MECHANISM OF AGING SUGGESTED FROM STUDY OF ALTERED DEATH RISKS

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1. Introduction

Questions we ask about aging need experimental investigation; for example, is aging to be explained as cellular change and, if so, is it a change in all cells of the organism or a relative change in populations of cells? On the other hand, should many of the common manifestations of aging be explained on an organizational or physiological level of body function? In the near absence of suitable experimental approaches to aging, analysis of vital statistics can reflect some consequences of aging in the way they encroach upon the average individual. Observations of this kind have been reported over the past 300 years and extensive statistical material is available in various life tables for many Western peoples over this period. The most significant feature of aging to be deduced from life tables is that morbidity and mortality increase more rapidly than the first power of time during adult life; the relation has been variously presented in terms of a power of time or with time as an exponent. I shall refer to this relation as a multiplicative increase of morbidity or mortality [1]. The biological interpretation follows that the physiological changes which generate these end stages of overt agedness grow multiplicatively with time or that the severity of their impact to induce aging is multiplicatively increased over time lived. In any event, given a multiplicative rise in death risk, life span becomes limited by it.

Francis Bacon [2] may have been the first to express a definite concept of the manner of aging of animals and to characterize a difference in life span by species. His listing of the various species by life span, written more than 300 years ago, agrees remarkably with present estimates. He developed a number of deductions about the relations between individual constitution and longevity that resemble those current today, such as the effects of leanness and body type. He should be credited as the first body-typer. It may be useful to reinvestigate some of the esoteric beliefs of Bacon, such as the life characteristics associated with hairy lower legs, hairy chests, large ears, and large nostrils. These matters are discussed in the following selections from Bacon's *History of Life and Death* [2]:

"Hairiness of the upper parts is a sign of short life, and they that have extraordinary much hair on their breasts, live not long; but hairiness of the lower parts, as of the thighs and legs, is a sign of long life."

"Leanness, where the affections are settled, calm and peaceable ···, [signifies] long life; but corpulency in youth foreshows short life; in age it is a thing more indifferent."

"Firm flesh, a rawbone body, and veins [lying] higher than the flesh, betoken long life; the contrary to these, short life."

"A head somewhat lesser than to the proportion of the body, a moderate neck, not long, nor slender, nor flat, nor too short; wide nostrils, whatsoever the form of the nose be; a large mouth, and ear gristly, not fleshy; teeth strong and contiguous, small or thin set, foretoken long life and much more, if some new teeth put forth in our elder years."

Bacon might be right about all of the signs he interpreted as prognosticating length of life; certainly he mentioned some that receive attention today. In the mid-twentieth century, we have derived some systematic associations that establish relative leanness, blood fats, blood pressures, regimen, and ancestry as predictors of life span in individuals of average health. It would be useful to know some of these in the differential detail that Bacon asserts. For example, is overweight indeed harmful only in the developmental and early adult period and of no consequence later in life? And is overweight causatively associated with life-shortening? Or is it instead a secondary sign of a harmful regimen that effects life-shortening by other means? These are difficult questions; but let us assume that there are individual differences leading to differences in life expectancy and, through the use of vital statistical data, let us try to estimate how these physiological and environmental factors cause the mortality risk of groups to increase multiplicatively with age.

2. Evidence for physiologic changes with age that may limit health

Some of the many changes that have been noted to occur with age are, on the average, linearly progressive declines of function; for example, change in the cardiac output is of this nature. Though various organs display this characteristic, some of the important visceral structures may maintain about the same blood flow throughout life. In some of the body systems, it is believed, their respective functions may decline only in their reserve, so that the effect is hidden when the body is unstressed. Many functional characteristics change only slightly and not in pace with the great upward surge of the mortality rate over adult life span. In some instances, however, we observe that changes do occur as a power function of time, quite similarly to increase of death risk. One of these is the measure of resting blood flow to the connective tissues; it declines approximately exponentially from early adolescence and apparently continues this decline in adult life [3]:

Age in years	Flow in ml blood per liter of muscle per minute
12	50
18	25
25	15
35	9
60	5

Perhaps this restriction in tissue nutriment largely explains the usual limitation of athletic performance to the youthful period. Another physiologically based model is also helpful in thinking about mechanisms of the vascular disease complication of aging. In coronary arteriosclerotic disease, the probability of incidence of overt symptoms increases as a multiplicative function of age through most of adult life. Gofman and his associates [4] have presented a plausible explanation. The walls of the arteries thicken throughout life, and the rate of thickening in any given artery appears to be related to the concentration of certain blood fats and the pressure of blood in that artery. This being the case, in general, the artery wall becomes progressively thicker as age increases. An increment of thickening of the artery wall occurs for each moment of exposure to fats and pressure; thus, the change of wall thickness is linear with respect to time. The artery, however, is a tube and the thickening takes place toward the inside. As the wall becomes thickened, the diameter of the opening of the tube becomes proportionally less; hence, the cross-sectional area of lumen available for the flow of blood is decreasing as the square of the luminal diameter and consequently as the square of the time. This model shows a reasonable fit between the relative increase in coronary heart disease deaths and estimates of constriction of the blood flow to the heart. The model equally applies to the whole arterial system, as arteriosclerosis is a generalized disease; it explains why vascular disease increases the probability of fatal occlusion as some power function of time lived. The model is an example of transformation of a linear change to effects that are multiplicatively worse with passage of time.

A model of aging is implicit in the Gompertz analysis of mortality statistics [1]. It is conveniently expressed as an exponential increase in the death rate with time throughout the adult life span. Another related model expresses the progression of the death rate in terms of the fifth, sixth, or seventh power of time [5]. The Gompertz model suggests that multiplication of the effects of each event of disorder occurs throughout the lifetime. The model has been used extensively in the study of effects of normal aging, radiation, smoking, and so on, where it may be shown that some effects compound with time and degree of exposure whereas other effects simply intensify the death rate characteristic of that age. Thus, radiation effect, genetic constitution, physical injury, and some of the infectious diseases produce through their action the equivalent of advancing of physiological age. Some of the morbidity experience due to traumatic injury can be equated to a time interval of aging, possibly because the effects of these injuries represent incompletely repaired disturbances that add to the usual

physiologic disrepair incurred as the average consequence of living. It seems from this model that disrepair of health grows proportionally as a consequence of the metabolic functions of the individual species. Gompertzian diagrams are useful to enable us to compare aging between species; the diagram is easily transformed into physiological terms, such as physiological age versus chronological age [6], [7], [8].

The alternative model, relating the increase in mortality or aging to approximately the sixth power of time lived, can lead to some additional and interesting speculations. There is no biologic process known, however, that suggests that specific components of metabolism can be accelerated as rapidly as indicated by such a power function of time; there is, however, the common impression that time goes faster and faster for us as we grow older. This model of aging is useful to show how several vital and mutually dependent functions may together contribute to the resistance against disease. We might visualize that each of the separate physiological systems is declining uniformly with age, that is, by a linear increment of change in each increment of time. The combined effect of all these systems, however, will not be that of linear change in the total functional vigor, since it has been assumed that each system is dependent upon the others. The effects of each multiply through interaction with the others, and thus change in health may vary as a power function of time, of a degree corresponding to the number of such interdependent functions. A function containing time to the sixth power may suggest six dependent physiologic systems—perhaps they are tissue systems or systems reflecting cellular vigor, or perhaps organs. Similar features between the Gompertz model and the power-of-time model tend to indicate that the effect of decay of physiologic function is multiplicatively worsened with time.

3. The Gompertzian model

The Gompertzian model has been especially useful in comparative study of aging in animals.

