

LE Magazine February 2006

REPORT

Antioxidants, Mitochondrial Damage, and Human Aging

By Edward R. Rosick, DO, MPH, MS



Throughout history, scientists have sought strategies for warding off the seemingly inevitable processes of aging and death. In recent decades, the free radical theory of aging has shed light on the degenerative changes that occur as people grow older.

This theory holds that the body produces reactive, unstable agents known as free radicals during normal metabolism and following exposure to ultraviolet light or environmental toxins. While natural antidotes to these free radicals—internally produced antioxidants—are abundant in youth, their levels decline with age. The imbalance between free radicals and the antioxidants needed to inactivate, or “quench,” them leads to a generalized state of oxidative stress that can damage lipids, proteins, DNA, and mitochondria throughout the body. Oxidative stress has been associated with myriad disease processes, including cancer, heart disease, and Alzheimer’s.

Scientific research suggests that minimizing deleterious free radical reactions by ensuring optimal antioxidant levels may hold the key to extending the healthy human life span. Studies have shown that people who live to be 100 years or older often demonstrate higher blood levels of antioxidants than their much younger counterparts. Furthermore, antioxidants may help protect against mitochondrial dysfunction, another harmful condition that commonly accompanies aging and disease states.

Numerous antioxidants—lipoic acid, green tea polyphenols, lycopene, and vitamins A, C, and E—have been associated with protection against many afflictions that commonly accompany aging, such as Alzheimer’s disease, muscle loss (sarcopenia), cataracts, and memory impairment. By protecting against the aberrant biochemical changes that occur with aging, antioxidants may thus represent a veritable fountain of youth.

Thirty years ago, most mainstream medical doctors viewed anti-aging medicine as sheer quackery. The accepted dogma of the time, taught in all medical schools, was that aging and its associated degenerative processes were unavoidable. Conditions such as memory loss, muscle degeneration, and vision deterioration were considered inevitable, not preventable. To even speak of ways to slow aging or prevent its physiological changes was akin to religious heresy in the Middle Ages.

Now, at the dawn of the twenty-first century, there seems to be a begrudging, reluctant, and yet very real change in mainstream medicine’s perception of anti-aging or age-management medicine. The reasons for this change are multifaceted and include:

- An explosion in knowledge of the intricate biochemical and physiological processes involved in aging.
- Growing demand from the rapidly aging, multimillion-strong baby-boomer generation for scientifically valid ways to ward off aging’s most debilitating effects. (By 2030, approximately 70 million Americans will be aged 65 or older, representing a doubling of this age group since 1998.)
- Cover articles in mainstream publications such as TIME magazine that have seriously examined age-management medicine.
- Multiple studies demonstrating that safe, readily available nutritional supplements may help counter many common diseases of aging such as heart disease, cancer, and Alzheimer’s, and may even retard the aging process itself.

HOW DO WE DEFINE AGING?

While most people can tell by sight alone whether someone is young or old, the medical community remains divided over what constitutes aging. The most widely accepted idea today is that aging is a multifactorial biochemical and physiological process that leads to overall cellular breakdown and death. Aging not only alters our physical appearance due to changes in skin, bones, and muscle tone, but also affects our internal organs. The heart and immune system become less efficient, and diseases that are rare in young people become increasingly more prevalent in older adults.

Several competing theories seek to explain which biochemical processes cause the physiological changes seen in aging. In one theory held in high regard by many gerontologists—the so-called “error theory of aging”—aging is primarily caused by external or environmental factors that inflict cellular damage, ultimately leading to organ damage and death. One way these “errors” can occur is through biochemical processes induced by the formation of free radicals, the unstable biochemical entities formed when energy is produced in the cells. While the body can partly neutralize the damaging effects of these radicals, its defenses become less efficient with advancing age. This can lead to damaged cells, tissues, and organs, which manifest as the physical declines of aging.

FREE RADICAL-INDUCED OXIDATIVE DAMAGE

Free radicals are thought to cause cellular degeneration by means of a chemical process known as oxidation. The concept that free radical-induced oxidative damage is a major contributor to aging was first proposed in 1955 by Denham Harman, MD, PhD.¹ Dr. Harman suggested that “the sum of the deleterious free radical reactions going on continuously throughout the cells and tissues constitutes the aging process or is a major contributor to it.”²

Another well-known scientist and proponent of the free radical theory of aging is Bruce Ames, PhD, a world-renowned researcher at the University of California, Berkeley. In multiple papers, Dr. Ames and his colleagues contend that “oxidant byproducts of normal metabolism cause extensive damage to DNA, protein, and lipid.” An increasing number of scientists argue that this damage (the same as that produced by radiation) is a major contributor to aging.³

Drs. Harman and Ames are not the only respected scientists to give credence to the free radical theory of aging. Numerous research papers detail the ways in which free radicals increase oxidative stress in aging humans and cause numerous disease states associated with aging.⁴⁻⁶ Besides damaging cells and organs, free radicals may adversely affect mitochondria, the organelles in each cell that literally provide the energy needed to sustain life.



