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Forum Mini Review

The Free Radical Theory of Aging

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ABSTRACT

Aging is the accumulation of changes that increase the risk of death. Aging changes can be attributed to development, genetic defects, the environment, disease, and an inborn process: the aging process. The latter is the major risk factor for disease and death after age 28 in the developed countries. In these countries, average life expectancies at birth (ALE-B) now range from 76 to 79 years, 6–9 years less than the limit of ~85 years imposed by aging. Aging changes may be caused by free radical reactions. The extensive studies based on this possibility hold promise that the ALE-B can be extended to >85 years and the maximum life span increased. *Antioxid. Redox Signal.* 5, 557–561.

INTRODUCTION

AVERAGE LIFE EXPECTANCY AT BIRTH (ALE-B) is a rough measure of the span of healthy, productive life—the functional life span. Efforts to increase this period are limited almost completely to the prevention and treatment of specific diseases. These efforts are becoming increasingly futile because of the inherent aging process (18, 24, 25, 27). In the future, progressively more effort will be devoted to slowing this process.

AGING

Aging is the progressive accumulation of diverse deleterious changes in cells and tissues with advancing age that increase the risk of disease and death (18, 24, 25, 27). This process may be common to all living things, for the phenomena of aging and death are universal. If so, both aging and the rate of aging are under genetic control to some extent for the manifestations of aging, and life span differs between species and individual members of a species. Further, like all chemicals and chemical reactions, the manifestations of aging—which reflect chemical composition—and the rate of aging should be subject to environmental influences.

This article is mainly limited to a discussion of mammalian aging because of the interest in finding measures to further increase the healthy human life span.

Aging changes can be attributed to developmental and genetic defects, the environment, disease processes, and an inherent process, referred to as "the aging process" (18, 24, 25, 27). The chance of death of an individual of a given age in a population—readily available from vital statistics data—serves as a measure of (a) the average number of adverse changes, *i.e.,* aging changes, accumulated by persons of that age, and (b) physiologic age, *i.e.,* "true age," in contrast to chronological age. The chances for death in a population determine the ALE-B. ALE-B is a rough measure of the span of healthy, productive life, *i.e.,* the functional life span.

EFFECT OF IMPROVED LIVING CONDITIONS ON AGING

Conventional means (CM) of increasing the ALE-B of a population by decreasing the chances for death through improvements in general living conditions, *e.g.,* better nutrition, housing, and medical care, are becoming increasingly futile (25, 27). This is illustrated in Fig. 1 by the curves of the logarithm of the chance of death versus age for Swedish females

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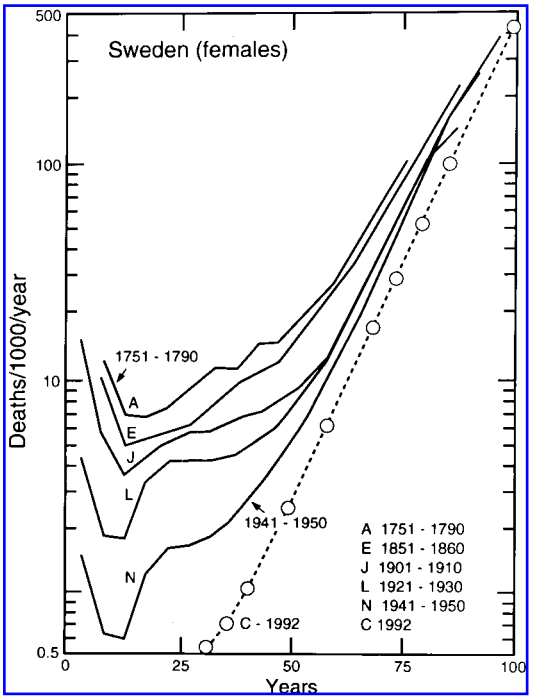

FIG. 1. Age-specific death rate of Swedish females in various periods from 1751 to 1992.

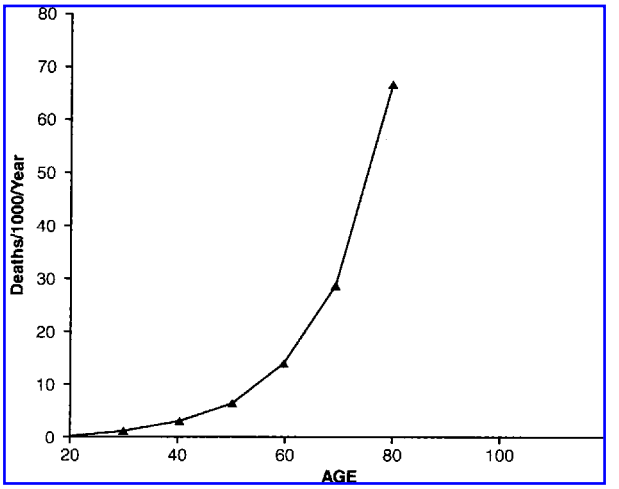

FIG. 2. Chance of dying in 1985 as a function of age: total population of the United States.

for various periods from 1751 to 1992 (37, 54); a straight line represents exponential increases with age. The chances for death in the developed countries are now near limiting values while ALE-B approaches plateau values of around 76 years for males and 82 years for females (25, 27).