Loeb and Northrup [7], Brody [8], and Pearl [9] have all presented somewhat similar arguments that death rate is an effective measure of relative physiologic age and have used the Gompertzian diagram to demonstrate these views. It is impressive to use the graphic method in presenting this argument. If we let the ordinate represent death risk on a logarithmic scale, in terms of deaths per unit of population per stated fraction of life span, with a linear scale of age in terms of fraction of life span as the abscissa, then a single curve in the form of a straight line approximately describes the biology of aging in humans, horses, dogs, rats, mice, and flies (figure 1). A corollary of this relation is the fact that the relative annual increase in the death rate as a consequence of aging is a constant fraction which depends upon the species concerned. This property of constancy of the relative increase in death risk with age is perhaps the most intriguing mystery about aging, and it provides, as well, one of the principal tools by which we can

examine the process of aging. The property of constant relative increase in death risk is often referred to as the "force of mortality." The force of mortality, measured in terms of either the rate constant or the equivalent "doubling time" for

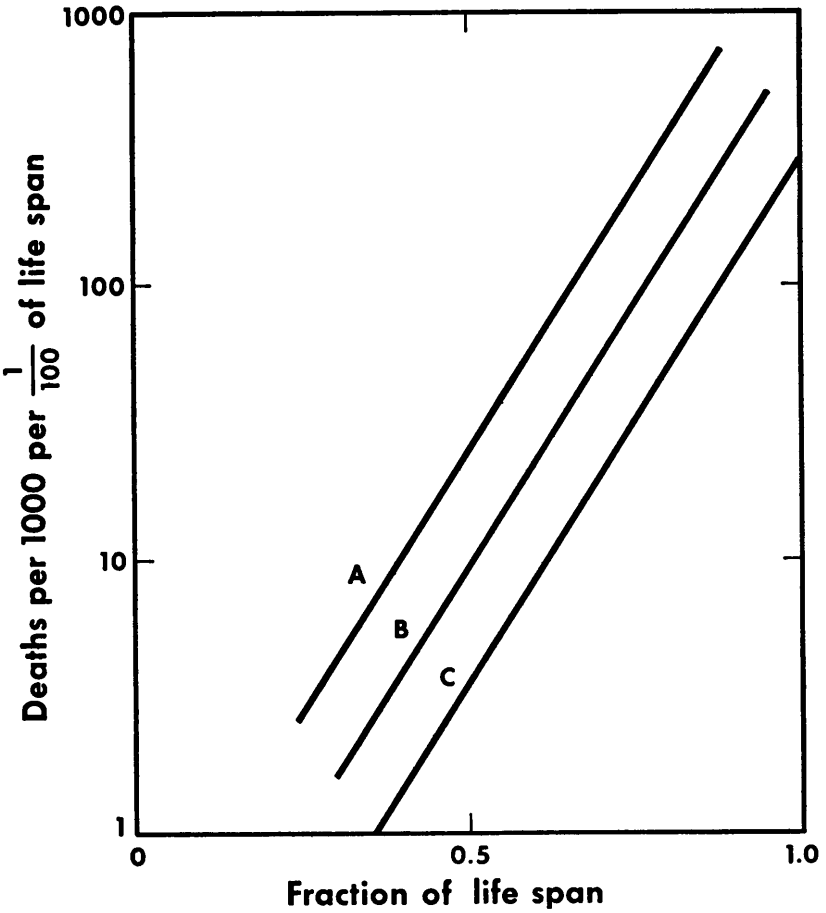

FIGURE 1

The force of mortality.
Similar curves apply to various species;
the corresponding life spans are approximately:
man, 100 years; mouse, 1000 days; fly, 1000 hours.
Curves *A*, *B*, and *C* represent successively better states, whether
with respect to genetic factors, overt disease, or environment.

death rates, varies with species, but, quite remarkably, it is usually the same under a variety of circumstances for a given species.

Not only does the death rate from all causes for a given population increase at a constant relative rate with age but also the rate for almost any selected cause of death increases at about the same pace. Many of these causes—cancer,

vascular disease, diabetes—are linked to the quality of internal metabolism. In adult human populations these causes frequently account for 60 to 80 per cent of the total deaths. It is reasonable to assume that these deaths are the result of aging in the sense that decay of functional vigor somehow underlies the onset of these functional failures. Additionally, the susceptibility to death from an infectious disease increases with age, and even the number of deaths attributed to accident shows this trend. Possibly, in the case of accident, it is the decrease in reparative processes and in the chance of survival following a given degree of accidental injury that is responsible for the increased mortality with aging. In any event, whether the initiating circumstances are internal or external, age on the average determines the probability of survival, and the death rate by age can be used as a measure of relative functional vigor or physiologic age of a defined population for the purpose of comparison with other populations.

4. Do individual differences in aging exist?

At this point it is convenient to discuss the question whether true differences in aging occur. This is a many-faceted problem, and all perspectives from which it is viewed do not necessarily lead to the same conclusion. For example, a reasonable case can be made for the argument that aging is invariant.

1. Despite some exceptions, the force of mortality is roughly constant under a variety of circumstances.

2. Risks of cancer death at specified ages (age-specific cancer mortality) are much more nearly constant from place to place and time to time than the risks of any other cause of death, possibly implying that aging as measured by cancer incidence may be more nearly a common characteristic of mankind than the variation in other causes or in the total death risk would lead one to believe. (The argument is weakened by the fact that differences in cancer risk between populations selected by time or place nevertheless are present.)

3. Where differences in age-specific death rate are observed, much of the variability might be attributed to genetic differences, inconsistencies in the methods of collecting vital data among the various population registries, and the local variation in intensity of action of specific causes. (Of course, local variation in the intensity of specific causes may be interpreted as evidence of individual differences in aging, and, as will be explained, there are methods for estimating aging trends in causes of death independently of some of the bias incurred by the varied conventions of classification within the subpopulations.)

It is the over-all contention of this essay, however, that differences in relative physiologic age and health at given chronologic ages do exist and are the result of specific factors that permit some modification of aging.

5. Changes in relative health of human populations in recent time

A striking decrease in death rates has been noted over the last hundred years and especially the last five decades. When the Gompertzian diagram is con-

structed according to the observations on death risk by age in a population of all ages followed for a calendar year, it is noted that the force of mortality increases at nearly a constant slope from those who are adolescents to the older ages. This has suggested to some the theory that aging begins after growth is completed. It is also noted, in comparisons at different calendar times, that improvement in health as measured by the decline in death rate is relatively greater at the younger ages. But, since adult health may be considered to be related to regimen and disease experience, especially in the developmental period, it is pertinent to analyze the characteristics of aging, not by comparing groups that attain different ages at a given calendar time, but rather by comparing death risk or life expectancy by age for individuals born at the same time. Acquisition of such data requires following the life history of each set of individuals born in a given year. Since such a group moves through the years as a unit or cohort, this method is termed "cohort analysis." A different impression of relative health emerges by the use of the cohort method. The death rates of women of Sweden have been presented this way in figure 2. The open circles indicate the last reported information by cohort; for example, of those born in 1900, the last age at which a death rate can be determined is that shown in the report for 1955, namely, age 55; for those born in 1940, it is age 15. From the life table report for 1955 are obtained the death rates corresponding to the row of dots linking the open circles. The dotted line increases exponentially from age 15 as though multiplicative aging began from that time. The cohort analysis, on the other hand, indicates that each cohort has a nearly constant death rate over the first 50 years of life. The death rate increases exponentially after age 50, but it is to be noted that the entire set of death rates at older ages is less for those born more recently. A possible projection of this model of aging is given by dashed lines in figure 2; the cohorts of young Swedish women have been projected beyond 1955 as they may appear if they follow this trend. On that hypothesis, death rate will remain as low as the cohort trend established during adolescence and early adult life, until each cohort is age 50; then the death rate will increase beyond that age in the usual multiplicative way. Should this be the course of death rate in these women, then we may expect that girls born in 1940 will live their lives on the average with one-tenth of the death risk associated with the corresponding ages of women reported for calendar year 1955. Perhaps the health of people living in Sweden may have already improved to that extent. This particular analysis of aging is consistent with an interpretation that decrements in health over life span are multiplicatively enhanced by time. It is also consistent with the circumstance that the death rate of each cohort of Swedish women remains constant in early adult life, but that each cohort born later maintains better health, even though most of these individuals, though younger, are extant at the same calendar time as the earlier cohorts and may be presumed to have the same environment.