ENERGY-MANUFACTURING MITOCHONDRIA

Mitochondria are specialized structures that produce energy by converting oxygen and nutrients into adenosine triphosphate, or ATP, an essential biochemical that powers the metabolic activities of the body’s cells.

Mitochondria are uniquely different from other cellular organelles in that they contain their own DNA, leading researchers to postulate that eons ago, mitochondria were free-living cells that were taken up and incorporated in larger organisms. Over a vast evolutionary time span, these two organisms developed a symbiotic relationship whereby the larger organism supplied the mitochondria with oxygen and nutrients, while the mitochondria supplied energy via the production of ATP.

The old adage that “there’s no such thing as a free lunch” applies to energy production by mitochondria. When energy is produced inside the mitochondrial membrane, free radicals, including superoxide anions and hydrogen peroxide, are likewise produced. These radicals can inflict considerable damage to the cellular structure of mitochondria as well as to mitochondrial DNA.

HOW FREE RADICALS DAMAGE MITOCHONDRIA

Many medical researchers now believe that free radical-induced oxidative damage is an important part of the aging process. Dr. Ames, Dr. Harman, and other scientists have written extensively on the biochemical mechanisms by which oxidative damage to mitochondria and mitochondrial DNA contributes to the decline in physiological function that defines aging.⁷⁻¹⁰

This process was succinctly summarized by researchers at National Yang-Ming University in Taipei, Taiwan, who wrote: “It has been shown that the rate of production of superoxide anions and hydrogen peroxide in mitochondria increases with age. Moreover, the intracellular levels of antioxidants and activities of free radical-scavenging enzymes are significantly altered in the aging process. These two compounding factors lead to an age-dependent increase in . . . free radicals that may escape the various antioxidant defense mechanisms and cause ever-increasing oxidative damage to various biomolecules in mitochondria and the cell as a whole . . . we suggest that this vicious cycle plays an important role in human aging and in the pathogenesis of age-related degenerative diseases.”⁷

Indeed, multiple lines of evidence implicate free radicals in many of the diseases associated with aging, such as heart disease, vision loss, sarcopenia, cancer, and Alzheimer’s disease.

ANTIOXIDANTS RETARD THE AGING PROCESS



To further complicate matters, research has confirmed that levels of endogenous (internally generated) antioxidants—including superoxide dismutase, catalase, and glutathione peroxidase—decline with advancing age. The question is, what can be done to guard against the biochemical onslaught of free radicals?

One approach embraced by holistically oriented physicians and their patients is to increase daily intake of antioxidants—biochemicals that counteract the effects of free radicals—through dietary sources and nutritional supplements. While many mainstream physicians still scoff at this idea, a growing body of research validates the importance of supplementing with antioxidants.

Drs. Harman and Ames have proposed that antioxidants can help defend against many age-related diseases and perhaps against aging itself. According to Dr. Harman, “the free radical theory of aging predicts that the healthy life span can be increased by minimizing deleterious free radical reactions . . . the data now available indicate this can be done by keeping body weight down . . . while ingesting diets adequate in essential nutrients but designed to minimize random free radical reactions in the body. Such diets would [contain] minimal amounts of components prone to enhance free radical reactions . . . and increased amounts of substances capable of decreasing free radical reaction damage, such as alpha-tocopherol [vitamin E], ascorbic acid [vitamin C], selenium, and one or more of the synthetic antioxidants. It is reasonable to expect this approach will decrease the morbidity and mortality due to degenerative diseases and nonspecific age changes . . . so as to result in an extension of 5 or more years in the span of healthy productive life.”²

An Italian study in 2000 lends credence to Dr. Harman’s conclusions. Although blood levels of antioxidants tend to decrease with age, the Italian researchers found that centenarians (people aged 100 or older) had markedly higher blood levels of vitamins A and E than their younger counterparts. They concluded, “it is evident that healthy centenarians show a particular profile in which high levels of vitamin A and vitamin E seem to be important in guaranteeing their extreme longevity.”¹¹

REPORT

Antioxidants, Mitochondrial Damage, and Human Aging

By Edward R. Rosick, DO, MPH, MS

PROTECTING THE MITOCHONDRIA

Even mainstream scientific publications now recognize the importance of mitochondrial function in aging and disease. A study in the *Annals of the New York Academy of Sciences* highlighted how mitochondrial dysfunction caused by free radical-induced oxidative damage is a common marker in both aging and age-related diseases such as cancer. The authors note that cancer is associated with aging, and that adults aged 65 or older account for 60% of all cancers and 70% of all cancer deaths. According to the authors, not only it is likely “that increased susceptibility of mitochondrial DNA to oxidative damage and limited DNA repair capacity of the proteins involved in mitochondrial repair play a significant role in mutagenesis of aging,” but “mitochondrial dysfunction that accompanies aging may exert a major influence on carcinogenesis.”¹²

