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Is There an Antiaging Medicine?

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In spite of considerable hype to the contrary, there is no convincing evidence that currently existing so-called "antiaging" remedies promoted by a variety of companies and other organizations can slow aging or increase longevity in humans. Nevertheless, a variety of experiments with laboratory animals indicate that aging rates and life expectancy can be altered. Research going back to the 1930s has shown that caloric restriction (also called dietary restriction) extends life expectancy by 30–40% in experimental animals, presumably at least partially by delaying the occurrence of age-dependent diseases. Mutations that decrease production of insulin growth factor I in laboratory mammals, and those that decrease insulin-like signaling in nematodes and fruit flies, have increased life expectancy as well. Other general strategies that appear promising include interventions that reduce oxidative stress and/or increase resistance to stress; hormone and cell replacement therapies may also have value in dealing with specific age-related pathologies. This article reports the findings of a consensus workshop that discussed what is known about existing and future interventions to slow, stop, or reverse aging in animals, and how these might be applied to humans through future research.

IT is reasonable to assume that slowing down human aging would delay the onset of a wide variety of age-related diseases, significantly increasing both health and longevity. However, as yet there is no convincing evidence that the administration of any specific compound, natural or artificial, can globally slow aging in people, or even in mice or rats. Claims to the contrary (e.g., that a specific hormonal or vitamin preparation can slow down aging) are not based on evidence. This report is based on a closed consensus workshop modeled after the National Institutes of Health Consensus Workshops. The purpose of the workshop was to discuss what is known about existing and possible future interventions that can slow, stop, or reverse aging in humans and how to promote this area of scientific research and medical practice.

What Is Antiaging Medicine?

Simply defined, "antiaging" medicine is any intervention that delays the development of age-dependent pathology and other adverse age-related changes that are not officially listed as diseases. False claims and bogus remedies for treating old age flood the marketplace, with no convincing evidence that administration of any specific compound, natural or artificial, can globally slow aging in people. Yet, not everything we hear about antiaging medicine is hype. Although the question remains open, the present state of knowledge is somewhat encouraging, based on results with laboratory animals.

Caloric Restriction

Extensive research on caloric restriction or dietary restriction has clearly shown that it is possible to retard the rate of aging and also extend both the life expectancy and maximum life span of animals. Weindruch and Walford summarized early research in this field (1). Subsequent studies have served to confirm and extend these findings, and to suggest possible mechanisms by which caloric restriction may alter biological aging (2–5). Caloric restriction extends life expectancy by 30% to 40% if initiated in early adulthood, and by about 20% if initiated in early middle age. As long as a diet maintains adequate content of essential nutrients, it is not a "poor" diet, but a low-calorie,

healthy diet. Presumably, caloric restriction slows down the rate of aging at the same time as it delays the occurrence of a wide range of age-dependent diseases and disabilities, such as cancer, immune senescence, cognitive decline, loss of muscle strength, and cataracts; it also reduces oxidative stress, and the damage it causes.

Genetic Manipulation

At least 15 different genetic manipulations induce life extension in organisms such as yeast, fruit flies, nematodes, and mice. Although many of these genes have been identified, it is not always obvious how the proteins coded by these genes are involved in the regulation of longevity. However, there are similarities between the longevity genes identified in mice and those identified in invertebrates. For example, growth hormone induces the production of insulin-like growth factor I (IGF-I) in mammals. Mutations that decrease production, either of growth hormone or its receptor in mice, increase life expectancy, as do mutations that decrease insulin-like signaling in nematodes and fruit flies. Thus, insulin and/or the IGF-I signaling pathway appear to be involved in longevity determination in a wide range of phylogenetically distant animal species (6). The results reported recently by Flurkey and colleagues (7) suggest that growth hormone deficiency also delays age-dependent collagen cross-linking and several age-sensitive indices of immune system status. This demonstrates that a single gene can regulate life expectancy and the timing of both cellular and extracellular senescence in a mammal.

Antioxidant Intervention and Resistance to Stress

The relevance of a stress such as production of reactive oxygen species to life expectancy, or to the rate of aging, is not known. Some epidemiological studies have suggested that dietary supplementation with vitamin E reduces the risk of cancer (8) and cardiovascular disease (9–11), but such observations are not universal (12). Furthermore, the longevity-extending potential of vitamin E in animal studies remains equivocal (13). McCall and Frei (14) have concluded in a review that "except for supplemental vitamin E, and possibly vitamin C, being able to significantly lower lipid oxidative damage in both smokers and nonsmokers, the current evidence is insufficient to conclude that antioxidant vitamin supplementation materially reduces oxidative damage in humans." The only robust finding that a pharmacological antioxidant can extend longevity in an animal model system is the report of Melov and colleagues (15) that EUK-134, a compound with both catalase and superoxide dismutase activities, significantly extends longevity in nematodes.

