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A SPECIAL CONSIDERATION OF THE AGING PROCESS, DISEASE, AND LIFE EXPECTANCY

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Hardin B. Jones

November 1, 1955

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Contents

Abstract 3
Life Span and Age-Specific Death Rate
Introduction 5
Historical Considerations 6
Processes Contributing to Increase in Life Span 7
Physiologic Age 25
Variation in Physiologic Age 30
Internal Homogeneity of Populations with Regard to Subpopulations, Physiologic Age, and Tendency Toward Disease 49
Major Disease Groups
Atherosclerosis 53
Smoking 56
Cancer and the Subpopulations Dying from Cancer. 56
The Onset of Disease and Life Expectancy 58
Summary 63
Acknowledgments 66
Bibliography 67

THE AGING PROCESS, DISEASE, AND LIFE EXPECTANCY

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ABSTRACT

This is an argument for a consideration of aging as a series of acquired deviations from optimal bodily function. The more deviation has been acquired from the optimal bodily balance, the more likely will disease experience be encountered. The more diseases are encountered and the more deterioration accumulates, the less is the chance of survival at any age of life. Acquired deviations from normal functional balance are visualized as growing so that they generate further deterioration in body functions. This process of extension of deterioration is apparently always at the same rate for all human populations at all places and at all times. It is probably an integral characteristic of body metabolism that extends the disease state so regularly that the death tendency for all populations of adults becomes doubled every 8.5 years measured from any reference age in which death tendency is determined.

Arguments and evidence are presented that we may consider the precise and logarithmic progression of the death tendency with increasing age of life to be a simple description of the circumstance that one disease experience probably leads to another. At any age the disease tendency for a sample population may be projected from a knowledge of past disease experience; and for the countries that are the most long-lived, life expectancy and the adult death rates - even though they are changing from year to year - are precisely predicted from the death tendency of these same adults when they were very young children.

Childhood disease experiences are very important to health in all ages of life. Diseases experienced at any time of life apparently add increments to physiologic decay. Diseases and unhygienic factors that in themselves do not cause death are probably important in fixing the tendency toward other diseases and limiting the average life expectancy.

The age-specific tendencies for development of any of the internal diseases--cancer, coronary heart disease, cerebral vascular disease, hypertension, diabetes, etc.--are not the same in the various samples of the world's population; there are very great differences even between countries of similar cultural character or within one country. There are ten to twenty years of difference in physiologic age if populations are to be compared at ages when each has the same tendency toward disease. These differences are interpreted to be true ranges of physiologic age for different populations in contrast to the usual concept of chronologic age.

The tendency to develop all the major diseases of adult life is seen to be diminishing steadily when people of the same age are compared throughout a century of calendar time for any of the populations of the western world. If the tendency to develop these diseases of internal origin may be taken as a measure of general intactness of body function, then the physiologic ages of the populations of the world are becoming more and more youthful at every chronologic age.

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LIFE SPAN AND AGE-SPECIFIC DEATH RATES

INTRODUCTION

Many known properties and functional capacities of the body are changing--to the detriment of our existence--as accumulated time increases from birth. Some changes appear to occur characteristically at a particular age, as though they may be the end points of other processes; some are gradual and subtle evolutions suggesting that the metabolism of the process may have begun in earlier life. The time relationships of all such changes are slow in terms of days or weeks. It is likely, however, that disfunction accumulates and adds to the further tendency toward deterioriation.

The general lessening of the perfusion of blood through the various tissues, the disturbances of lipid metabolism and the growth of atherosclerotic deposits, the rarefaction of the bony structure, the mineralization of the soft tissues, obesity, sclerosis, and atrophy or hypertrophy -- are easily comprehended as deterioriations that limit the extent of body function in proportion to the amount of change that has accumulated.

There may be as many general forms of aging as there are diseases and pathologic etiologies of disease, but great individual variation in the degree of physiologic decline may always be found.

This essay is a general consideration of the aging process and of the interplay of disease and physiologic function in that mechanism. It shows that deterioriation is the associated sequel of disease, that the metabolic derangements that express themselves through the appearance of internal diseases develop on a time scale of characteristic speed, that disease is only relative and proportional to the past exposure to disease, and that as calendar time passes, modern civilization is experiencing a lessening tendency toward all the major diseases at every age of life.

Some readers may be puzzled by statements in this paper that cancer and other degenerative diseases appear to be on the wane, even though much current literature gives the impression that cancer, heart disease, etc., are increasing. This discrepancy can be explained by the declining tendency toward infectious diseases early in life which allowed larger numbers of individuals to reach ages when these internal diseases are more likely to occur. The absolute number of cancer and internal disease deaths per unit of the population has increased, but the tendency towards internal diseases is smaller if disease- or death-incidence measurements are made for individuals at the same year of life. The entire population is now living longer and the

average age when internal disease will probably occur is delayed, even though death will largely result from internal diseases rather than infectious diseases.

The argument is constructed upon an evaluation of population death-rate functions and causes of death. The mathematical logic of this analysis is presented verbally and in terms of graphic presentation. The beginning is a consideration of the rate at which populations die. A convenient form of this information is the progression of the death rate as chronologic age increases. In life tables this function is given as "q_x", the proportion of individuals dying during that year of life out of the number of persons alive at its beginning; and this function will be given as the age-specific death rate, the number of deaths per year per 1000 persons of a given age.

The argument is presented for the male alone for the purpose of uniformity and simplicity, but there are no known discrepancies that would disallow the drawing of similar conclusions from the examination of populations of women.

HISTORICAL CONSIDERATIONS

Probably people of every culture must have been aware of the force of mortality that is described in the graphic considerations of the age-specific death rates, Fig. 1, 2, 3, 4, 5, 6. During early adult life of all known civilizations the rate of death has always been considerably below the values that are reached progressively as the death tendency increases during the adult life span. The general statement of this relationship is that the older a person becomes the much more likely he is to die. The regularities of the progression of death tendency are indeed remarkably consistent, and were recognized in construction of early life tables for man. The first mathematical description of the progression in intensity of the death-rate function with increasing age is credited to Benjamin Gompertz,[5] who in 1825 established that the dwindling of the numbers of individuals alive as life tables progressed to the older ages was the consequence of a uniform logarithmic increase of the tendency to die with increasing age. The function labeled "q_x" in modern life tables is at other times referred to as the Gompertz function. Fortunately, however, Mr. Gompertz's death-tendency functions do not apply to our civilization except in India and the Virgin Islands, because the level of disease has regressed remarkably during the last 125 years in response to more hygienic living conditions. The Gompertz values are shown in Fig. 1 with representative values of the age-specific death rate for differing contemporary populations and for a selection from our immediate past. Several general deductions can be made from an inspection of this figure of the age-specific death rate functions:

(a) The tendency to die at all ages of life has decreased progressively since about one hundred years ago, and the greatest relative change in the decreased susceptibility to death has occurred in the youthful and childhood periods of the life span.

