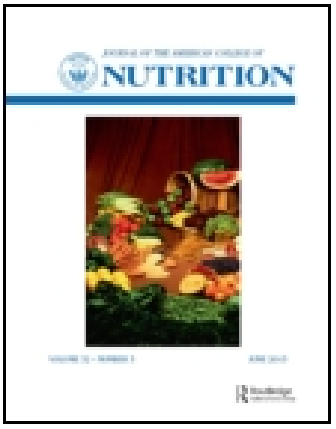

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D Harman

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Nutritional Implications of the Free-Radical Theory of Aging

Denham Harman

University of Nebraska College of Medicine, Omaha

Aging is the progressive accumulation of changes with time associated with and/or responsible for the ever-increasing susceptibility to disease and death. These time-related changes are attributed to the aging process. This process may be due in part to free radical reactions, largely those involving oxygen, going on continuously throughout the cells and tissues.

Dietary manipulations expected to lower the rate of production of free-radical reaction damage have been shown to 1) increase the life span of mice, rats, fruit flies, nematodes, and rotifers, as well as the life span of neurospora, 2) inhibit development of some forms of cancer, 3) enhance humoral and cell-mediated immune responses, and 4) slow development of amyloidosis and the autoimmune disorders of NZB mice. Free-radical reactions may also play a significant role in the deterioration of the cardiovascular and central nervous systems with age.

It is reasonable to expect, on the basis of present data, that the healthy life span can be increased by five or more years by keeping body weight down, at a level compatible with a sense of well-being, while ingesting diets adequate in essential nutrients but designed to minimize random free-radical reactions in the body.

Key words: aging, free radicals, longevity, antioxidants, diet

INTRODUCTION

Life expectancy at birth in the United States rose rapidly from a value of 47.2 years in 1900 to 67.2 years in 1954–1955 and then more slowly to the present value of 73.3 years on an advance towards a plateau value of 74–76 years [1]. Today the average life span—a rough measure of the period of healthy productive life—is the highest in history in the United States and other developed countries; it is about ten years less than the maximum average life expectancy at birth [2,3] and around 30 years less than the maximum life span.

Improvements in nutrition contributed to past increases in life expectancy, further improvements may do so in the future. One promising approach is based on the possibility that free-radical reactions contribute to the degradation of biological systems [4–8].

Free-radical reactions, initiated by both enzymatic and nonenzymatic means, go on continuously throughout the cells and tissues. Because of the high chemical reactivity of the intermediates, free radicals, formed in free-radical reactions, it would be expected that all components of the body would be constantly subject to some degree of chemical change in a more-or-less random manner.

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Address reprint requests to Dr. Denham Harman, Millard Professor of Medicine and Professor of Biochemistry, University of Nebraska College of Medicine, Omaha, NE 68105.

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Enzymes have evolved that help limit the rate of production of free radical reaction damage to "tolerable" levels. They include: 1) heme-containing peroxidases (catalase is an important member of this group), which serve to "safely" lower the steady-state concentration of hydrogen peroxide and hydroperoxides [9], 2) the selenoenzyme, glutathione peroxidase (GSH-Px) [10] which catalyses the reduction of hydrogen peroxide to water and of hydroperoxides to alcohols and water, and 3) superoxide dismutases (SD) [11], metalloproteins that catalyse the conversion of the superoxide anion to hydrogen peroxide and oxygen.

In addition, singlet oxygen ($^1O_2$), a highly reactive form of oxygen, can be converted to "normal oxygen" by compounds such as β-carotene and α-tocopherol.

Further reductions in the rate of production of damage by free-radical reactions should be possible through at least three dietary changes: 1) reduce intake of calories—this will lower the level of free-radical reactions arising in the course of normal metabolism, 2) minimize dietary components, such as copper and polyunsaturates, that tend to increase the level of free-radical reactions, and 3) add to the diet one or more compounds capable of slowing free-radical reaction damage, such as 2-mercaptoethylamine (2-MEA), α-tocopherol, butylated hydroxytoluene (BHT), 1,2-dihydro-6-ethoxy-2,2,4-trimethylquinoline (Santoquin, Ethoxyquin), and selenium to increase the level of glutathione peroxidase.