Thus, as living conditions in a population approach the optimum, and premature deaths a minimum, the logarithmic curve of the chance of death versus age shifts toward a limit determined by the sum of (a) the irreducible contributions to the chance of death by aging changes that can be prevented to varying degrees by CM, *e.g.,* those due to the environment and disease, and (b) contributions that can be influenced little, if at all, by CM, *i.e.,* those due to the innate aging process. The now near-limiting chances for death rise almost exponentially after about age 28. Only 1–2% of a cohort die before this age (54).

THE AGING PROCESS

The inherent aging process is the major risk factor for disease and death in the developed countries after age 28 (25, 27). It limits ALE-B to ~85 years (25, 27) and the maximum life span (MLS) to ~122 years (31). Aging rates are low early in life but rapidly increase with age, illustrated in Fig. 2 by a plot of the chances for death in 1985 for the United States population as a function of age (25, 27). The innate aging process is caused by chemical reactions that arise in the course of normal metabolism which, collectively, produce aging changes that exponentially increase the chance of death with advancing age even under optimal living conditions.

FREE RADICAL THEORY OF AGING

The free radical theory of aging (FRTA), and the simultaneous discovery of the important, ubiquitous involvement of free radicals in endogenous metabolic reactions, was proposed in 1954 (14, 23). The FRTA arose from the application of a broad background in chemistry and biology to a consideration of aging phenomena from the premise that a single common process, modifiable by genetic and environmental factors, was responsible for the aging and death of all living things. The FRTA postulates that the common aging process is the initiation of free radical reactions (FRRs). These reactions, however initiated, could be responsible for the progressive deterioration of biological systems over time owing to their innate ability to produce random change due to the high chemical reactivity of the intermediate free radicals.

The FRTA was extended in 1972 (15) with the suggestions that (a) most FRRs were initiated by the mitochondria at an increasing rate with age, and (b) the life span is determined by the rate of free radical damage to the mitochondria. Consequences of mitochondrial aging were discussed in 1983 (19). Collectively, the FRRs initiated by the mitochondria constitute the inherent aging process. Later, it became clear (28, 30) that improvements in general living conditions increased ALE-B by decreasing the FRRs associated with suboptimal living conditions.

The FRTA suggests that measures to decrease (a) the chain lengths of FRRs, *e.g.,* with antioxidants such as vitamin E, and/or (b) their rates of initiation, *e.g.,* by minimizing copper, iron, and other oxidant catalysts, can lower the rate of formation of aging changes, even under optimal living conditions, and in turn decrease the rate of aging and of disease pathogenesis. Many studies now support this possibility (13, 18, 20–25, 27, 31, 32).

INCREASING THE AVERAGE AND MAXIMUM LIFE SPANS

In the developed countries, living conditions are near optimum, the aging process is the major risk for disease and death after age 28, and the ALE-Bs are approaching the maximum of ~85 years. The latter will continue to be increased by efforts to minimize the deleterious effects of free radical damage by improving CM. However, the aging process will progressively lower the rate of these increases to zero as the ALE-Bs approach 85 years (29).

Nutrition has played a significant role in the past in increasing ALE-B while having little or no effect on the MLS (5, 16, 18, 26). The effectiveness of future attempts to increase ALE-B should be enhanced by using diets carefully selected to minimize free radical damage (1, 2), possibly with the aid of microarray technology (40).

Attempts to slow the innate aging process (28) have the potential to significantly increase both the ALE-Bs and the MLS. For example:

- Caloric restriction decreases superoxide formation, and hence the rate of aging (50, 53), but it also decreases ATP formation, which seriously limits clinical application.
- Supplementing the diet with compounds such as *N-tert*-butyl-α-phenylnitrone (31) depresses superoxide radical formation by competing with O_2 for electrons from the respiratory chain.
- Supplementing the diet with substances such as acetyl-L-carnitine plus (*R*)-α-lipoic acid (12) helps to maintain mitochondrial function with age (28).

Both the ALE-Bs and the MLS should also be increased by minimizing the life-shortening mutations associated with early life using antioxidant-rich maternal diets and antioxidant supplements (28).