Hormone Replacement Therapy

The circulating levels of growth hormone, testosterone, estrogen, dehydroepiandrosterone (DHEA), and other hormones decrease with age. However, the question of whether melatonin levels also decrease with age is controversial (16). Although some hormone replacement strategies have been shown in clinical trials to modify some of the physiological attributes associated with aging, negative side effects occur frequently with those interventions shown to have some benefit, such as growth hormone. Negative side effects occur less frequently with interventions for which evidence of benefit is either absent or equivocal, such as DHEA. Although the epidemiological data are overwhelmingly positive regarding some health benefits of estrogen replacement therapy, a recent study has raised a concern about ovarian cancer after long-term use (17). In another example, Anisomov and colleagues (18) reported that melatonin supplementation increases the mean life expectancy of mice by approximately 5%. However, they also found that spontaneous tumor incidence increased in the melatonin-treated mice. Thus, clinical trials are needed to determine whether long-term hormone supplementation is both efficacious and safe in humans.

Estrogen Replacement Therapy

Estrogen replacement therapy (ERT) represents a special case of hormone replacement therapy and deserves particular attention here because of its long clinical history and apparent record of success in increasing the quality of life in postmenopausal women. Estrogen is particularly recommended for the prevention of osteoporosis, but it may also reduce the risk of dementia (19) and cardiovascular disease (20–23). The incidence of cardiovascular disease in women is negligible before menopause and increases dramatically thereafter. Some epidemiological data have suggested that ERT reduces the occurrence of coronary artery disease, and possibly cerebrovascular disease, by 25% to 50% in treated women compared with non-users (24). These findings are supported by evidence that estrogen has a beneficial effect on cholesterol metabolism and deposition, contributing to the inhibition of atherosclerotic plaque formation in arterial walls. It has been estimated that favorable changes in plasma lipids may account for approximately 25% of the cardioprotective effect of estrogen. The influence of estrogen on carbohydrate metabolism, atheroma formation, and cardiovascular hemodynamics may also play an integral role in the overall beneficial effect of estrogen. Animal and human studies have shown that the administration of estrogen leads to a restoration of endothelial function, an increase in cardiac output, an increase in arterial flow velocity, a decrease in vascular resistance, and a decrease in systolic and diastolic blood pressure (25). However, the conclusion that estrogen protects postmenopausal women against cardiovascular disease is now being questioned, based mainly on experiments examining secondary prevention in women with preexisting heart disease (26).

ERT has been called the first true antiaging therapy. However, no results have yet been reported of randomized studies that compare effects of ERT with placebos, beginning at the menopausal transition, in women with no known preexisting coronary heart disease or dementia.

The Growth Hormone Paradox

It has been well documented that circulating levels of growth hormone (GH) drop with increasing age (27–29). It has also been shown that GH replacement in adults with pituitary disease and GH deficiency has beneficial effects on body composition, reducing fat and increasing lean body mass, muscle strength, and bone mass (30–33). Rudman and colleagues (34) investigated whether GH injections in older

men would restore muscle mass typical of younger men. They injected GH three times a week into 12 men over a period of 6 months and looked for changes in body composition and IGF-I levels. They found that IGF-I levels did rise and that lean body mass increased while fat mass decreased, suggesting that GH injections did reverse the changes in body composition that were due to age and deconditioning. This report encouraged the use of growth hormone as an antiaging intervention.

Recent data obtained with mice suggest that lifelong overproduction of GH reduces longevity in mice (35), whereas underproduction or an inability to respond to GH increases it (36–37). Transgenic mice overexpressing GH exhibit severe kidney lesions and increased incidence of neoplasms, and overproduction of GH in adult humans leads to a condition known as acromegaly, which is characterized by excessive growth of certain organs and tissues (especially bone), but also premature heart and lung failure. Thus, efforts to restore circulating GH to youthful levels in older individuals may be misguided.

Furthermore, the evidence from both nematodes and fruit flies suggests that decreased activity of the insulin-like signaling pathway is associated with increased life expectancy, rather than the reverse. Thus, further research is needed before the GH supplementation in humans encouraged by many "antiaging" clinicians can be considered either safe or useful for long-term intervention.