Fortunately, ample evidence suggests that diets rich in fruits and vegetables—and thus high in antioxidants—have significant protective effects against many age-related diseases. In addition, preliminary evidence indicates antioxidants exert direct protective effects against mitochondrial damage caused by free radicals. In another article in the *Annals of the New York Academy of Sciences*, the authors reviewed how certain antioxidants such as coenzyme Q10, N-acetylcysteine, and lipoic acid may neutralize the excess production of free radicals inside the mitochondria.¹³

BENEFITS OF LIPOIC ACID, ACETYL-L-CARNITINE

Lipoic acid is considered an important antioxidant and crucial for a variety of mitochondrial reactions. In Europe, doctors prescribe lipoic acid to treat liver diseases and polyneuropathies. Recent research has shown that lipoic acid may be a useful adjunct in the fight against pathological and age-related changes seen in the brain.

One study examined how lipoic acid modulates neurotransmitters in the brains of aged rats. The older rats given lipoic acid supplements increased their levels of several important neurotransmitters, including dopamine, serotonin, and norepinephrine.

Postulating that this increase could be due to lipoic acid’s antioxidant action, the authors concluded, “supplementation of lipoic acid could represent a viable therapeutic approach to diminish oxidative stress in the central nervous system and thereby modulate the levels of neurotransmitters during [aging].”¹⁴

Another study, coauthored by Dr. Ames, found that in aged rats, lipoic acid and acetyl-L-carnitine significantly protected mitochondria from oxidative damage and age-associated decay. According to the authors, “feeding old rats acetyl-L-carnitine plus lipoic acid restores mitochondrial function, lowers oxidants . . . improves the age-associated decline in ambulatory activity and memory . . . and prevents mitochondria from oxidative decay and dysfunction.”¹⁵



ANTIOXIDANTS THAT COMBAT ALZHEIMER’S

In addition to lipoic acid, other antioxidants can help protect the brain against the ravages of aging. Beta-carotene and vitamins C and E show great promise in the fight against Alzheimer’s disease. Alzheimer’s, the most common cause of dementia in adults aged 65 and older, affects more than 15 million people worldwide. One major change that occurs in the brains of Alzheimer’s sufferers is generalized oxidative damage to neurons. However, current prescription medications for Alzheimer’s focus only on increasing levels of the neurochemical acetylcholine, not on combating oxidative damage to neurons. Multiple studies support the idea that antioxidants have a place as a front-line therapy against Alzheimer’s.

One such study of 442 elderly Swiss patients directly correlated higher blood levels of two common antioxidants (beta-carotene and vitamin C) with better memory.¹⁶

A study published in the *Archives of Neurology* in 2004 examined Alzheimer’s risk in people who took antioxidant supplements. The study found that “use of vitamin E and vitamin C supplements in combination is associated with reduced prevalence and incidence of AD [Alzheimer’s disease]. Antioxidant supplements merit further study as agents in the primary prevention of AD.”¹⁷

VITAMIN E MAY PREVENT MUSCLE LOSS

As people age, not only do their bones become brittle, but their muscle tissues shrink and atrophy, a condition known as sarcopenia. It has been estimated that between the ages of 20 and 80, skeletal muscle mass decreases by 35-40% in men and women. While brittle bones secondary to osteoporosis certainly contribute to the greater incidence of hip fractures and other debilitating injuries in the elderly, leg weakness caused by sarcopenia is a major contributing factor to the falls that cause hip fractures. When sarcopenia robs people of their ability to walk, climb stairs, or perform the simple task of getting in and out of a chair, it confines them to an unhealthy, sedentary lifestyle.

While studies are ongoing, some researchers believe that intramuscular mitochondrial DNA damage caused by free radicals may be a significant factor in the loss of muscle mass seen in the aged.⁶ The use of antioxidants—specifically, vitamin E—may help prevent sarcopenia in the elderly. A report from Johns Hopkins examined the relationship between plasma levels of antioxidants and muscle strength in women aged 70-79. Higher carotenoid and alpha tocopherol (vitamin E) levels were independently associated with greater muscle strength,¹⁸ leading the authors to conclude that sarcopenia in older adults may result in part from oxidative stress, and that antioxidants may be protective.

LUTEIN, ZEAXANTHIN PROTECT VISION

Many longitudinal studies show that high intake of carotenoids—the phytochemicals responsible for the red to yellow pigmentation in fruits and vegetables—can protect against various age-related disease states, including vision loss. Two of the most useful carotenoids for combating age-related vision loss caused by cataracts are lutein and zeaxanthin.