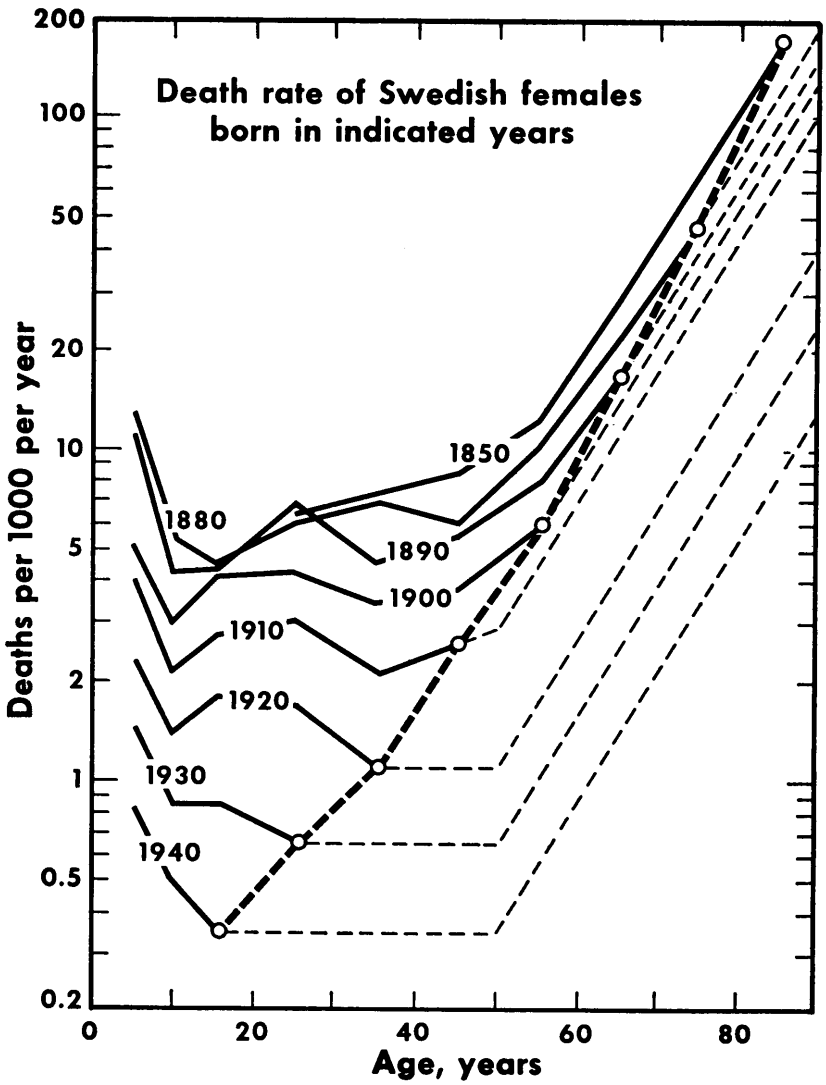

FIGURE 2

Death rate by age of cohorts of Swedish females.

6. Infectious disease, life span, and aging

It is an established fact that mortality from infectious diseases has almost disappeared over the past century and that much of this change has occurred during the last 50 years. It is tempting at this point to divert the discussion into a consideration of how and why these diseases have diminished their toll. It is obvious that many specific remedies have been applied against these infections

in terms of both individual care and preventive public health measures. Yet, while mortality from most of these diseases shows a consistent trend downward, with greater relative gain in more recent times, there has nevertheless been little decisive concurrence of major discoveries with declines in the total mortality. The effect of antibiotics, it is true, is seen dramatically in the decline in deaths from tuberculosis and pneumonia from 1940 to 1950, but the downward drift in death rates from all causes for this decade is consistent with the expectancy extrapolated from the trend of the last 50 to 100 years. Consequently, we may suppose that the gains in relative health are attributable to a large number of factors probably acting continuously over this period. It is possible that the decline in infectious disease may have had its origin in improvements in living conditions and nutrition—trends that began to accelerate in the late nineteenth century. If this be the explanation of the trend, the specific contributions of vaccination, pasteurization, and antibiotics have been additional gains not immediately observable in an already improving system of resisting disease. As will be discussed later, agents such as vaccination and antibiotics may have a more pronounced beneficial effect when viewed over the whole life span than their specific, immediate action in producing a decline of mortality from an acute infectious event.

The most obvious factor responsible for the increase of life expectancy recently is the decline of mortality associated with the infectious and childhood diseases. Prior to 1900, tuberculosis was the leading cause of death at nearly all ages; the tuberculosis death rate has since fallen to 10–15 per cent of its former value and is still declining rapidly. Scarlet fever, whooping cough, and diphtheria have nearly vanished as measurable causes of death. With the possibility of suppression of streptococcal infection, rheumatic fever may also disappear. The sum of all these benefits has been that humans, especially children, have recently been exposed to less total disease trauma and risk of death, so that a much larger proportion of infants survive and develop into adults. This fact is largely responsible for the shift in mean life expectancy at birth in Western countries from about 30–35 years in 1900 to about 68–75 years today. The situation is analogous to that of two individuals who start out with equal fortunes not subject to replenishment. The one buying fewer items and spending less per item (characteristics usually common to both economics and health) will have more of his fortune remaining at any time; indeed, the difference between the thrifty individual and the spendthrift may be very great.

In the adult ages, deaths from these infectious processes diminish, perhaps because of the increased prevalence of naturally acquired immunity to these diseases and the likelihood that those of lesser resistance have already disappeared from the population to a large extent. Consequently, if we examine either death rate or life expectancy, it appears that there is less apparent change per year of age for adults than for very young children with regard to life-table death risk. It is easily demonstrated, also, that the death rates and life expectancies for older adults at any selected age show less range of variation in a compared sequence of calendar years. In fact, the older the age selected for the

comparison, the less the apparent variation. Generalization from this important fact, however, leads to extremely divergent opinions concerning the process of aging.