Telomeres and Telomerase

The discovery that inserting and expressing the human gene for telomerase in human fibroblasts and retinal pigment epithelial cells markedly increases the proliferative potential of these cells (38) led to some undeserved optimism about future mortality rates. Although there are theoretical reasons for believing that there may be some tissues in which proliferative failure contributes to the declining physiology associated with aging, those tissues have yet to be unequivocally identified. Experiments with mice deficient in telomerase activity have shown that the absence of telomerase does lead to premature pathology in the form of increased skin lesions and genetic instability and decreased resistance to stress (39). However, because most mouse cells normally contain telomerase activity and most human cells do not, Shay and Wright (40) point out that understanding this difference "will be essential for designing and interpreting experiments that investigate how replicative senescence, telomeres and telomerase are involved in aging and cancer."

A premature telomere-based replicative block occurs in cells from patients with premature aging syndromes such as Werner's Syndrome and progeria. This observation suggests that replicative senescence, possibly as a result of increased cell turnover caused by the primary molecular defect, may contribute to some of the human aging phenotypes that are seen in these patients and in normal aging. The advances in our understanding of the evolutionary forces that produce aging strongly argue that replicative aging of cells would be only one of many different processes that contribute to aging. Although it is an important area of research to pursue, there is an insufficient basis at present for claiming that preventing telomere shortening would influence any aspect of aging. Telomerase deficiency in humans does lead to premature skin lesions (41), but this does not mean that patients with dyskeratosis congenita are aging prematurely.

Stem Cells and Cell Replacement Therapy

Gene manipulations possible in laboratory animals appear to have limited potential for direct application in humans, although they do provide insight into important biological factors in longevity determination in model systems. In contrast, the potential of cell replacement therapy in reversing some of the adverse effects of aging appears to be substantial. Aging is accompanied by some loss of tissue function, which is at least partially due to either the age-related loss of cells from the tissue or an increased proportion of dysfunctional cells. One example is the loss of specific types of neurons, which causes a variety of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. Until the causes of this neuronal loss can be identified and prevented, cell replacement appears to be a theoretical alternative. Gage has reviewed the current status of, and the potential for, use of stem cells for cell replacement therapy in the central nervous system (42). Preliminary results using fetal stem cells to restore function to paralyzed rat limbs have recently been reported (43).

The recent isolation of nearly totipotent cells, such as human embryonic stem (ES) cells, offers an even greater range of opportunities (44). These cells express telomerase and appear to maintain an immortal phenotype even after extended culture in vitro. Cells and tissues derived from such cultures may provide the unique advantage of possessing a large replicative capacity and broad differentiation potential. An example of the utility of this approach is that myocardial precursors derived from mouse ES cells appear to graft into mature myocardium, apparently forming gap junctions with the neighboring myocardial cells and beating in synchrony (45). Such strategies for transplantation in the heart may eventually lead to novel therapies for arrhythmias and even the restoration of heart function following ischemia or heart failure. More significantly, the replicative immortality and undifferentiated state of human ES cells may lead to targeted genetic modifications and subsequent differentiation into many medically relevant cell types.

However, it is important to note that formidable hurdles are yet to be overcome (46). First, cells derived from established human ES cell lines will probably not prove to be immunologically compatible with most patients. This may be resolved by immunosuppressive therapy, genetic modification of the cells to reduce immunogenicity, or possibly the creation of a chimeric immune system in the patient to induce tolerance. The recent discovery of cell reprogramming through nuclear transfer offers a path to the reprogramming of a patient's cell, thereby reverting it to an autologous ES cell (47). This approach has the advantage that immunocompatibility would likely result. In addition, telomeres are reconstructed in the process (48). However, the ethics of ES technology and the use of nuclear transfer in medicine is currently a matter of intense national debate (49), and implementation of the technology may be slowed by limita-

tions imposed on National Institutes of Health funding for stem cell research. Finally, it remains to be seen whether such new tissue (even if it were autologous) would be adequately vascularized and subsequently function appropriately in the patient.

How to Test Potential Interventions

On the basis of caloric restriction and other dietary and genetic intervention results with animal models, one can now make a principled argument that further research along well-defined lines could produce a rational testable strategy for interventions that might slow aging and/or decrease vulnerability to age-associated diseases in people. However, many of the articles describing interventions in animals that may extend life expectancy and health span that appear sporadically in the gerontological literature are compromised by one or more design flaws, and few have been accompanied by pathology assessment. Thus, a rigorous standardized testing program in mice is needed to identify the most promising interventions for possible human clinical trials (50). The National Institute on Aging has recently initiated such a program.

Conclusions

The term "antiaging" has often been used to refer to both basic and clinical studies in this research area, but antiaging has acquired a tarnished image in the gerontological community (51). The workshop participants agreed that instead of "antiaging" medicine, the term "longevity medicine" should be considered by the scientific community, and that it should apply to all means that would extend healthy life, including health promotion, disease prevention, diet, exercise, and cessation of tobacco use, as well as advanced medical care and new discoveries that result from basic research.

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Appendix

For Further Reading

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