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The aging process: Major risk factor for disease and death

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ABSTRACT **Aging is the accumulation of changes responsible for the sequential alterations that accompany advancing age and the associated progressive increases in the chance of disease and death. Average life expectancies at birth in the developed countries are now approaching plateau values as the aging changes associated with the environment and disease near irreducible levels. The inborn aging process is now the major risk factor for disease and death after around age 28 in the developed countries and limits average life expectancy at birth to approximately 85 years. Future significant increases in average life expectancy—a rough measure of the healthy, productive life-span, i.e., the functional life-span—in these countries will be achieved only by slowing the rate of production of aging changes by the aging process. Many theories have been advanced to account for the aging process. The free radical theory of aging is discussed briefly. The importance attached to increasing the functional life-span dictates that aging hypotheses be explored for practical means of achieving this goal while work continues toward a consensus on the cause(s) of the aging process. Efforts to further increase the functional life-span by conventional measures are now almost futile, whereas those directed toward slowing the aging process are just beginning. These new efforts show promise.**

Aging is the accumulation of changes responsible for the sequential alterations (1, 2) that accompany advancing age and the associated progressive increases in the chance of disease and death. The chance of death—readily obtained from vital statistics data—serves as a measure of the number of such accumulated changes, i.e., of physiologic age, while the rate of change of this parameter with time measures the rate of accumulation, i.e., the rate of aging.

The chance of death for humans drops precipitously after birth to a minimum figure around puberty and then increases with age to a value beyond which it rises almost exponentially (1–5) at a characteristic rate so that few individuals reach age 100 and none live beyond about 115 years (6). That is, the chance that a combination of aging changes capable of causing death will occur in a given individual increases progressively with time beyond some age. Improvements in general living conditions—better nutrition, housing, medical care, public health facilities, accident prevention—decrease the chance of death (2, 5), more so in the young than in the old, as illustrated in Fig. 1 by the curves of the logarithm of the chance of death versus age for Swedish females for various periods from 1751 to 1988 (4, 7).

Today in the developed countries the chance of death rises almost exponentially after about age 28 (3, 7, 8). These chances are now near limiting values; only 2–3% of a cohort die before age 28, while average life expectancies at birth—determined by the chances for death—approach plateau values of around 75 years for males and 80 years for females; average life expectancy at birth for white males and females in the United States from 1950 to 1988 (3, 9) are shown in Fig. 2 and the corresponding Swedish data to 1987 (7) in Fig. 3. Japan is at present an exception to the other developed countries. Life expectancies for the Japanese (ref. 10 and Fig. 4) have risen rapidly from the fifties in 1950 so that by 1987 they had become the longest-lived population. Japanese women in 1989 had a life expectancy of 81.8 years and the males of 75.9 years; these figures are still rising linearly at 0.38 year per year (10). Thus, as living conditions in a population approach optimum, the curve of the chance of death versus age shifts toward a limit. This is determined by the irreducible production in individuals of aging changes associated with environment and disease plus those formed by an inborn process, the aging process. The latter produces aging changes at an apparently unalterable, exponentially increasing rate with advancing age. The aging rate should vary from person to person, due to differences in genetic and environmental factors that modulate production of aging changes and thus contribute to differences in the age of death and of the onset of disease. The contributions of the aging process to aging changes are small early in life but rapidly increase with age due to the exponential nature of the process. This is illustrated in Fig. 5, where the chance of death in the United States in 1985 (3) as a function of age is superimposed on a plot of the average life expectancy at birth in the United States (3) from 1900 to 1985.