(b) At some period in adult life, the age-specific death rate begins to increase by its characteristically regular exponential function, which is of

such form that the semilogarithmic presentation in Fig. 1 (a logarithmic scale for the units of the age-specific death rate while the units of time are linear) shows a straight-line relationship between the age-specific death rate and age. It indicates that at a time 8.5 years later than any selected age on the graph the age-specific death rate is twice as great as the value at that selected age. This measurement is determined by the slope of the line on the graph, and the fact that all the human populations have essentially the same slope in the latter half of adult life means that the doubling time of "q_x" is the same for all populations--as though physiologic deterioriation, in an average sense, is progressing on a very accurate time schedule controlled by body metabolism.

(c) While the rate of progression of the death rate has a constant value (8.5 years' doubling time), the age-specific death rate itself has changed progressively to less intense values during this calendar century, and the relative intensity of these age-specific death rates remains characteristically less intense in proportion throughout the adult ages. It will be shown that the age-specific death rate during adult life is a measure of physiologic age. In this respect, since the family of curves of age-specific death rates are moving to less intense values, it appears that the physiologic age of our civilization no longer deteriorates so rapidly as it used to, so that the physiologic age is more youthful now at any age of comparison than it was in past years.

PROCESSES CONTRIBUTING TO INCREASE IN LIFE SPAN

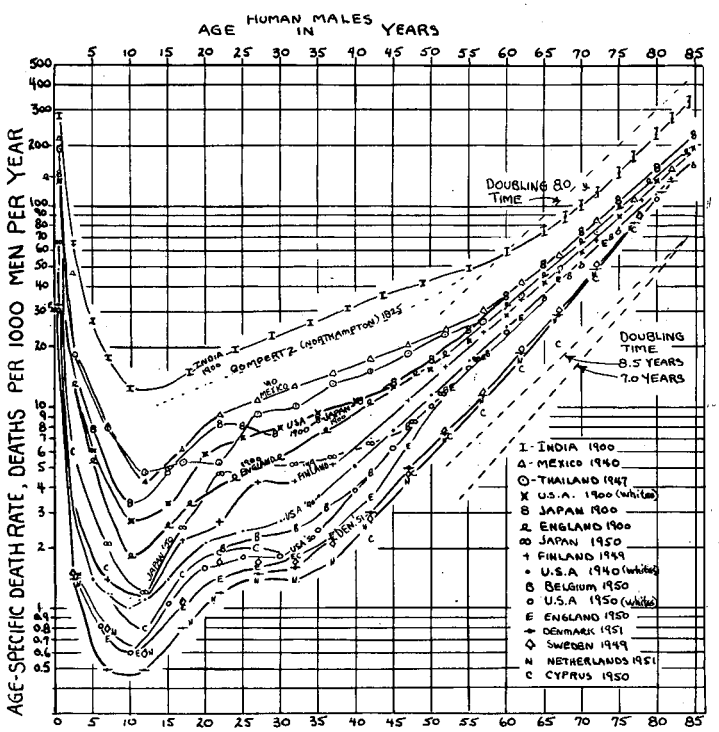
There are actually two general processes that are contributing to the increase in the life span: one is a great reduction in the toll of disease during the youthful period of life, which permits ever increasing numbers of individuals to reach adult life and the older ages of the life span; the other process is shown to be a related consequence--but it has not been considered before--in that each newer generation acquires less and less deterioration. In this way the physiologic age of each new generation is remaining more youthful at the same chronologic age of life. This effect is a subtle one that can scarcely be detected in comparisons made between one decade and another, but in the past century's accumulated change it appears as great as an addition of five to ten useful vigorous years to the average person's life before he develops disabling disease.

The nature of death-rate function (Fig. 1, 2, 3, 4, 5, 6) demands serious attention, for it is not a casual association of change with age; its regularity suggests that it may reveal much about the life-limiting changes and the way they are acquired. Loeb and Northrup[8] in 1917 and Brody[1] in 1923 have suggested physiologic interpretation for this function as a measure of vitality or physiologic age. Pearl,[10] in 1927 and 1928, believed that the general form of the death-rate function indicated that every one must have just so much vitality, which is used up without replacement until he dies upon its exhaustion. A more exact analogy is the interpretation of Loeb, Northrup, and Brody, that at any age the rate of loss of this vitalness (which is a measure of the tendency to live) is proportional to the amount of the vitalness that has already been lost. Another appropriate form of the concept of vitality may assist in the development of the problem. This is that we may regard the

Fig. 1. The age-specific death rate from all causes of death. Selected countries are given with examples from their immediate past. Note the reduction in disease rate throughout life and particularly in the early part of life. All countries are approaching a physiologic increase of the death rate of 8.5 doubling time in the later part of the life span. The Netherlands, Sweden, Denmark, and Cyprus are shown to have an apparent doubling time of 7.0 years. This is explained in the text. As diseases of early life recede, the logarithmic progression of the death rate in adult life appears earlier and earlier and at a lower intensity of the death rate.

The age-specific death rates are arranged on a logarithmic scale against time on a linear scale. A straight-line relationship on this graph indicates that the rate of expression of disease deaths at any time is a function of accumulated change due to disease and death in the past.

All death-rate values are for the various ages of individuals in a population on the indicated calendar year.


AGE IN YEARS
HUMAN MALES
AGE-SPECIFIC DEATH RATE, DEATHS PER 1000 MEN PER YEAR
DOUBLING TIME
DOUBLING TIME
8.5 YEARS
7.0 YEARS
I - INDIA 1900
Δ - MEXICO 1940
⊙ - THAILAND 1947
X U.S.A. 1900 (white)
B JAPAN 1900
R ENGLAND 1900
∞ JAPAN 1950
+ FINLAND 1949
• U.S.A 1940 (white)
B BELGIUM 1950
o U.S.A 1950 (white)
E ENGLAND 1950
DENMARK 1951
◇ SWEDEN 1949
N NETHERLANDS 1951
C CYPRUS 1950

MU-9905

Fig. 2. The age-specific death rates expressed as population cohorts having approximately the same birth date. Note the common tendency for the progression of the death rates to have a slope of 8.5 years' doubling time on this semilogarithmic plot. The age-specific death rates are shown to be receding to relatively lower age-specific rates; this change has accompanied a lowering of the death rates in earlier life of these same cohorts. Each cohort continues to die on its own death pattern in spite of the fact that these individuals are living in association with younger cohorts of a more favorable resistance to disease.

Circles show the predicted age-specific death rates for current cohorts of young swedes.