The generalization usually drawn from the fact that environmentally caused

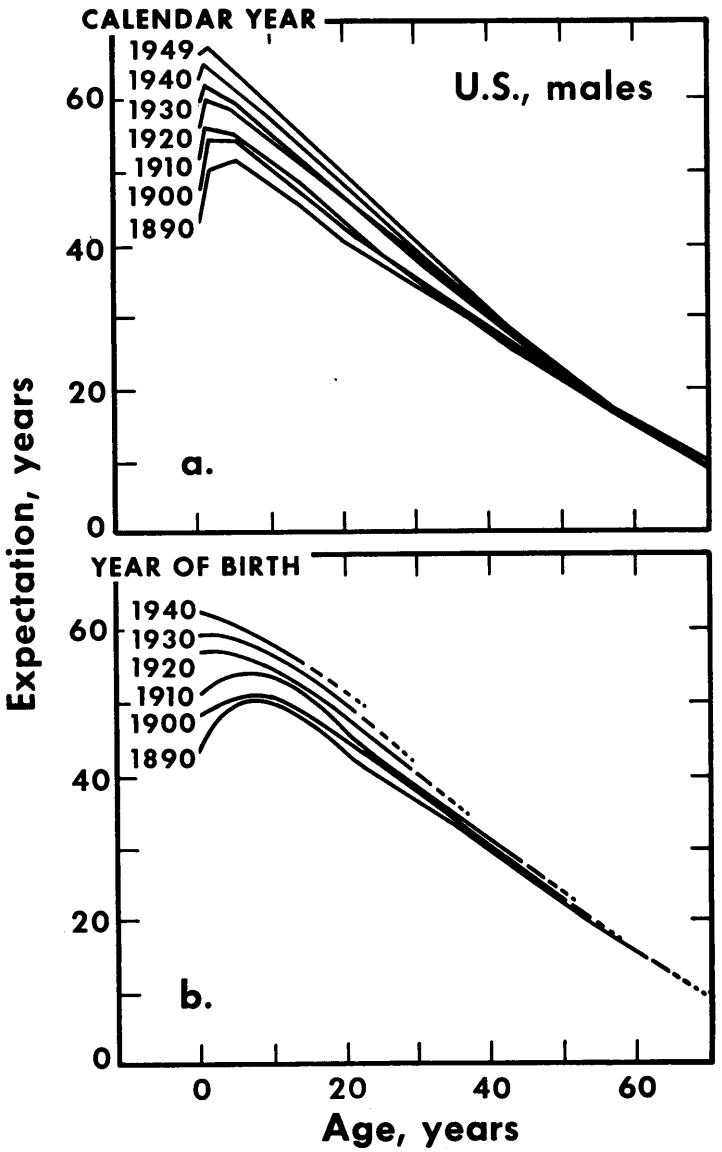

FIGURE 3

Life expectancy of United States males
(a) by calendar years, 1890–1949, and
(b) by cohorts, 1890–1940.

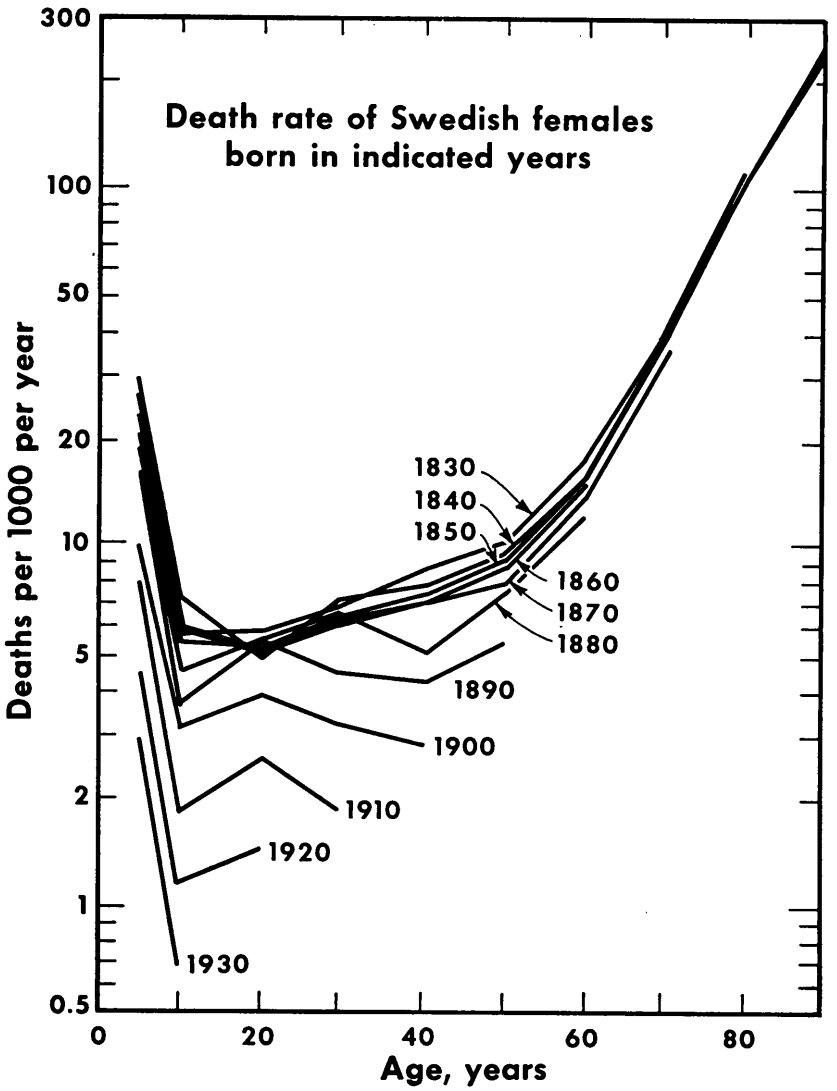

FIGURE 4

Death rates of Swedish females by cohorts, 1830–1930.

gains in life expectancy or death rate in a given population decrease with age is that basic factors of aging are invariant and that internal aging eventually takes control, in spite of gains related to reduction in environmental hazard.

Quite a different generalization may be reached from this same information if we employ an analysis of aging based on continuity of disease experience as a controlling factor in determining the morbidity and mortality of a population. This is a more effective way of separating the two distinct phenomena involved:

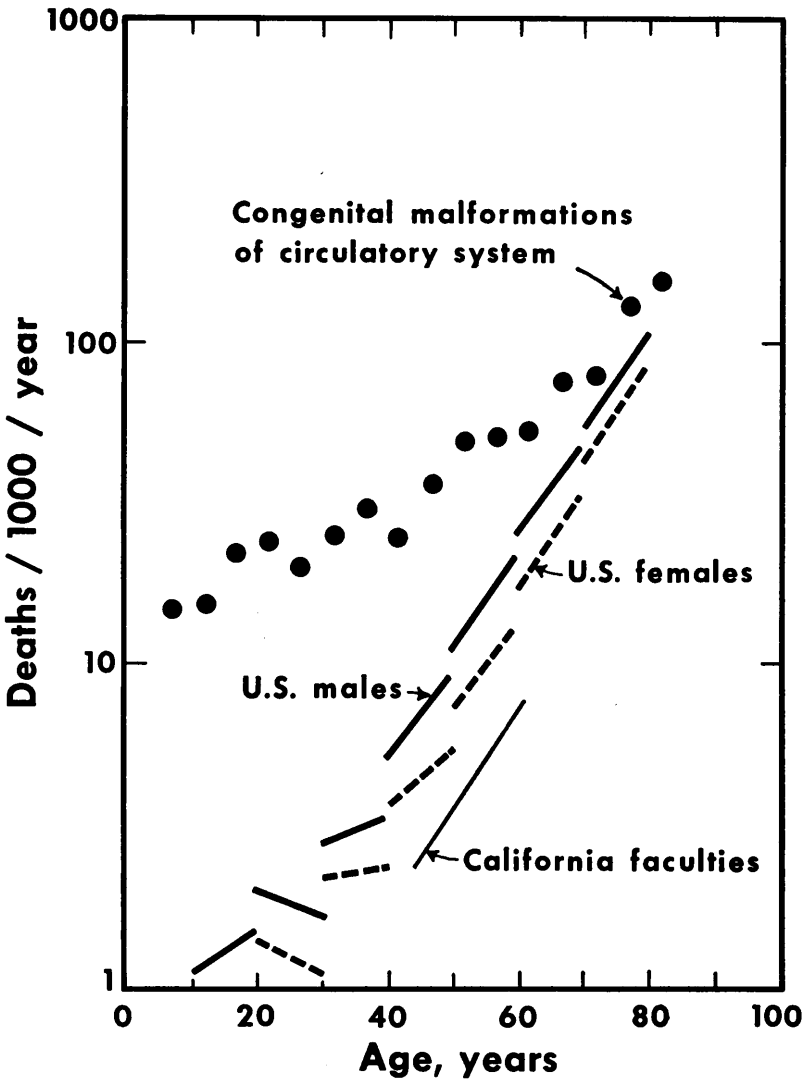

FIGURE 5

Death rates of various United States categories:
(1) cohorts of U.S. males, 1940–1950;
(2) cohorts of U.S. females, 1940–1950;
(3) college faculty members, ages 20–64, California, 1949–1951;
(4) abstract population dying of congenital malformations of the circulatory system, U.S., 1954–1955.
The wide difference between categories (3) and (4) is noteworthy.

