves described by Ely and Harman, there is no disagreement between the conclusions of their two theories. Only the conditions of the populations are different. On the historic survival curves discussed by Harman (2), intakes of essential nutrients have been almost never optimal and seldom adequate. On the survival curves described by ENT, the intakes of AA, ubiquinone, and other essential nutrients

are required to range from adequate to optimal, depending on which curve in the family is considered, and are predicted to result in slower aging and a longer, higher quality life.

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