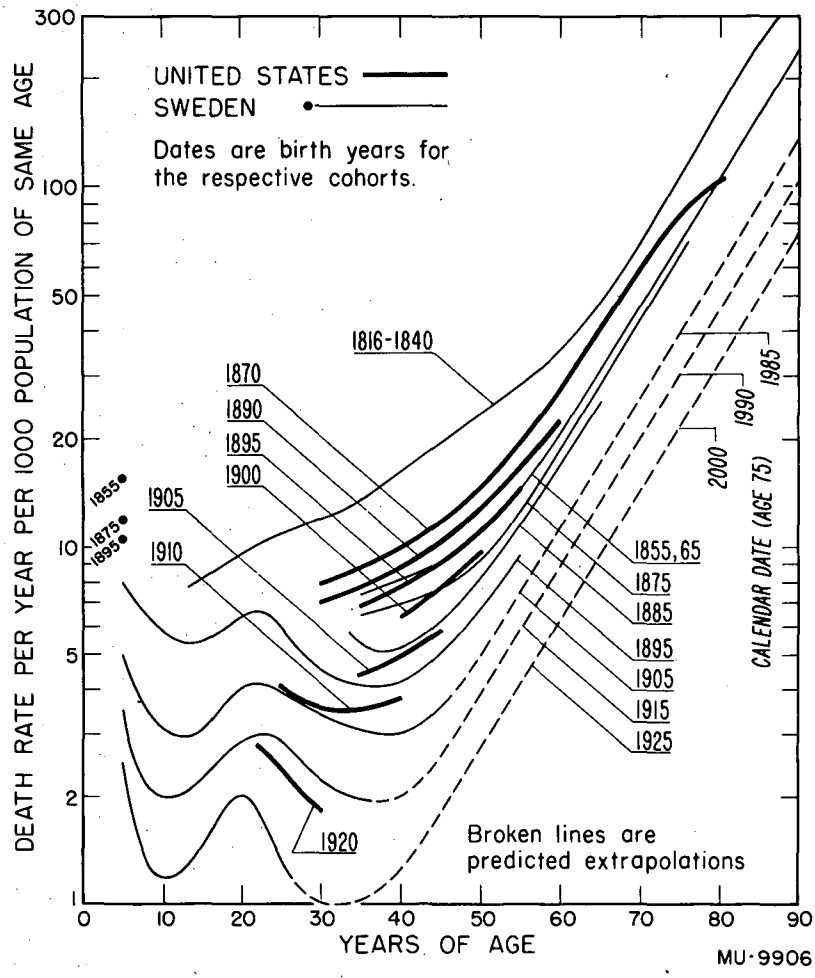

UNITED STATES
SWEDEN
Dates are birth years for the respective cohorts.
DEATH RATE PER YEAR PER 1000 POPULATION OF SAME AGE
YEARS OF AGE
CALENDAR DATE (AGE 75)
1816-1840
1870
1890
1895
1900
1905
1910
1920
1855
1875
1895
1855,65
1875
1885
1895
1905
1915
1925
1985
1990
2000
Broken lines are predicted extrapolations
MU-9906

Fig. 3. Abstract populations of the Netherlands; each disease group dies only of the disease indicated. The function is an all-causes-of-death function for a population that dies of only a single cause. The method of calculation is described in the text. Tuberculosis, cirrhosis, nephrosis, and cancer are shown to be distinctly different from the average causes of death in the population; they are not average causes of death because of the much greater age-specific intensity of the death-rate process. Hypertension and coronary heart disease appear to qualify much more as diseases to which the average population may have an equal tendency. They are in the same position as the all-causes-of-death function for the Netherlands. This analysis is based upon the 1953 death list of the Netherlands.

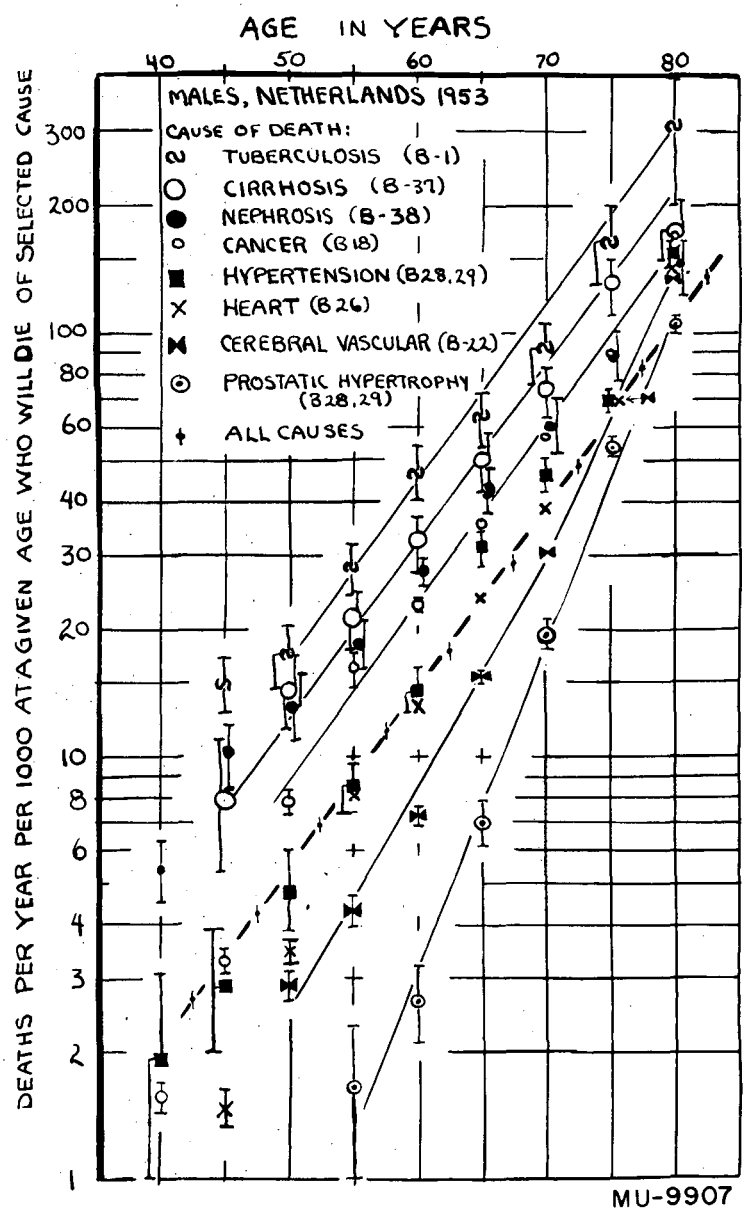
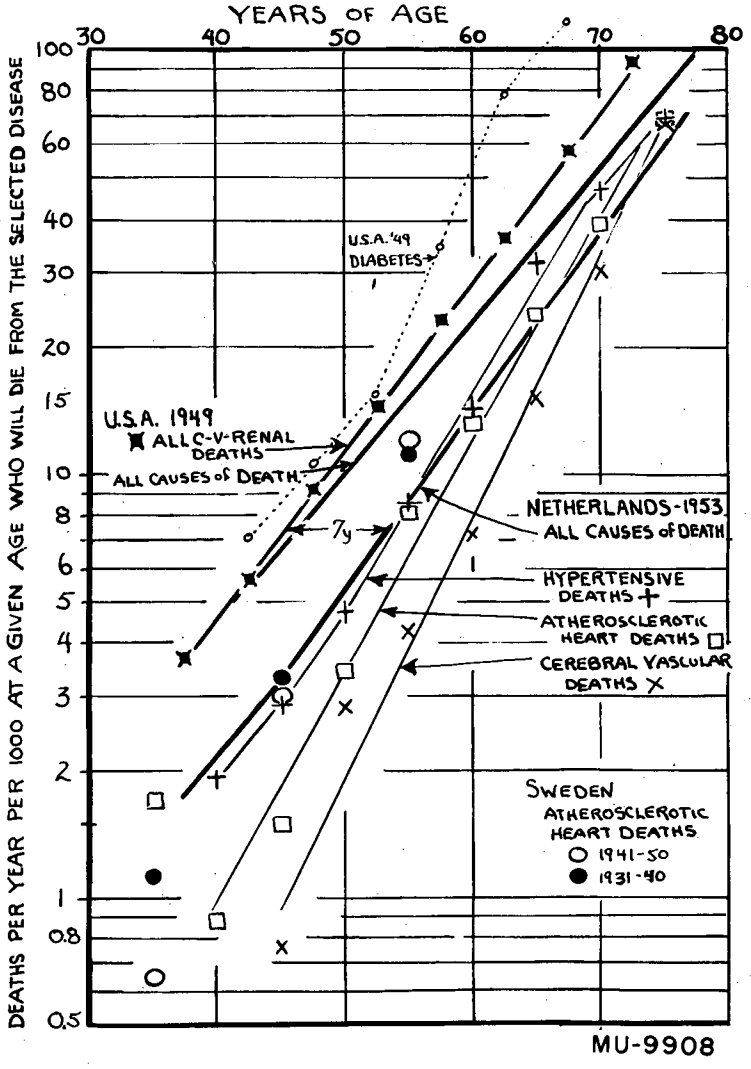