the effects of time on the aging process and on the health characteristics of the environment. In figures 3 and 4, comparisons are made between groups that have attained the stated ages in designated calendar years. For groups of different ages their early years were spent in different environments. Average disease experience has changed drastically in the last century. Those who are 60, for example, lived their childhood and developmental life over 40 years ago, when control of childhood diseases was much less effective.

7. Childhood health in relation to adult health

Beginning at least a century ago, death rates have been declining for all ages. A special feature of this change is that the gains have not been equally apparent in all ages of life at the same calendar time. An especially pronounced instance of this kind is an effect observed in the vital statistics of Sweden: soon after 1855 and again after 1885, early childhood mortality dropped rapidly without corresponding declines in adult death rates at the same calendar time. After the intervals of time necessary for these cohorts of children to become adults, the population showed corresponding improvement in adult health. Childhood mortality in Sweden thus becomes a good basis of prediction of adult mortality when considered from a predictive age in childhood to those same cohorts 45 years later [6].

Correspondence of childhood mortality with adult mortality is especially strong in the cohort analyses of the northern European countries; these are the countries that have achieved the lowest death rates in all ages and, of course, a specially impressive gain in the lowering of mortality in early life. The cohort trend shown in figure 2 is consistent with other populations. This trend is also apparent in a limited cohort analysis for the United States (figure 5). In this graph of death risk by age, cohorts of population are shown plotted over the 10-year span 1940–1950. It is noted that, at all ages, 1950 groups of males or females have a lower total death risk than do 1940 groups at the same ages. Analysis of the gain in health by cohorts [6] shows that the gain is distributed throughout the various causes of death. Decline in tubercular deaths may account for a quarter of the decline in mortality. Tuberculosis and rheumatic fever are the two diseases that have contributed most conspicuously to long-standing adverse effects on health from early disease. The life-span effect of tuberculosis seems to depend upon the continuance of active infection in some degree. Support for this view is seen in the dramatic improvement of general health in Japan in very recent times; though a causal connection would be difficult to establish, it is noteworthy that a rapid decline in tuberculosis deaths is associated with the improvement of death rates at all ages [6].

8. Late effects of streptococcal infection

The life insurence *Impairment Study* [10] reviews experience in the pool of policyholders for a number of circumstances of physical impairment known at

TABLE I

HEART-MURMUR CASES REPORTED IN LIFE INSURANCE "IMPAIRMENT STUDY" (1951)

GROUP*	ALL DEATHS			MALIGNANT NEOPLASMS			VASCULAR LESIONS OF CENTRAL NERVOUS SYSTEM			HEART AND CIRCULATORY DISEASES			DIGESTIVE DISEASES			ACCIDENTS AND HOMICIDES		
	Obs.†	Ex.‡	SMR§	Obs.	Ex.	SMR	Obs.	Ex.	SMR	Obs.	Ex.	SMR	Obs.	Ex.	SMR	Obs.	Ex.	SMR
A.....	947	527.4	180	109	77.8	140	33	19.0	174	532	178.6	298	21	29.3	72	56	74.3	75
B.....	177	80.9	263	10	8.1	124	7	1.5	465	115	23.3	493	6	4.4	136	11	11.5	96
Total..	1124	608.3	185	119	85.9	139	40	20.5	195	647	201.9	320	27	33.7	80	67	85.8	78
C.....	155	158.2	111**	14	18.7	75**	Not reported			72	49.0	147**	7	9.6	73	26	20.5	127

* Description of group classification of policyholders:
Group A = Constant murmur without hypertrophy or rheumatism
Group B = Constant murmur without hypertrophy or rheumatism with history of tonsillitis or streptococcic infection
Group C = Inconstant murmur without hypertrophy or rheumatism

† Obs. = Observed.

‡ Ex. = Expected.

§ SMR = Standardized mortality ratio.

** Differences significant at $p < .01$.

the time of issue of each policy. In the groups affected with heart murmurs, it may be presumed that health appeared good in other respects, since they were granted insurance. The difference between those with constant murmur and those with intermittent murmur may be assumed to be small. A comparison is nevertheless made between these two groups, excluding those with cardiac hypertrophy or experience of rheumatism, and it may be seen (table I) that the presence of a constant murmur involves a significant increase of risk over the presence of an inconstant murmur. As expected, the death risk from cardiovascular disease is extraordinarily high in both groups, in keeping with the usual impressions concerning the linkage of heart murmurs with a tendency toward vascular accident. Cerebral vascular disease is also elevated, but the surprising fact is the elevation of cancer risk.

The three major causes of death in the general population are all elevated in association with heart murmur, so that an evaluation of aging with regard to the presence of a murmur suggests that this condition is roughly equivalent to an over-all increment of aging, as gauged by the advancement of risk of the major causes of death. No suggestion is implied, however, that each cause of death is equally intensified in association with heart murmur; but the possibility that, on the average, some streptococcal involvement is associated with the occurrence of heart murmurs, even in the absence of rheumatic symptoms, does suggest that some of the decline in death risks associated with improvement of childhood health may well be the average consequences of reduced frequency of streptococcal infections.

The effects described for the cases of heart murmur without known rheumatism are intensified in the group with overt rheumatic symptoms. It seems probable that rheumatic fever complications exist in a continuum of grades of severity, so that late streptococcal infection effects in a general population may be considerably greater than those estimated from a description of the incidence of clinically evident complications of rheumatic fever. The drastic long-term effects of both rheumatic fever and tuberculosis in health and death risk throughout life span suggest that all the infectious diseases may have the same kind of deleterious effect. If this be true, however, there is no estimate of the relative detrimental effect of each, nor is it known whether such long-term effect would depend upon long-lasting active disease, as in the example of tuberculosis, or upon the aftermath of sclerotic changes in critical tissue areas, as in the case of rheumatic fever.

9. Acute and long-term effects of illness

In radiation exposure both immediate mortality (associated with radiation sickness) and long-term effects on the death rate, simulating aging, have been shown to depend upon the degree of exposure. Acute radiation exposure effects can be modified by change of the rate at which a given total dose is administered and by applications of antibiotics, reticuloendothelial transplants, shielding of

spleen or bone marrow, and so on, without influencing the long-term aging effect of irradiation. It appears, then, that acute effect per se is not the feature determining aging; rather, aging results from some other characteristic feature of radiation exposure that is unaffected by the above remedies for acute exposure. In acute illness, too, there is likely to be a narrow margin at times between survival and death, where an extra increment of morbidity may tip the scales toward death and yet not appreciably worsen the extent of recovery if recovery, indeed, ensues. A remarkable example of this system in humans can be drawn from the vital statistics of prisoners of war.

10. Health and mortality of prisoners of war

It is quite comforting to know that prisoners of war in most circumstances of confinement have not shown an excessive mortality following release from internment. Prisoners held by Japan in the Pacific area did show excessive mortality during their imprisonment and, in the one instance of reported follow-up for six years thereafter, have persisted in showing an elevated death risk equivalent to aging.