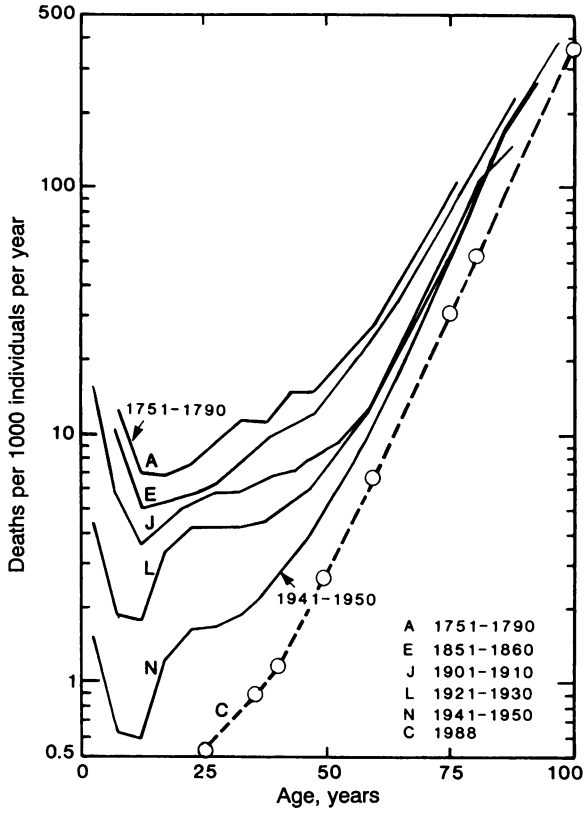

FIG. 1. Age-specific death rates of Swedish females from 1751 to 1950 (adapted from ref. 4; data for 1988 are from ref. 7).

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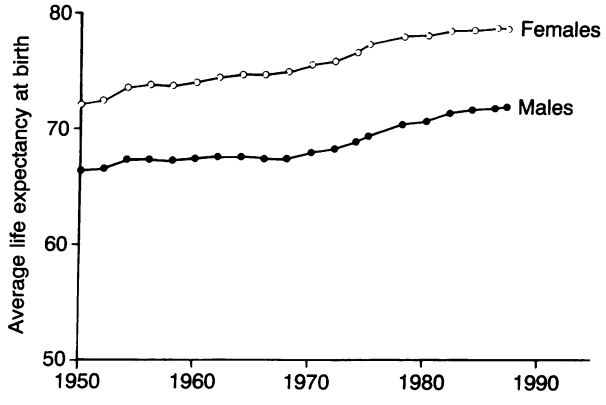

FIG. 2. Average life expectancy at birth since 1950 in the United States.

The aging process is now the major risk factor for disease and death after around age 28 in the developed countries. The importance of the aging process to our health and well-being is obscured by the protean nature of its contributions (2) to nonspecific change and to disease pathogenesis. As "risk factors" for diseases are detected and minimized the chance of death decreases toward that determined by the aging process, while the associated average life expectancy at birth approaches a maximum of about 85 years (11–13). Average life expectancy at birth in the developed countries is today about 10 years less than the potential maximum, largely due to premature deaths from cancer and cardiovascular diseases. "Conquest" of these two disorders would increase average life expectancy at birth by about 3 and 6 years, respectively, based on total United States population data for 1979–1981 (14). In light of the foregoing, the failure to "win the war against cancer" (15) is understandable. It is also reasonable to expect that past reductions in cardiovascular diseases (16, 17) will not be repeated in the future unless efforts are directed to slowing the aging process.

Future significant increases in average life expectancy at birth in the developed countries will only be achieved by slowing the rate of production of aging changes by the aging process. Because the average period of senescence is not known, the average life-span at birth serves as rough measure of the span of healthy, productive life, i.e., the functional life-span. Many theories have been advanced to account for the aging process (18–20). For example, the effects of aging have been attributed to molecular crosslinking (21), changes in immunological function (22), damage by free radical reactions (23) and senescence genes in the DNA (24). No one theory is generally accepted: "this remarkable process remains a mystery" (25); "it is doubtful that a single theory will explain all the mechanisms of aging" (26, 27).

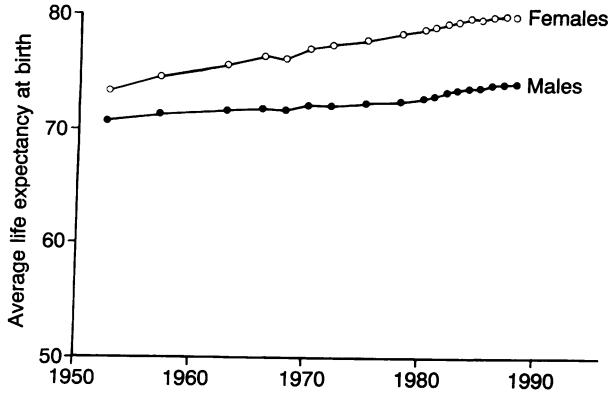

FIG. 3. Average life expectancy at birth since 1950 in Sweden.