AGE IN YEARS
40
50
60
70
80
MALES, NETHERLANDS 1953
CAUSE OF DEATH:
TUBERCULOSIS (B-1)
CIRRHOSIS (B-37)
NEPHROSIS (B-38)
CANCER (B18)
HYPERTENSION (B28,29)
HEART (B26)
CEREBRAL VASCULAR (B-22)
PROSTATIC HYPERTROPHY (B28,29)
ALL CAUSES
DEATHS PER YEAR PER 1000 AT A GIVEN AGE WHO WILL DIE OF SELECTED CAUSE
300
200
100
80
60
40
30
20
10
8
6
4
3
2
1
MU-9907

Fig. 4. Age-specific death rates for all causes of deaths and for abstract subpopulations of the Netherlands and the United States. Physiologic age is markedly different for these two countries; it is clearly indicated by the all-causes-of-death function. The abstract populations show the same difference in physiologic age and establish beyond doubt that the intensity of development of atherosclerotic disease is postponed by 7 years in the Netherlands compared to the United States. The abstract population of diabetics suggests that after 50 there is a marked worsening of the average diabetic compared to the average population with regard to tendency to disease and death.


YEARS OF AGE
30
40
50
60
70
80
DEATHS PER YEAR PER 1000 AT A GIVEN AGE WHO WILL DIE FROM THE SELECTED DISEASE
100
80
60
40
30
20
15
10
8
6
5
4
3
2
1
0.8
0.5
U.S.A. '49
DIABETES
U.S.A. 1949
ALL C-V-RENAL DEATHS
ALL CAUSES OF DEATH
7y
NETHERLANDS-1953
ALL CAUSES OF DEATH
HYPERTENSIVE DEATHS +
ATHEROSCLEROTIC HEART DEATHS □
CEREBRAL VASCULAR DEATHS X
SWEDEN
ATHEROSCLEROTIC HEART DEATHS
○ 1941-50
● 1931-40

MU-9908

Fig. 5. The age-specific death rates of abstract subpopulations destined to die of cancer. The Netherlands and Sweden are shown by the extremes of the population subgroups of urban and rural ways of life. The cities of Sweden and the Netherlands suggest a slightly higher intensity of carcinogenesis but only in mid-life. Both rural and urban Sweden have changed by 4 to 5 years of physiologic age in the intensity of carcinogenesis since 1911. This degree of change is also apparent in the average death tendency of the Swedish population. A selected subpopulation of males dying only of cancer of the stomach is not plotted but shows the same relative shift in physiologic ages toward more youthful death rates by 1951; see Table II and the text.