If free-radical reactions contribute to the degradation of biological systems and if the level of deleterious reactions can be lowered significantly by diet as suggested, then such dietary alterations should have a beneficial effect. There are a number of studies that support this possibility, for example:

EFFECT OF DIET ON LIFE SPAN

Caloric Reduction

Humans of less than average weight have a relatively long life span. Results of rat experiments parallel experience in man. For example, with Sprague-Dawley rats, "when food intake was restricted by 33 or 46% (starting at weaning), levels that prevented fat accumulation and had little retarding effect on skeletal growth, longevity was extended and onset of disease was delayed [12];" similar results were obtained in a more recent study [13].

Dietary Fat

Increasing the amount and/or degree of unsaturation of dietary fat would be expected to increase the level of more-or-less random free-radical reactions. The results of a study [14] in which mice and rats were fed a semisynthetic diet containing 5%, 10%, or 20% (by weight) of either lard, olive oil, corn oil, or safflower oil as the sole source of lipid are summarized below; in this as well as other mouse and rat experiments to be described, the diet was started shortly after weaning:

C3H/HeJ female mice: increasing the amount and/or degree of unsaturation of the dietary fat shortened the average life span.

Swiss male mice: no apparent relationship between dietary fat and life span.

Sprague-Dawley male rats: life spans of the 5% and 10% groups were not related to dietary fat. The life spans of the 20% groups tended to become shorter as the degree of unsaturation was increased.

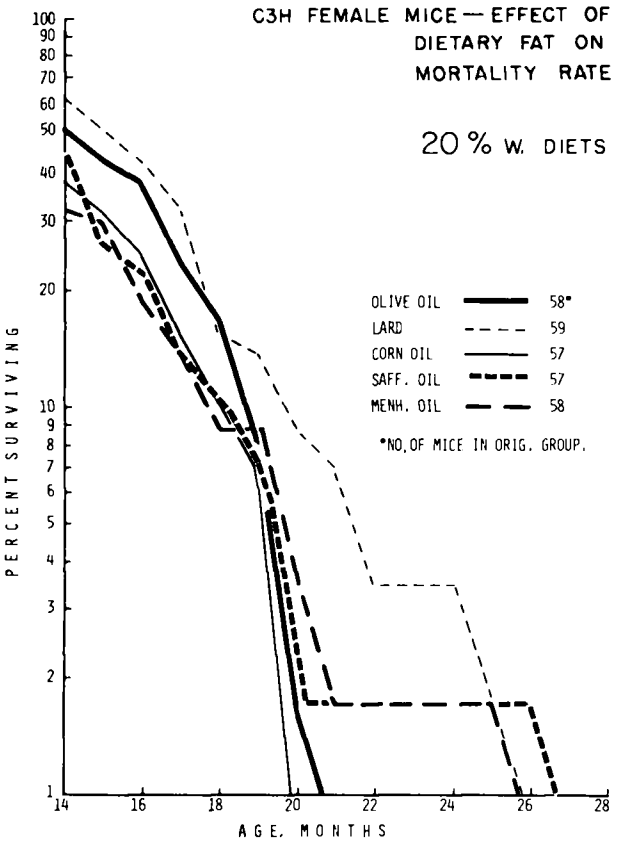

Fig. 1. Effect of 2-mercaptoethylamine on the life span of male LAF_1 mice.

Dietary Protein

Increasing the dietary content of easily oxidized amino acids might increase the level of free-radical reactions and thereby decrease life expectancy. This proved to be the case [15]: addition of 1% histidine or 1% lysine by weight to a semisynthetic diet containing 20% of casein by weight as the sole source of protein decreased the life span by 5% and 6%, respectively. Conversely, average life expectancy was increased by 13% when the casein was replaced by a soybean protein that contained a lesser amount of easily oxidized amino acids [15].