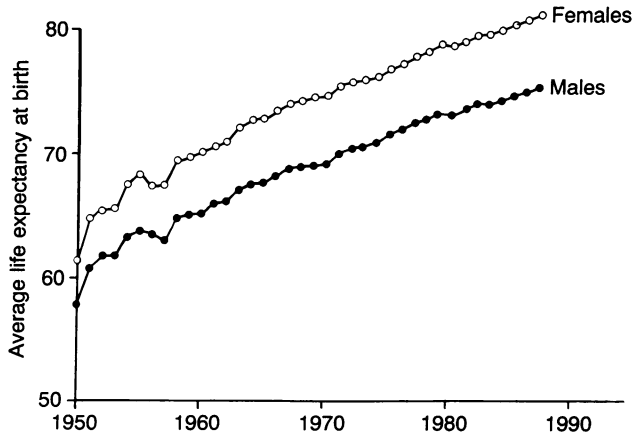

FIG. 4. Average life expectancy at birth since 1950 in Japan.

The importance attached to increasing the functional life-span dictates that aging hypotheses be explored for practical means of achieving this goal while work continues toward a consensus. The free radical theory of aging (23, 28–30) shows promise of application today. This theory is based on the chemical nature of free radical reactions (31, 32) and their ubiquitous prominent presence in living systems. Probably the vast majority of these reactions are enzymatic ones involved in maintenance and function, while the remainder, initiated by nonenzymatic means and by "leakage" of free radicals from enzymatic reactions, cause more-or-less random change. In mammals O_2 is the main source of damaging free radical reactions; the effect of these free radicals on biological systems is an active field of study (33–35). The aging process may be simply the sum of the deleterious free radical reactions going on continuously through the cells and tissues.

Support for the free radical theory of aging (23) includes: (*i*) studies of the origin and evolution of life, (*ii*) studies of the effect of ionizing radiation on living things, (*iii*) dietary manipulations of endogenous free radical reactions, (*iv*) the plausible explanations it provides for aging phenomena, and (*v*) the growing number of studies that implicate free radical reactions in the pathogenesis of specific diseases.

The free radical theory of aging predicts that the life-span can be increased by slowing the rate of initiation of random free radical reactions and/or decreasing their chain lengths. The former should be achieved by decreasing dietary intake of easily oxidized components, caloric intake, and temperature; the latter should be achieved by increasing the concentrations of free radical reaction inhibitors in the body or by increasing the resistance of body constituents to free radical attack. Studies are in accord with these predictions. For example, lowering the degree of unsaturation of lipids in the diet of C3H female mice increased the mean life-spans (36), decreasing the caloric intake of rats by 40% while maintaining essential nutrients increased average life-span by around 40% and maximum life span by 47% (37), and the addition of free radical reaction inhibitors to the diet increased the average life-span of all species studied (23), in many cases by 20% or more; in contrast, only three compounds, 2-mercaptoethanol (38) and two pyridine derivatives (39, 40) have been reported to increase the maximum life-span of mice. The general failure of antioxidants to increase the maximum life-span may be largely due to depression of mitochondrial function (41–47) by the compounds at concentrations that are below those needed to slow mitochondrial aging.

The free radical theory of aging provides a plausible explanation for the relation between disease and aging. A disease is a combination of changes, usually forming a readily recognized pattern, that have detrimental effects on function