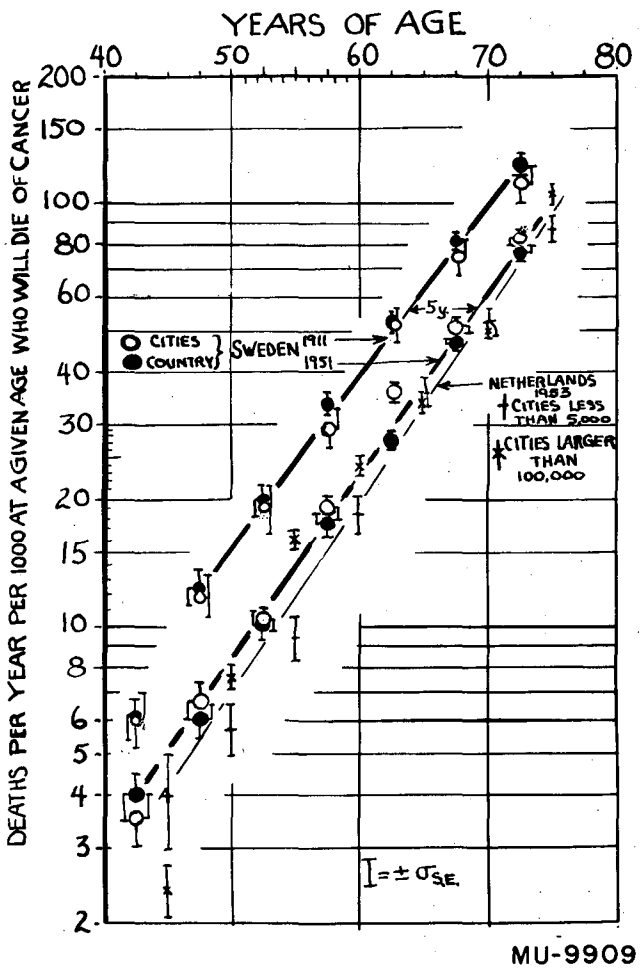
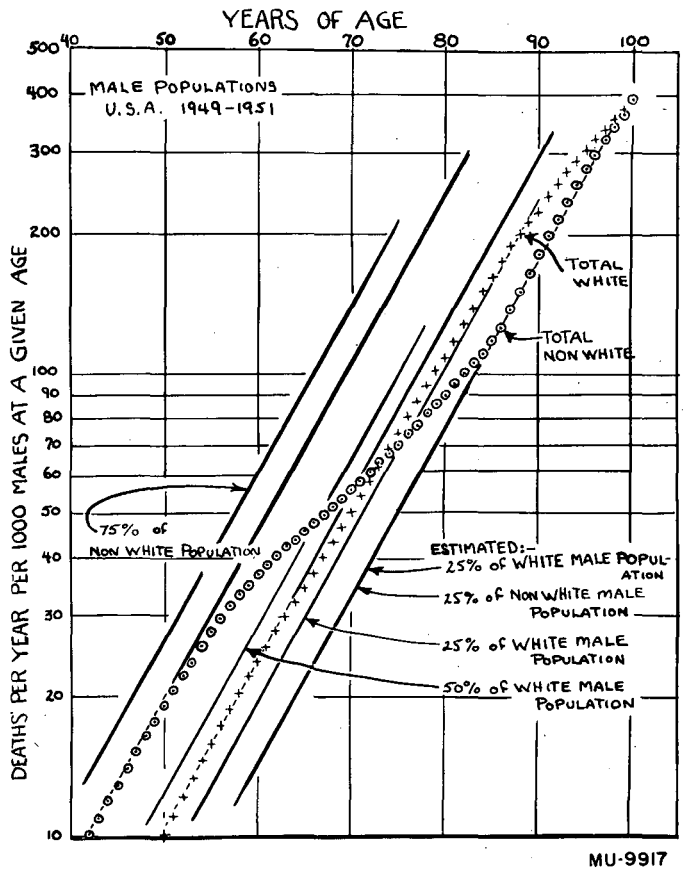

YEARS OF AGE
40
50
60
70
80
DEATHS PER YEAR PER 1000 AT A GIVEN AGE WHO WILL DIE OF CANCER
200
150
100
80
60
40
30
20
15
10
8
6
5
4
3
2
CITIES
COUNTRY
SWEDEN 1911
1951
5y
NETHERLANDS 1953
CITIES LESS THAN 5,000
CITIES LARGER THAN 100,000
I = ± σS.E.
MU-9909

Fig. 6. The inhomogeneity of the population of the United States with respect to incidence of death as a uniformly progressing change. When the death rate is relatively low the population that supplies the deaths seen, at any age of low death rate, remains rather constant in internal composition of subgroups, each of which has a different tendency toward disease and death. When the death rates become greatly different between associated subgroups of a population the subgroup having the much higher death rate reaches an age at which it is consumed by death very rapidly by the high death rate of that age. The remaining population becomes more homogeneous and is progressively more characteristic of the remaining lower-death-rate group which survives. The United States is possibly more heterogeneous with regard to its subgroups than are some of the other countries shown in Fig. 2. It is noted particularly that the bending over of the curve of the population of the United States by cohort (Fig. 2) is explained on the basis of its composition by subgroups of differing death rates. The approximate positions of the subgroups as characterized by age-specific death rate are indicated in the figure for both the white and the nonwhite (Negro) subpopulations. The most favorably lived white males or negro males of the United State have the same life-expectancy pattern as the average of the entire male population of eigher Sweden, the Netherlands, Denmark, or Norway, today.


YEARS OF AGE
40
50
60
70
80
90
100
500
400
300
200
100
90
80
70
60
50
40
30
20
10
DEATHS PER YEAR PER 1000 MALES AT A GIVEN AGE
MALE POPULATIONS
U.S.A. 1949-1951
TOTAL WHITE
TOTAL NON WHITE
75% of NON WHITE POPULATION
ESTIMATED:-
25% of WHITE MALE POPULATION
25% of NON WHITE MALE POPULATION
25% of WHITE MALE POPULATION
50% of WHITE MALE POPULATION
MU-9917

lessening of vitality as the accumulation of damage to body function that has already occurred. In this sense it may be argued that the rate at which damage is incurred is proportional to the damage that has already been acquired in the past.

To the extent that they have been investigated, these functions of uniformly logarithmic physiologic decline apply to populations of all animals when time is considered on a scale appropriate for that animal's life span; see the comparison of doubling times of the death-rate progression in Table I.

Table I

Doubling times of the progression of the death rate for the fly, the mouse, the guinea pig, and man.

Drosophila (at 25°C)	8.5 days
Mouse (laboratory)	2.8 months
Guinea pig (laboratory)	8.0 months
Man	8.5 years

In most small-animal populations the progression of the tendency to die begins early in life, at very low intensities. Loeb and Northrup felt that both in the fly and in man there was evidence for considering the mechanism of aging as a reaction of the second order, which means that a primary process must take place before the reaction that produces aging may begin. Thus, if the reaction is of the second order, there should be a time early in life when aging has not progressed. The human death rate, indeed, after being at a high intensity in infancy, usually reaches a rate that changes very little in childhood and youth prior to its progressive increase in adult life. However, the duration of the period of life when the death rate is not increasing appears to be becoming shorter and shorter with each new generation (see Fig. 1); and yet the age-specific death rate -- at the time when progression in intensity of death rate begins -- has become less intense. Thus it does not appear that youthfulness in adult life could be gained by simulating the rate of death that has been associated in the past with the relatively lower death rate of youths.