In Santo Tomas Internment Camp and related prisons in the Philippines, 435 deaths in approximately 6400 internees were observed during a 3.4-year period (January 4, 1942 to June 4, 1945) [11]. The excess mortality is greater in males and is equally distributed over the range of ages; standardized mortality ratios (SMR) of 236 for males and 130 for females are obtained by applying estimates to the sample vital statistics reported by Pearson as of 1945. Subsequent follow-up of these people is not reported.

A roughly parallel situation is reported by Bergman [12] with respect to mortality of internees in Java in 1944 and 1945. The age-distributed mortalities are presented in figure 6. Here is the accounting of 10,350 male civilians, aged from 10 to 85 years, followed from February, 1944 until August, 1945, or prior death (744 died). They are shown in comparison with the corresponding vital statistics of the male Australian population for the period 1944–1945. A remarkable feature of the effect of environment on age-distributed mortality can be appreciated in this diagram. Mortality for each age is increased by the same proportion regardless of age. Equivalent elevations of death risks, affecting all ages, are observed repeatedly under environmental conditions of various kinds [6]. As the environment deteriorates further—or, more likely, as the internees deteriorate through protracted exposure to conditions of infection and starvation—the death risk increases, so that the rate during 1945 is approximately double that registered for 1944. In this instance, too, the stress affects the death risk to the same relative extent at all ages.

The lines representing the average age-distributed mortality in figure 6 do not express the situation affecting the individual; each individual's risk is changing in the way illustrated by the two examples drawn upon the figure, corresponding to cohorts beginning internment at ages 30 and 65. These individual

risks increase sharply; the death rate increases by a factor of 3 during the first year of internment and is nearly eight times its initial value by the end of the second year. These two illustrative examples portray a change in the force of mortality during exposure. At the same time they reflect the acute period of starvation and disease to which the survivors were also exposed. The inference

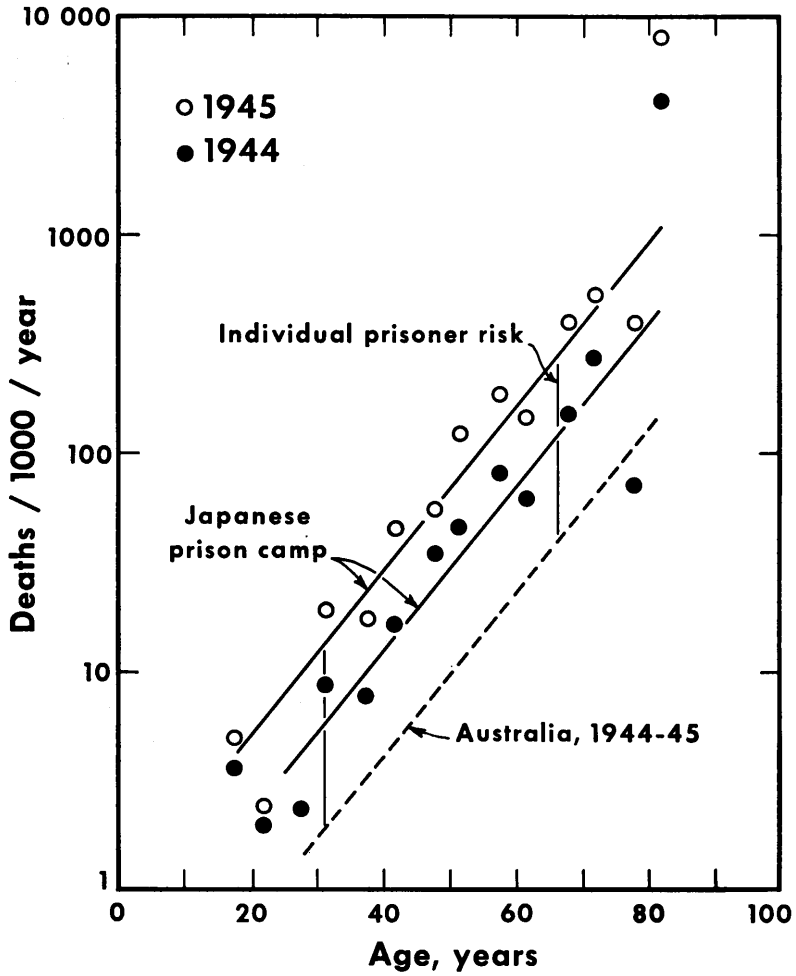

FIGURE 6

Death rates of Australian prisoners of war, 1944–1945.

follows that these individuals may have incurred some permanent decrease of health, even though liberation and subsequent care led to a recovery of the major attributes of health. Bergman writes: "The process itself [decline of health with internment] is fortunately not irreversible. Every physician with experience among ex-prisoners knows that many of them made remarkable recoveries. They

regained their physical ability and mental fitness to an astonishing degree; most of them are at work again, although they remain more gray and wrinkled than fits their real age" ([12], pp. 16–17).

A postinternment follow-up is available for United States armed forces personnel. It is only the group interned by Japan, largely from the Philippines, that is materially affected, according to the 6-year follow-up reported. While follow-up to the present time would be more meaningful than just the 6-year study presently available, it appears likely that such internees have, on the average, experienced some 4–8 years of aging as a result of this experience and nearly the same reduction of life expectancy if these risks continue [6]. Whether the causes of this situation are true injuries persisting from the morbidity experiences incurred during internment or the composite effect of various residual states of chronic infection is difficult to say. It is remarkable that, under the circumstances of multiple acute afflictions in each person during this period, recovery left so little effect upon average health.

The example of death-rate change in prisoners of war is helpful in understanding some of the subtleties in interpretation of vital data bearing on the problem of aging. Thus, the ordinary life-table method gives the impression correctly that death rate is increased by internment uniformly for all ages, but it leads to an incorrect assumption about the force of mortality; correctly viewed by cohort analysis, force of mortality is shown to be extraordinarily intensified. The later follow-up of the internees suggests that much of the "aging" induced by internment persists.

Starvation and war-caused duress of less severity than in the case of these prisoners afflicted the entire population of the Netherlands during 1945. These people experienced for a short period the same sort of relative intensification of death risk at all ages as in the case of prisoners of war; but, even in the next year, the residual effect of the experience was imperceptible. Starvation sufficient to increase the average mortality of a population by 70 per cent, acting for less than a 1-year period, appears to impart no lasting effect.

11. Metabolic events known to be associated with aging

11.1. *Blood lipids.* Evidence accumulated over many years has linked serum cholesterol levels with arteriosclerosis. At various periods in the study of lipid metabolism, each of the chemically determined categories of serum lipids has been associated quantitatively with arterial disease. Gofman et al. [13] introduced a major technical innovation that has resulted in an even more specific linkage between blood-lipid levels and arteriosclerosis, since their extension of ultracentrifuge theory established a method of analytical separation of serum lipids in their native molecular states. These lipids are found to be an array of lipoproteins, varying in both quantity and kind of complex lipid fraction and in characteristic molecular weight. With the aid of this tool, the risk of recurrence

of a vascular disease accident (table II) was shown to be dependent upon the patient's serum lipoprotein level [14].