FREE RADICAL REACTIONS AND LIFE

A reasonable explanation for the ubiquitous presence of free radicals in biological systems that naturally follows from the chemical nature of these reactions is provided by studies on the origin and evolution of life (4, 6–8, 17, 18, 45, 46, 52, 57), summarized in Table 1, and the growing knowledge of FRRs in aging, degenerative diseases, and mutation.

Life apparently originated spontaneously ~3.5 billion years ago from amino acids, nucleotides, and other basic chemicals of living things produced from the simple, reduced components of the primitive oxygen-free atmosphere by FRRs, initiated mainly by ionizing radiation from the sun. The products of these reactions, including simple self-replicating progenitors of DNA, reflected the innate chemical properties of the atoms and molecules from which they were formed, as well as the environment in which they were produced.

The FRRs involved in the origination of life also served to provide compounds in the environment necessary for the survival and growth of the first protocells, and to produce more or less random FRR-mediated changes throughout the cells. Some changes were inheritable, improving the ability of the offspring to survive and function, *i.e.,* to evolve, whereas others were aging changes that led to cell death, an essential part of evolution. Apparently from the beginning the protocells selected inheritable changes that led to the internalization of these two essential functions of ionizing radiation.

In short, the origin and evolution of life may be due to (a) FRRs, in particular to their inherent ability to induce random change, and (b) the ability of the organisms to select inheritable changes that enhanced function and life span. It is remarkable that life with its beautiful order owes its origin to, and is sustained by, a class of chemical reactions whose outstanding characteristic is their unruly nature. Further, life span and function evolved in parallel with the ability of organisms to cope with damaging FRRs.

TABLE 1. OVERVIEW OF THE ORIGIN AND EVOLUTION OF LIFE

Years ago	*Main events*
3.5 billion	Basic chemicals of life formed by free radical reactions, largely initiated by ionizing radiation from the sun. Life begins, excision and recombinational repair processes evolve.
	Ferredoxin appears:
	$RH \text{ or } H_2S + CO_2 \xrightarrow{h\gamma} CH$
2.6 billion	Blue-green algae appear:
	$2H_2O \xrightarrow{h\gamma} 4H + O_2$
1.3 billion	Atmospheric O_2 reaches 1% of present value.
	Anaerobic prokaryotes disappear. Eukaryotes become dominate cells. Eukaryotes + blue-green algae → the green leaf plants.
	Eukaryotes + a prokaryote able to reduce O_2 to H_2O → animal kingdom.
	Emergence of multicellular organisms and plants.
	Meiosis evolves.
500 million	Atmospheric O_2 reaches 10% of present value. Ozone screen allows emergence of life from the sea.
65 million	Primates appear.
5 million	Man appears.

The innate aging process may be simply the sum of the age-inducing FRRs going on continuously throughout the cells and tissues. In the beginning, the reactions were apparently largely initiated by UV radiation from the sun and, to a lesser extent, by volcanic activity, and now almost all arise endogenously from enzymatic and nonenzymatic FRRs.

The numerous, and steadily increasing, studies of model aging systems, *e.g.,* yeast, *C. elegans, Drosphilia,* and mice (3, 9–11, 33–36, 39, 41, 44, 47, 49, 50, 55, 56, 58), are in accord with the above brief discussion of the origin and evolution of life. This was to be expected assuming that all life arose in essentially the same manner and was subjected to similar evolutionary forces.

PERSPECTIVE

Knowledge of the biochemical changes associated with age is extensive and growing steadily. Many would argue that the present increasing ineffectiveness of efforts to significantly raise the ALE-Bs is a result of inadequate knowledge of aging (38, 42, 43, 48, 51, 53). This may not be the case, but the result of insufficient application of current knowledge.

A steadily growing number of scientists support the FRTA because studies based on it have been fruitful and show promise of serving as a guide for future efforts (12, 28, 31) to further increase the human functional life span.

The FRTA was proposed in November 1954. The continuing increasing strong support for the FRTA raises the possibility that it is no longer a theory, but a fact, *i.e.,* FRRs are the major, and possibility the sole, cause of aging. Although all may never accept this possibility, it now seems very likely that the assumption that there is a basic cause of aging is correct and that the sum of the deleterious FRRs going on continuously throughout the cells and tissues is the aging process or a major contributor to it. Whatever the final answer, it is now apparent that the FRTA can serve as a useful guide in the increasingly important search for practical methods of further enhancing the human functional life span and decreasing the period of senescence.

ABBREVIATIONS

ALE-B, average life expectancy at birth in a population; CM, conventional means of increasing the ALE-B of a population by decreasing the chances of death through improvements in general living conditions, *e.g.,* better nutrition, housing, and medical care; FRR, free radical reaction; FRTA, free radical theory of aging; MLS, maximum life span.

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