In terms of a chemical reaction rate, it is not certain whether the aging process is a reaction of the first or the second order. It seems likely that the flatness with respect to time in early life of the human death-rate curve does have a special meaning. It is lower than the adult rate of aging to death, but considerably higher than would be expected from an extrapolation of the death-rate function of adult life. The explanation that I believe accounts for the relatively constant death rate of the period of youth is:

(a) accidents, which are not appreciably related to age as a cause of death until much later in life, are relatively more abundant than physiologic

causes of death;

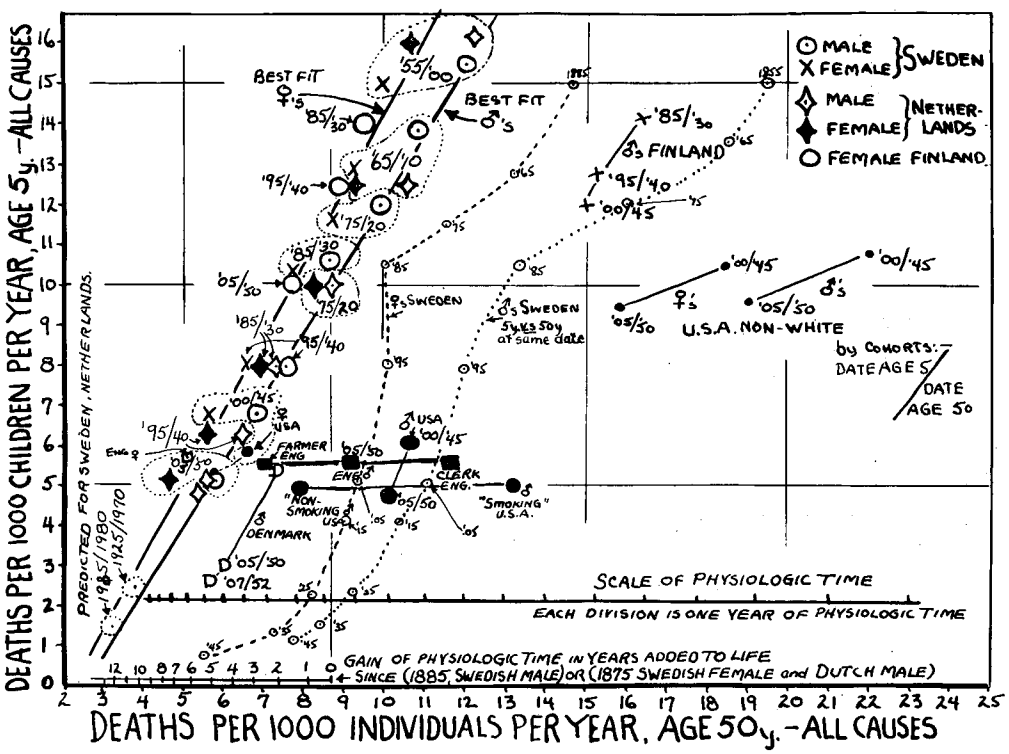
(b) encounters with infections and childhood diseases are more likely at the younger ages; and

(c) A subtle maiming of the physiologic function of some children results from exposure to unfortunate and intensely prevalent disease injuries during infancy. These children become a special population expecially prone to develop other diseases, but they are hidden in the general population. It can be seen (Fig. 1) that the death rate in the first year of life is still appallingly great; as a measure of the severity of disease in its effect upon the surviving population, it can be said that there are more deaths in the first year of infancy among those who are born alive than are seen to accumulate in the same population up to thirty years of age. Not all the children who are seriously affected by the coincidence of several diseases during infancy die, but some of the survivors recover with a retention of a higher susceptibility to other diseases. If only one-fourth as many as those who die of the rigors of infancy survive this period, the serious metabolic deficiencies that persist are enough to account for the more abundant numbers of children dying than would be expected from extrapolation of the adult death-rate function into childhood. These predicted unfortunate individuals are estimated to form a population of perhaps several grades of lessened vigor, and their average death rate per 1000 individuals per year would be roughly estimated as 70 or more deaths per year for the individuals in that subpopulation. This intensity of the age-specific death rate is not reached in the general surviving population until after the 70th year of age. (It is interesting to note that the small population of individuals who die of multiple slcerosis, when transformed into an abstract population so that the age-specific death rate of a population of multiple selerotics may be estimated, gives a value that coincides with this estimated death rate for the approximate time in life when such disease might be expected to appear. Acute leukemia as a population also fits this function. Whether other forms of disease in childhood also give such a suggestion is not known.)

Several further arguments may be considered. It appears that there is no measurable tendency for a period of high death rate and high disease rate to select out weak individuals to die, leaving a stronger and more vigorour population of survivors; the survivors as a population always have a higher death rate and the entire population is on the average worse for having had the experience. On the other hand, populations that have a low infancy and childhood mortality have a lower tendency to develop disease throughout life at any year of age. It can be seen in Fig. 1, 2, and 7 that those individuals who spent their earlier life in a more intensive environment of disease and death tendency are continuing to die at a rate that is characteristic for their generation, and that the younger and younger generations of individuals born in the immediate past -- each of whom in succession has been more favored than earlier generations -- are living longer and with progressively less tendency toward the development of common diseases.

Early in adult life the death tendency as measured by the death rate at any age begins to increase rapidly with increasing ages of the population.

Fig. 7. Factors of health throughout life and childhood health. The patterns of death-rate intensities of populations appear to be established early in life. Death rates of all ages have been diminishing steadily since the early nineteenth century. Death rates at five years and at 50 years are also associated in intensity at any calendar year, but the linear progression for the same cohorts compared at 5 years and when they become 50 years shows a very remarkable and linear relationship in which time is not calendar time but degree of physiologic improvement, or physiologic time. While it is not to be concluded that Sweden and the Netherlands have achieved the optimum in possible hygienic climate, the figure suggests that these two countries have achieved the greatest relative health throughout life yet observed. The women in Finland is at the same position as she would have in more favorably lived countries, in consideration of the level of childhood she has experienced. The population of Denmark is one of the most favorably lived, but the relationship suggests that it should be even more favorably lived than it is now. The man in Finland is suggested to have a greater-than-average death rate both because of childhood disease experience and adult life hazards. Some of the marked deviations of the adult-life death rates in the populations of the United States, England and Wales, and Finland appear to be on a basis of factors of disease that were not revealed in the childhood disease pattern and can therefore be expected to be found in disease provocations in adult life. The physiologic scale of time indicates that even the marked shift of the adult death rates in these instances to less favorable positions allows the factor of childhood health to be of major importance in establishing the health of adult life. The extremes of the subgroups of England and the United States are shown in a position which assumes that these subgroups had the same childhood disease experience as the entire country to which they belong. This assumption is exceedingly unlikely; it is quite probable that much of the spread of adult death rates of these subgroups might be explained upon the childhood disease experiences, also, were they know.