Antioxidants

A number of studies have shown that the addition of antioxidants, such as 2-MEA and BHT, to the diet can increase the life span of mice [16–18], rats [19], drosophila [20,21], nematodes [22], and rotifers [23], as well as the life span of neurospora [24]. In the case of mice, addition of 1.0% (by weight) of 2-MEA to the diet of male LAF_1

mice (Figure 1) [16], starting shortly after weaning, increased the average life span by 30%; this increase is equivalent to raising the human life span from 73 years to 95 years. Corresponding increases produced by 0.5% Santoquin in the diet of male and female C3H mice [17] were 18.1% and 20.0%, respectively. Although it has been relatively easy to increase the average life span of mice, the increases were not accompanied by any certain extensions of maximum life span.

EFFECT OF DIET ON DISEASE PROCESSES

Lowering the level of free-radical reactions might be expected to decrease the incidence at any given age of those specific diseases in which such reactions play an etiologic role. Diseases for which accumulating evidence implicates free radical reactions in pathogenesis include cancer, atherosclerosis, hypertension, senile dementia, and disorders of the immune system.

Cancer

From radiation studies, it would be anticipated that decreases in the level of endogenous free-radical reactions would be associated with decreased tumor incidence. A number of studies now support this possibility, for example: 1) the mammary tumor incidence of C3H/HeJ female mice increased as the amount and/or degree of unsaturation of the dietary fat increased [14], 2) the incidence of breast cancer in women increases as the amount of fat in the diet increases [25], 3) the tumor incidence of Sprague-Dawley female rats fed a semisynthetic diet, with safflower oil as the sole source of lipid, was decreased by adding α-tocopherol acetate to the diet at a level of 20 mg/100 g of diet [26], 4) butylated hydroxyanisole (BHA) and Santoquin inhibited the carcinogenicity of benz(α)pyrene (BP), and 7,12-dimethylbenz(α)anthracene (DMBA) on the forestomach of the mouse [27], 5) dietary antioxidants were effective in reducing the number and severity of ultraviolet-light-induced squamous cell carcinomas in the skin of hairless mice [28], and 6) "The declining American death rate from gastric carcinoma appears to be associated with the introduction of breakfast cereals, particularly wheat cereals rich in tocopherols. . . . It is likely that the decline of mortality from gastric carcinoma in 1947 is associated with the introduction of the antioxidant preservatives BHT and BHA at that time" [29].

Likewise, in areas where the selenium intake is relatively high, the incidence of some forms of cancer tends to be low [30–32]; presumably the effect is due to an increased rate of removal of hydroperoxides—a potential source of damaging free-radical reactions—owing to a relatively high level of glutathione peroxidase in the tissues of individuals with high selenium intake.

Cardiovascular Disease

About 60% of all deaths are due to cardiovascular disease; atherosclerosis and hypertension are the two major underlying causes.

Atherosclerosis. Arterial injury predisposes to the development of atherosclerotic lesions [33]. Peroxides and other compounds formed by the peroxidation of serum and vessel wall lipids and proteins may serve as a constant direct or indirect irritant contributing to the development of atherosclerosis [34]. Data supportive of this possibility include: 1) free-radical reactions are going on continuously in the serum [35]; 2) polyunsaturated fatty acids constitute about 30% of the total fatty acids in the lipids of both serum [36]

and atheroscleotic plaques [37]; 3) ceroid is present in plaques [38–40]; 4) the rise in the incidence of cardiovascular disease in the last 50 years was accompanied by a 7% increase in consumption of saturated fats, but the rise in polyunsaturated fats was 37% [41]; 5) lipid peroxides inhibit the prostacyclin synthetase found in the arterial wall, thus predisposing to thrombus formation [42]. In addition, in studies of selenium deficiency in man [43] and pigs [44,45], the deficiency is associated with myocardial and vascular damage. Furthermore a study [46] of the effect of selenium and vitamin E on myocardial necrosis induced by isoprenaline treatment or coronary artery ligation, indicates that free radical reactions are continuously present in the cardiovascular system and that the rate of accumulation of damage produced by them is slowed largely by glutathione peroxidase. In addition the incidence of cardiovascular disease is low in areas where the dietary intake of selenium is high and vice versa [31,47,48].