These potent antioxidants are thought to help prevent cataracts by protecting the eye lens from the damaging effects of ultraviolet radiation and endogenous free radical formation. Three recent studies have demonstrated that people with a high intake of lutein and zeaxanthin have significantly lower risks of developing cataracts compared to those with a low intake.¹⁹⁻²¹ In addition, research has shown that even in people who have already developed cataracts, lutein supplementation can help improve vision.²²

CONCLUSION

Age-management medicine is about more than just extending the years of life. Its goal is to lengthen and optimize the years of healthy, functional living by preventing the diseases that commonly afflict older adults. With a little common sense and healthy everyday behaviors—including regular exercise, a diet rich in fruit, vegetables, and lean protein, and use of antioxidant supplements—you can ensure that you have both the chance and the capacity to enjoy a long, healthy life.

References

1. Harman, D. Aging: a theory based on free radical and radiation chemistry. The University of California Radiation Laboratory Report, No. 3078. 1955 Jul 15; Univ. of California, Berkley, CA.
2. Harman D. The aging process. *Proc Natl Acad Sci USA*. 1981 Nov;78(11):7124-8.
3. Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. *Proc Natl Acad Sci USA*. 1993 Sep 1;90(17):7915-22.
4. Barja G. Free radicals and aging. *Trends Neurosci*. 2004 Oct;27(10):595-600.
5. Junqueira VB, Barros SB, Chan SS, et al. Aging and oxidative stress. *Mol Aspects Med*. 2004 Feb;25(1-2):5-16.
6. Ashok BT, Ali R. The aging paradox: free radical theory of aging. *Exp Gerontol*. 1999 Jun;34(3):293-303.
7. Wei YH, Lu CY, Lee HC, Pang CY, Ma YS. Oxidative damage and mutation to mitochondrial DNA and age-dependent decline of mitochondrial respiratory function. *Ann NY Acad Sci*. 1998 Nov 20;854:155-70.
8. Mandavilli BS, Santos JH, Van Houten B. Mitochondrial DNA repair and aging. *Mutat Res*. 2002 Nov 30;509(1-2):127-51.
9. Cadenas E, Davies KJ. Mitochondrial free radical generation, oxidative stress, and aging. *Free Radic Biol Med*. 2000 Aug;29(3-4):222-30.
10. Wei YH, Lee HC. Oxidative stress, mitochondrial DNA mutation, and impairment of antioxidant enzymes in aging. *Exp Biol Med (Maywood)*. 2002 Oct;227(9):671-82.
11. Mecocci P, Polidori MC, Troiano L, et al. Plasma antioxidants and longevity: a study on healthy centenarians. *Free Radic*

12. Singh KK. Mitochondrial dysfunction is a common phenotype in aging and cancer. *Ann NY Acad Sci.* 2004 Jun;1019:260-4.
13. Miquel J. Can antioxidant diet supplementation protect against age-related mitochondrial damage? *Ann NY Acad Sci.* 2002 Apr;959:508-16.
14. Arivazhagan P, Panneerselvam C. Neurochemical changes related to ageing in the rat brain and the effect of DL-alpha-lipoic acid. *Exp Gerontol.* 2002 Dec;37(12):1489-94.
15. Liu J, Atamna H, Kuratsune H, Ames BN. Delaying brain mitochondrial decay and aging with mitochondrial antioxidants and metabolites. *Ann NY Acad Sci.* 2002 Apr;959:133-66.
16. Perrig WJ, Perrig P, Stahelin HB. The relation between antioxidants and memory performance in the old and very old. *J Am Geriatr Soc.* 1997 Jun;45(6):718-24.
17. Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. *Arch Neurol.* 2004 Jan;61(1):82-8.
18. Semba RD, Blaum C, Guralnik JM, et al. Carotenoid and vitamin E status are associated with indicators of sarcopenia among older women living in the community. *Aging Clin Exp Res.* 2003 Dec;15(6):482-7.
19. Lyle BJ, Mares-Perlman JA, Klein BE, Klein R, Greger JL. Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam Eye Study. *Am J Epidemiol.* 1999 May 1;149(9):801-9.
20. Brown L, Rimm EB, Seddon JM, et al. A prospective study of carotenoid intake and risk of cataract extraction in US men. *Am J Clin Nutr.* 1999 Oct;70(4):517-24.
21. Chasan-Taber L, Willett WC, Seddon JM, et al. A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in US women. *Am J Clin Nutr.* 1999 Oct;70(4):509-16.
22. Olmedilla B, Granado F, Blanco I, Vaquero M. Lutein, but not alpha-tocopherol, supplementation improves visual function in patients with age-related cataracts: a 2-y double-blind, placebo-controlled pilot study. *Nutrition.* 2003 Jan;19(1):21-4.