DEATHS PER 1000 CHILDREN PER YEAR, AGE 5y. -ALL CAUSES
DEATHS PER 1000 INDIVIDUALS PER YEAR, AGE 50y. -ALL CAUSES
MALE
FEMALE
SWEDEN
MALE
FEMALE
NETHERLANDS
FEMALE FINLAND
BEST FIT
BEST FIT
FINLAND
SWEDEN
SWEDEN
5y.&5oy at same date
U.S.A. NON-WHITE
by COHORTS:
DATE AGE 5
DATE AGE 50
PREDICTED FOR SWEDEN, NETHERLANDS.
1985/1980
1925/1970
FARMER ENG
CLERK ENG.
"NON-SMOKING" USA
"SMOKING" U.S.A.
DENMARK
USA
SCALE OF PHYSIOLOGIC TIME
EACH DIVISION IS ONE YEAR OF PHYSIOLOGIC TIME
GAIN OF PHYSIOLOGIC TIME IN YEARS ADDED TO LIFE
← SINCE (1885 SWEDISH MALE) OR (1875 SWEDISH FEMALE and DUTCH MALE)

MU-9914

This is at a time when death from internal causes is proportionally greater than death from accidents and childhood diseases, and by this time such small subpopulations as may exist with intrinsically high death tendencies should have already died away. The resulting average population shows a regular logarithmic increase in the death rate with increasing age from this age until the population has been consumed by death. Figures 1 and 2 indicate a wide range of differences in the age-specific death rates, even though the adult death rate is essentially the sum of tendencies to develop cancer, heart disease, cerebral vascular disease, etc., and is, therefore, a measure of physiologic age. The differences between various populations in the tendency for these internal diseases to develop are as though the time scale has been displaced in one direction or another and the range of differences between various countries in physiologic time to reach the same death rate are of the order of 10 to 15 years. It can be imagined that the countries represent rather characteristic and stable averages and that within each there must be subpopulations of considerably greater range of physiologic age; for this reason alone it may be estimated that the range of individual differences in physiologic age over the world may be of the order of 30 years of physiologic time difference. With respect to the individual, it is possible that he may proceed along the way of aging in some succession of little to big jumps, depending upon whether mosquito bites or tuberculosis or some other event is the provoking incident that leads to the accumulated increment of damage.

The benefit of scientific discovery, public health hygience, and medicine has become apparent as a tremendous improvement in the health of humans at every age of life, and no greater measure of this benefit may be made than the observed favorable displacement of the physiologic age and of the time of appearance of internal disease by many years. Even though an estimated 5 to 15 useful years has now been added (see Fig. 2), the process of gain in youthfulness is not at an end, and it seems to be accelerating rather than diminishing in further gain. Possibly this may be because diseases are still being eliminated, and of course such agents as antibiotics may effect in our present generation of children a greater reduction of diseases in adult life than we may yet imagine, owing to an amelioration of the current diseases of childhood and the associated avoidance of injury that might with time become compounded into a contributing cause of adult illness.

The most immediate effect of the postponement of diseases is a longer life. It would appear that since all the diseases are similarily delayed (although perhaps not all in the same proportion) by deferment of the appearance of any of them, no effect should distress a population whose average life is so increasing. The effect appears only to add useful years to the life span. People should, as a consequence of this change, be able to work more efficiently for a longer period, or to enjoy a longer, more healthful postretirement life. Age no longer has meaning as an absolute value. With chronic disease and death postponed by some years, the average population cannot in a physiologic sense grow older than it used to, for in a physiologic sense the maximum age is reached when the body has become too disturbed in function to remain alive -- we cannot be older than we are when we die from the average internal cause of death. The trend of increasing life span and

postponement of disease are seen then to result in the situation that at every chronologic year of age the populations are physiologically more youthful. This, with the fact that physiologic age is maximal at death, means that physiologically each of these populations is becoming more youthful, that the hazard of aging is not that a population will spend more years in senility. The economic factors indeed may be more to our advantage than commonly supposed. It is currently argued that more and more of the population are living to retirement. This is true in the sense that in 1900 the average man who was born alive lived to be approximately 55 years of age, whereas he now lives to be approximately 71 years of age (white males, U. S. Life Table 1949-1951). During the past fifty years of calendar time a person has become less old when he does reach 71 than he was in 1900. He is estimated to be at the physiologic age of the average person living in 1900 who was 66 years of age. The relative difference may be applied to any age of comparison as approximately 5 years of difference in physiologic age. Fifteen years have been added to the useful life span all together, and five of these years have not counted toward his physiologic age on the 1900 scale of aging. An increase of fifteen years in the useful life of the average person is a significant gain in his efficiency as an individual unit of society. His social costs, birth, education, youth, and final institutional care when he is disease-ridden are relatively fixed average costs per person. Against this must be weighed the fact that his profession-life has been extended from a range of age 18 to age 55 (37 years for work) to a working range of age 18 to 70, for 52 years. (The age 70 is assumed on the basis that retirement could be set by physiologic age, which on the comparative time scale is noted to be such that 70 in 1950 is the same as 65 years of age in 1900). The gain in relative efficiency of the individual man is then the difference between 37 and 52 years, which is a gain of $\frac{52 - 37}{37} =$ 0.4 or 40%. When such an increase in efficiency is multiplied by the whole population it is a factor of great economic gain, benefitting the family and the country as well as becoming an increment in real wealth.

The fact that the rate of accumulation of disease is proportional to disease experiences and damage in earlier life leads to the deduction that the way to avoid disease is never to have disease. It is interesting to speculate, however, that we may be able to achieve an even greater preservation in physiologic health by the elimination of our more trivial diseases; the successful removal of such "benign" diseases as the common cold, chicken pox, measles, etc., may be more effective in lessening the disease tendency of later adult life than anything we may attempt to do to improve those who are now adults. It is also possible that there may be advantages in delaying the exposure to childhood diseases as long as possible.

PHYSIOLOGIC AGE

The use of the rate of death at any age as a measure of physiologic age was proposed by Brody.[1] Probably no other test now available could measure as exactly the intactness of the average physiologic function. If one compares the adult ages of two populations, of similar civilizations the United States and the Netherlands, in reports of 1949 and 1950, the United

States shows twice as great an age-specific rate of death as the adult ages in the Netherlands. In spite of this lack of similarity, if the internal causes of death such as cancer, diseases of the heart, the liver, the brain, the intestinal tract, diabetes, anemia, renal disorders, etc., are totaled they account for 85% and 80% of all deaths that occur in the 45-to-65-year age groups of males in the United States and the Netherlands respectively. In addition to these deaths that are determined by the internal environment of metabolism, it is also a definite fact that tendency to survive accidental injury, pneumonia, bronchitis, influenza, and tuberculosis is decreasing with age at the same logarithmic doubling function as the general tendency to die. Thus it appears that the ability to recover from all internal and external sources of diseases may be described by a similar relative function, so that one is justified in considering that the sum of the causes of death is related to physiologic factors changing with age at the same relative rate and determining the odds of survival for the average person in a population. We may speak of the physiologic age of a person or a population either with respect to one system of disease or some combinations of systems, or with respect to the entirety of possible causes that may induce death in that population. An example of physiologic age difference is the comparison of the populations of the United States and the Netherlands. In both countries men die of similar causes, but the proportions of each cause vary. The sum of deaths is an age-specific death rate nearly twice as great for the average male in the United States as in the Netherlands. The average tendency toward cancer is at the same level in the two countries; the difference is largely accounted for by the higher incidence and more intense rate of development of atherosclerosis in the United States than in the Netherlands; see Table II and Fig. 4. The two countries are different on the average by 5 to 8 years in physiologic age in the tendency for the development of cerebral vascular disease and coronary heart disease. The argument for this special consideration of the aging process indicates that if the factors responsible for the development of atherosclerosis in the United States were lessened then cancer incidence in all probability would be lessened also to some extent. The fact that the cancer incidence in the two countries is now at the same level suggests that both are more intense than need be. The United States has a cancer tendency that is probably intensified by other deterioriating diseases, and the Netherlands rate of cancer is higher than it should be in proportion to the abundance of other diseases, suggesting that some of the environmental factors (perhaps such as a greater-than-average urbanization) of the Netherlands may be acting more extensively on the whole population than in the United States.