Hypertension. The etiology of most cases of hypertension is unknown, ie, essential hypertension. The single most important factor in the production of hypertension is an increase in peripheral resistance in the small blood vessels, mainly arteriolar [49].

The free-radical reactions postulated to contribute to atherosclerosis may also play an etiologic role in hypertension. Studies in support of this possibility include: 1) by analogy with the effects of ionizing radiation [50], the free-radical reactions in serum and vessel walls may contribute to the development of arteriolocapillary fibrosis [35]; 2) the hypertension of the toxemia of pregnancy is associated with elevated serum levels of copper [51,52] and lipid [53] and depressed levels of ascorbic acid [54]; 3) the increased incidence of hypertension [55] in women on "the pill" is associated with increased serum copper [56] and lipid levels [57]; and 4) lipid peroxides inhibit production of prostacyclin, a compound that tends to decrease vessel tone [58,59].

Senile Dementia

The central nervous system (CNS) may be particularly susceptible to degradation by free-radical reactions because the neurons are fixed postmitotic cells with unique connections between them and a predilection for readily peroxidized highly unsaturated fatty acids, particularly docosahexanoic acid (22:6ω3). Docosahexanoic acid, either free or in triglyceride form, as well as the precursor linolenic acid (18:3ω3), is avidly removed from the diet and incorporated into brain 22:6ω3 phospholipids [60]. Brain 22:6ω3 is tenaciously retained.

Lipofuscin (age pigment) is formed by oxidation-polymerization of lipids, probably largely mitochondrial, and proteins [61]. Age pigment accumulates with age [62] in the various areas of the central nervous system (CNS) in parallel with the activities of oxidative enzymes [63,64]. The accumulation of lipofuscin can be slowed by antioxidants [65]. Vitamin E deficient diets increase CNS lipofuscin and depress function [66].

Free-radical reactions may be significantly involved in formation of the senile plaques (neuritic plaques) associated with senile dementia of the Alzheimer's type [60,67]. The first changes seen in the development of the plaques are alterations in the mitochondria of the axon terminals [68]. These mitochondrial changes may be due to peroxidation, for the mitochondria have both a high degree of lipid unsaturation and a high rate of O_2 utilization.

Thus, minimizing dietary polyunsaturated lipids particularly docosahexanoic acid and its precursors and increasing intake of compounds capable of minimizing free radical reaction damage may slow deterioration of the CNS with age.

Disorders of the Immune System

The immune system declines with age [69]. Antioxidants should offset this decline to some extent for they have been shown to enhance both humoral and cell-mediated immunity [70]. For example, addition of 0.25% Santoquin or 0.5% 2-MEA (by weight) to the diet of mice increased the humoral response of spleen cells by 94% and 79%, respectively. Selenium also increases immune system activity [71].

Development of amyloidosis and the autoimmune disorders of NZB and NZB/NZW mice is inhibited by antioxidants [72]. Thus, addition of 0.25% Santoquin to the diet markedly inhibited amyloid formation in LAF_1 mice, while the same compound increased the average life span of male NZB mice by 32%. These results were probably due in part to a slower rate of loss of T-suppressor cell function in the presence of antioxidants.

COMMENT

These data demonstrate that free-radical reactions shorten life span, contribute to the development of cancer (at least of some forms), have adverse effects on the immune system, and most likely play a significant role in the degradation of the central nervous and cardiovascular systems. The data further demonstrate that the natural defenses of living things against deleterious free radical reactions can be significantly improved by diet.

Formulation of human diets, adequate in essential nutrients but designed to minimize random free-radical reactions in the body, may reasonably be expected to increase the healthy life span by slowing accumulation of nonspecific deleterious changes and the development of specific diseases.

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