TABLE II

RECURRENCE OF MYOCARDIAL INFARCTION

Source: Jones et al. [14]
Normal = 42 mg. per cent

Serum S_f° 12–20 Lipoprotein in Per Cent of Normal	Recurrences per Patient-Year of Observation	Recurrences per 1000 per Year
Less than 83	0/17	(0)
83–119	3/50	60
120–43	4/51	78
144–90	10/110	91
191–238	11/70	157
Greater than 238	11/61	180

Other methods of appraising the relative risk of myocardial infarction associated with serum lipoprotein levels have been employed, including a direct prospective measure of this risk from individuals characterized in their preattack state [15]. The distribution of lipid levels in the general population base is considerably different from that in the clinical population of survivors of myocardial infarction originally studied. Observations on the general population lead to the conclusion that the span of relative risks of occurrence of myocardial infarction extends from 0.2 of the average for the lowest 10 per cent to 3.0 times the average for the highest 10 per cent, classified on the basis of the fraction of low-density serum lipoproteins having a flotation constant S_f° 0–400 [15]. This range corresponds to a fifteen-fold variation in intensity of the vascular disease risk. Other blood-lipid measures are also significantly associated with enhanced coronary disease risk. Dawber et al. [16] have shown that those in the upper ranges of serum cholesterol elevation incur six times as great risk of coronary disease attack as the group having the lowest cholesterol concentration.

Reduction of the heart disease risk appears practicable, using dietary methods for lowering the disturbed elevations of serum lipoproteins [17]. Reversibility of the process by which lipids are deposited in xanthoma tuberosum lesions, which is thought to be biochemically related to the phenomenon of arteriosclerotic deposition of lipid materials, has been observed during prolonged periods (6 months or more) of suppression of serum lipids through diet and heparin injection in such patients. It is not known, however, whether the lowered risk of recurrence of myocardial infarction depends upon any particular phase of the dietary change. Decreased frequency of recurrence is at least associated with lowered lipid levels; the accumulated arteriosclerotic changes may not revert so quickly, if at all.

11.2. *Other physiologic states associated with altered life span.* The distribution of blood pressures in the population of those free of overt disease centers about a considerably lower value than in the groups of individuals who have survived myocardial infarction. Estimations of the relative probability of incurrence of myocardial infarction made on the basis of blood pressure suggest that blood pressure has about equal importance with serum lipids in the estimation of heart-disease risk [4], [16]. Blood pressure and blood lipids are only very slightly correlated, so that their usefulness in predicting the risk is additive. On the other hand, overweight, a factor of considerable importance as a basis of estimating life expectancy, may not supply additional information beyond that contained in the lipid and blood-pressure data, because of the strong positive correlations between overweight and either blood pressure or serum lipids.

Other factors that are associated with life-span differences are smoking, marital status, sex difference, differences between urban and rural life, and occupational factors. The common feature of the effects of each of these factors is that the displacement of mortality rates associated with each persists to about the same extent throughout the adult ages available for comparison. In each instance, circular arguments arise as to whether excess mortality is the effect of the environment or whether the environment has been chosen by people having intrinsically different health.

Eventually perhaps it may be possible to examine the complex structures of these current debates concerning what is cause, what is effect, and what is random in the observed associations. The strength of current arguments is based upon the degree of consistency in direct evidence—on the fact that these group differences do exist and with remarkable reproducibility of the differential mortality in samples drawn from different places and times. An interesting comparison may be drawn to summarize several of these associations; for example, the single, heavy-smoking male, sedentarily employed in a large United States city, may be compared with a married, nonsmoking female living in rural Scandinavia. If all these factors are assumed to be independent and additive, one would predict a difference in physiologic age, and an approximately similar difference in life expectancy, of 20 to 35 years. Other comparisons are equally striking in terms of life-table displacements equivalent to aging: 70 per cent overweight may be equated with 15 years' aging; a change from the 25th percentile to the 75th percentile of serum lipoprotein levels, with 17 years' aging; the smoking of one package of cigarettes per day throughout adult life, with 7 years of aging. Other comparisons are given in table III.

11.3. *Diabetes mellitus.* Diabetes mellitus is a prime example of a disease induced by lack of a single hormone—in this case, insulin. Physiologic and pathologic changes subsequent to the onset of diabetes, however, may be vastly complicated. Prior to the discovery of insulin, diabetes was typified by a high mortality throughout the survival period of the diabetic. Following the discovery and use of insulin, mortality began to decline and has continued to decrease up

TABLE III

PHYSIOLOGICAL AGE AND LIFE-SPAN DIFFERENCES

Source: Jones [27]

REVERSIBLE		PERMANENT	
Comparison	Years	Comparison	Years
Country versus city dwelling†	+5	Female versus male sex†	+3
Married status versus single, widowed, divorced	+5	Familial constitutions‡	
Overweight*		2 grandparents lived to 80 yr	+2
25 per cent overweight group	−3.6	4 grandparents lived to 80 yr	+4
35 per cent overweight group	−4.3	Mother lived to age 90 yr	+3
45 per cent overweight group	−6.6	Father lived to age 90 yr	+4.4
55 per cent overweight group	−11.4	Both mother and father lived to age 90 yr	+7.4
67 per cent overweight group	−15.1	Mother lived to age 80 yr	+1.5
or: an average effect of 1 per cent overweight	−0.17	Father lived to age 80 yr	+2.2
		Both mother and father lived to age 80 yr	+3.7
Smoking**		Mother died at 60 yr	−0.7
1 package cigarettes per day	−7	Father died at 60 yr	−1.1
2 packages cigarettes per day	−12	Both mother and father died at age 60 yr	−1.8
Atherosclerosis***			
Fat metabolism			
In 25th percentile of population having "ideal" lipoprotein concentrations	+10	Recession of childhood and infectious disease over past century in Western countries	+15
Having average lipoprotein concentrations	0	Life Insurance *Impairment Study*//	
In 25th percentile of population having elevated lipoproteins	−7	Rheumatic heart disease, evidenced by:	
		Heart murmur	−11
		Heart murmur + tonsillitis	−18
In 5th percentile of population having highest elevation of lipoproteins	−15††	Heart murmur + streptococcal infection	−13
		Rapid pulse	−3.5
		Phlebitis	−3.5
Diabetes‡‡		Varicose veins	−0.2
Uncontrolled, before insulin, 1900	−35	Epilepsy	−20.0
		Skull fracture	−2.9
Controlled with insulin		Tuberculosis	−1.8
1920 Joslin Clinic record	−20	Nephrectomy	−2.0
1940 Joslin Clinic record	−15	Trace of albumin in urine	−5.0
1950 Joslin Clinic record	−10	Moderate albumin in urine	−13.5

† Central Bureau of Statistics (Statistiska Centralbyrån) (1917, 1953); National Health Service of Denmark (1914, 1921; 1937, 1949); Federal Security Agency (1940–55).

* Dublin et al. [20].

** Hammond and Horn [21].

*** Gofman [22].

// Society of Actuaries [10].

†† This 70 per cent difference in distribution of lipoproteins, between 25 per cent versus 5 per cent highest, is equivalent to a total of 25 years in relative displacement of physiologic age.

‡ As measured in 1900. These effects may be measurably less now, as environment is changing to produce greater differences between parents and progeny.

‡‡ Joslin et al. [18].

to the present time. The mortality rates in table IV have been estimated from survival numbers given by Joslin et al. [18].