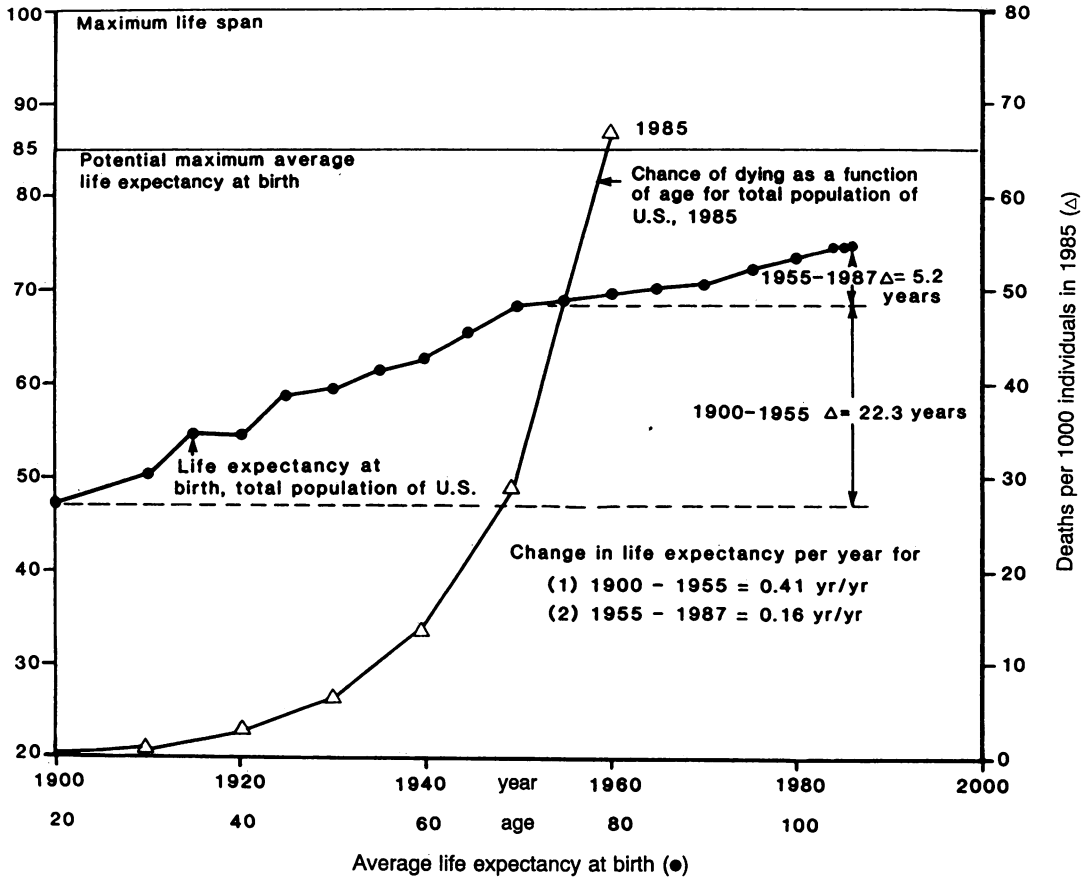

FIG. 5. Average life expectancy at birth since 1900 (●) and the chance of dying in 1985 as a function of age (△) for the total United States population.

and that in some cases may lead to death. The ubiquitous free radical reactions would be expected to produce progressive adverse changes that accumulate with age throughout the body. The "normal" sequential alterations with age can be attributed to those changes more-or-less common to all persons. Superimposed on this common pattern of change are patterns that should differ from individual to individual owing to genetic and environmental differences that modulate free radical reaction damage. The superimposed patterns of change may become progressively more discernable with time and some may eventually be recognized as diseases at ages influenced by genetic and environmental risk factors. Aging may also be viewed as a disease, differing from others in that the aging pattern is universal. The probability of developing any one of the "free radical" diseases should be decreased by lowering the free radical reaction level by any means (e.g., food restriction, antioxidants) and in the case of a specific disease, lowered further by decreases in contributing environmental factors (e.g., cholesterol in atherosclerosis). The growing number (23, 34, 48) of free radical diseases includes the two major causes of death, cancer and atherosclerosis, as well as other common degenerative disorders. Data on the beneficial effects of antioxidants on the free radical diseases are accumulating rapidly (49).

Whatever the eventual consensus on the cause(s) of the aging process, attempts to minimize free radical reaction damage in humans are likely to increase the functional life-span. It is reasonable to expect that application today of the free radical theory of aging will decrease the morbidity and mortality due to degenerative diseases and nonspecific age changes and possibly also increase slightly the maximum life-span, so as to result in an extension of 5 or more years in the span of healthy productive life.

Efforts to further increase the functional life-span by conventional measures are now almost futile, whereas those directed toward slowing the aging process are just beginning. Slower aging does not necessarily imply that the percentage of impaired older individuals in the population, and the attendant burden on society (50, 51), will rise with increases in average life expectancy as it has in the past (50) in response to improvements in general living conditions. Successful efforts to increase the life-span of animals based on the free radical theory of aging resulted in shortened senescent periods (23, 30); the average life-spans at birth were increased while maximum life-span rose little, if at all. Slower aging would also benefit society. The additional years of use of the skills gained over a lifetime should increase productivity. More importantly, slower aging will help to fulfill man's natural desire for a longer healthy life.

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