TABLE IV

MORTALITY OF DIABETICS DURING FIRST TEN YEARS OF THE DISEASE BASED ON CASES TREATED AT THE JOSLIN CLINIC [10]

Calendar Period	Years of Diabetic State	Deaths per 1000 per Year
Pre-insulin:		
1897–1914	All intervals, 0–10	213
1914–22	All intervals, 0–10	192
Insulin era:		
August, 1922–December, 1929	0–2	95
	3–10	147
1930–36	0–2	41
	3–5	57
	6–10	103
1944–51	0–2	20
	4–10	60

Before the use of insulin, diabetes had a feature in common with cancer in that the death rate for any affected group was high, about 200 deaths per 1000 per year, and the rate was essentially unrelated to the duration of the disease though slightly age-dependent with higher death rates at the younger ages [6]. Subsequent to the employment of insulin, the death rate fell dramatically and concurrently became dependent on the duration of the disease, increasing with the duration. At the present time, the effect of diabetes on the death rate appears to be a multiplication of the general population death rates by a constant factor of approximately 1.7. In units of physiologic aging, this is equivalent to about 6 years. The analysis of mortality risk I have made for diabetic cases treated at the Joslin Clinic implies that diabetics using insulin escaped the immediate, acute effects of the disease but "aged" more rapidly than the general population. In the early experience with insulin, once the diabetic patient was rescued from the high risk of dying in coma, he showed an initial death risk close to that of the general population of the same age; but thereafter, the death rate increased rapidly. The analysis shows, however, that by 1930, when treatment with insulin had been supplemented by other advances in medical care, the force of mortality became less and it continued to decrease subsequently. The effect was as though accelerated aging was very pronounced in the early history of the use of insulin; aging was perhaps induced then by the incompleteness of the control of carbohydrate and fat metabolism. Characteristic of the disease in the 1920's was the tendency for the diabetic patient to develop arteriosclerosis rapidly and to have other advancing complications of degeneration of vital tissues; all of

these changes simulate the effects of aging. The acceleration of aging in the diabetic was marked in the partially controlled diabetic of that period; subsequently, as methods for controlling the diabetic state improved, the excess rate of aging was reduced progressively. The modern period has been marked by a succession of discoveries affording better management of the diabetic. Throughout this example we can perceive a model of aging in which physiological or metabolic disturbance in humans has acted to increase the rate of aging, and the effect seems to be in proportion to the degree of metabolic disturbance. Accelerated aging is also the plight of some diabetics today who, for one reason or another, are refractory to the usual means of control of the disease. The observed acceleration of aging of the diabetic is remarkably parallel to that of the individual with elevated blood fats and blood pressure, or the obese individual. In the examples of diabetes and other disturbances of metabolism, the force of mortality must then be greater than normal, indicating an accelerated rate of aging analogous to the effects of chronic irradiation.

11.4. *Cancer as a metabolic disease affording insight into aging.* Individuals having malignant tumors are known to have particularly high death rates, frequently in excess of 200 deaths per 1000 cancer patients per year. (Estimated on the basis of the death rate over a very small increment of time, in contrast to life-table death rates that are deaths in a defined population followed for one year.) Such death rates characterize all such patients, beginning with the onset and remaining the same for the group over the duration of follow-up. In consideration of this constant death risk throughout the duration of malignant tumors, it appears that the ability to remain alive in the cancer state does not decline during the course of the disease. This suggests that the host of the cancer is able to cope with this burden, as might a juggler; but the condition is essentially unstable and has a high and constant probability of giving way to terminal disturbances. These terminal events lead to the rapid demise of the patient and may themselves be intensified multiplicative failures of function. It is also instructive to point out that the occurrence of death in cancer is not always accompanied by the fulminating growth of neoplastic tissue; deaths from intercurrent disease are just about as likely to occur as recurrence of the malignancy [6]. Thus one may argue that the crucial events characteristic of aging are those of the terminal state in cancer, and the less significant ones are those that lead to the overt appearance of cancer.

Another somewhat paradoxical situation is deduced from the life-table characteristics of cancer patients. Abstract death rates [19] were constructed as though these individuals were predestined from some early point in life to die of cancer. For this artificially defined population, the death rates and the force of mortality are nearly the same as for the general population; in both groups the death rate represents all causes of death, even though, by definition, the first group dies only of cancer. Now we may appreciate a situation that may explain the course of aging more generally. The apparent value of the death rate by age of those who will die of cancer is similar to the total death risk at the same age in

the general population. Thus we can deduce that the force of mortality or the relative rate of increase of death risk, whether derived from consideration of the defined abstract population or from the rise in the incidence of cancer through the adult ages, is really a measure of the events that determine the risk that cancer may develop. Once this outcome occurs and overt malignancy is present, a new and overriding factor is introduced which tends to mask the earlier process. The extremely high death rate, practically independent of age, which is characteristic of clinically confirmed cancer is superimposed on the slowly accelerating course of the events leading up to the overt condition. Thus the multiplication of the preliminary events has led to the clinical evidence as a final step. The subsequent degenerative changes which, in the event of cancer, may be regarded as the consequence of aging rather than a part of the aging process itself, no longer follow the typical course of the force of mortality but occur in fact at very much higher and constant death risks.

The terminal state of cancer, in which metabolic changes of a rapidly progressive and life-limiting nature develop, can perhaps be considered as a model of aging change, however, in the following way. At age 50, the average risk of dying, based on all causes of death, is about 10 chances per 1000 per year. If cancer is evident, the risk becomes about 200–300 chances per 1000 per year; and, in the terminal decline of malignant disease, the death risk is perhaps in excess of 1000 deaths per 1000 per year. (Estimated, as before, on the basis of the death rate over a very small increment of time.)

Let us assume that the carcinogenic aging process has resulted in metabolic disorganization similar in behavior to that which characterizes diabetes [6]. Following the discovery of insulin, a means was at hand to prevent death of the diabetic in coma and thus to enable him to escape the immediate, acute effects of the disease; but he "aged" more rapidly than the general population, nevertheless, and the results of that aging were evident in his sensitivity to the degree of metabolic control he exercised. Metabolic instability caused by metabolic disturbances insufficient in themselves to produce acute illness led to a very rapid progression of degenerative changes, essentially throughout the body, and the death rate increased correspondingly. However, the average death rate of such a population at any age does not reflect their average health, in this model, but merely gives some indication of the number of individuals in that population that have become metabolically unstable and will therefore rapidly reach the end of an otherwise healthy life. It is possible, in consideration of such events, that what we have come to look upon as aging may not really gauge the decline of health, since degenerative failure occurs afterward. It is possible that the changes that we regard as aging, because they are the many little steps on the Gompertzian slope, or the force of mortality, are not inherently health-limiting; but they may be the events that have set the odds that more rapidly multiplicative stages in degenerative change then may ensue.

The equivalent model can be applied to cardiovascular disease and aging. Artery wall disease certainly underlies vascular occlusive events. The events in

aging are in part those that alter the artery wall; and, to the extent that these changes can be prevented, the later sequelae can be postponed or avoided. It is not the thickening of the artery wall that is the immediate health-limiting condition, however. The observed crippling and degenerative changes of cardiovascular disease are linked to the occurrence of vascular occlusion, which usually arises as a consequence of thickening of the artery wall. Arterial occlusion destroys tissue and thereby generates a great increment of aging, viewed as a loss in the over-all functional capacity of the body.

12. Summary

I recently had a conversation with the marine biologist, Loren Carlson, who described to me accelerated aging at the time of spawning in salmon; inexplicably, aging runs its course in a few days, regardless of the mildness of the journey to spawn, and it is marked by general and fulminating degeneration of the fish. Perhaps comment on these models of aging will stimulate physiological investigation of the processes.

It is possible that the commonplace events that, to the eye, are seen as aging are not of much importance in determination of the ability to remain alive, and even to function in a useful and satisfying way. Alternatively, we may understand aging through its severe physiological and chemical changes. I purposely leave the impression that I regard such understanding as important, but my exclusion of discussion at the cellular level does not reflect disregard for that subject. Quite possibly, cellular aging is the event underlying the characteristic slope of the force of mortality; if that be so, then this process initiates the later crucial events in aging. These later steps, however, may be very amenable to physiologic control in the ways suggested in the above models.

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