A restatement of some of the evidence of the interassociation of disease tendency may be helpful to the reader. An interesting variation of the general argument of the nature of the aging process is that the death rates from all of the major and most of the minor diseases associated as causes of death must be and are increasing with increasing age at the same general rate as the progression of the age-specific death rates. Brody[1] and Simms[12] have also established the same argument of the similar pattern of change with age for all the common diseases, as did Loeb and Northrup[8]. There are several variations from perfect agreement in the death rate or progression of the doubling time in the death rate or with the progression of the incidence of disease at a given age. There are however, no

Table II

Comparisons of death rates (males); all causes of death and abstract cancer death rate

Age, Class-Int.	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+
All Causes of Death											
Sweden 1901-1910	6.72	7.59	8.82	10.73	13.73	18.6	26.1	39.5	62.0	101.3	. . .
Sweden 1951	. . .	1.94	3.21	5.12	8.10	12.8	20.7	32.8	57.0	95.3	143.5
Netherlands 1953	1.35	1.71	2.65	4.20	6.95	11.3	17.7	28.2	48.4	82.0	135
United States 1949	2.42	3.66	5.55	8.67	13.4	19.7	28.9	43.9	63.0	92.0	136
Abstract cancer death rates. Deaths per year per 1000 of cancer at given age											
All cancers											
Sweden Country n →	18	32	73	137	195	271	325	329	299	184	102
1911-1912 d/1000	1.4	2.6	6.1	12.3	20.0	33.7	52.3	81.3	125	167	. . .
Cities n →	5	26	35	64	84	103	134	134	107	54	44
d/1000		4.2	6.0	11.8	19.1	29.5	51.5	74.3	112	124	. . .
Sweden Country n →	27	49	70	121	169	263	378	474	553	522	476
1951 d/1000	1.8	2.9	4.0	6.0	10.2	17.6	27.4	46.7	76	132	. . .
Cities n→	22	36	80	116	192	275	359	391	426	308	272
d/1000	1.1	2.2	3.6	6.7	10.6	19.2	35.9	50.6	83	130	. . .
U.S.A. White n →	999	1660	2580	4430	7330	10800	13760	14780	14170	11720	10791
1949 d/1000	1.2	2.1	4.1	6.5	11.7	18.9	28.9	52.6	78	114	. . .
Netherlands, 1953											
All d/1000		1.1	2.0	4.5	10.0	18.5	27.8	45	74	130	
Cities > 100,000 d/1000		0.6	1.5	5.6	10.2	19.5	28.5	46	81	145	
Towns <5000 d/1000		1.3	2.8	4.0	8.0	12.5	25.0	41	66	120	
Cancer of the Stomach											
Sweden n → 11		32	75	128	179	229	245	232	167	79	32
1911-1912 d/1000		4.0	9.8	18.4	28.8	51.3	76.6	106	228	. .	. .
Sweden n → 7		9	29	61	84	129	215	235	275	244	230
1951 d/1000		. . .	3.1	7.6	12.3	17.2	46.7	70	138	. .	. . .

differences that cannot be explained by the introduction of reasonably possible arguments concerning minor differences in the various subpopulations that are contributing to the disease concerned. The death-rate progression with age is exceedingly similar for heart disease, cerebral vascular disease, cancers, diabetes, anemias, nephrotic disease, hypertensive disease, influenza, pneumonia, bronchitis, and tuberculosis. The similarities are so striking and there is so little evidence to substantiate any differences that I feel constrained to propose that all these diseases are related to common physiologic factors and that every mechanism of disease would through its relationship with these physiologic factors tend to intensify the tendency for other diseases to develop. This is a restatement of the opinion expressed earlier that every disease episode does some damage to physiologic function. The general statement may be transformed into the correlative statement that when any of the major causes of death is enhanced there should be a tendency for other diseases to be increased also. It will be shown that this is the usual tendency in the various populations and subpopulations of the world. However, it is equally apparent that any of the known diseases may have been specifically provoked by environmental factors that are more directly in contact with a given functional system of the body than this described effect, which diffuses to the body as a whole through the interplay of physiologic function. In addition to internal associations between disease processes, we must also keep in mind that several environmental factors, each primarily related to a different disease, may also be interrelated in their tendency to be abundant in that environment. The general theory of disease may have to be more complicated than the charming example Darwin gave of the ecological relations of old maids, cats, mice, bees, clover, cows, milk.

Examination of the progression of the age-specific death-rate functions for the populations given in Fig. 1 shows the general truth that the rates of progression of these rates of dying are very similar for all the populations, but there are some exceptions. The general truth of the 8.5-year doubling time of the death rate applies to such populations as the United States and countries that have close to or higher than this death rate. Inspection of the progression of the age-specific death-rate functions of such countries as Sweden, Denmark, the Netherlands, Norway, and Cyprus -- all these countries have been experiencing recently an extremely rapid reduction in the death rate -- indicates that the doubling time of the death-rate function is apparently speeded to approximately 7 years' doubling time instead of the commonly observed 8.5-year doubling time of the progressive increase in the age-specific death rate. The effect is such that if one compares the rate of death in the individuals that are in the older ranges of life -- especially over 70 years of age -- the improvement in freedom from disease appears to have been lost. Superficially it would seem that -- like Cinderella -- when our metabolic time runs to a certain age we then lose an artificially gained advantage. Such observations have contributed to earlier beliefs of fixed limits to life, perhaps based upon genetic or cellular limits to the life span. However, careful examination of the factors that are associated with the populations showing 7 years' doubling time leads to entirely opposite conclusions.

Fig. 2 gives a comparison of the populations of Sweden, Denmark, Finland, and the United States in such a way that the line of each age-specific

death rate is for individuals who were born in a given country about a given calendar year. (I am very grateful for the suggestion of Mr. Olof Orlinder that this point be tested by the preparation of the age-specific death rates in this way and for his providing material on the death rates of the Swedish population from which this function is constructed. Mr. Orlinder is at the Statistical Office of the City of Stockholm. Mr. Henry Hamtoft and Miss Marie Lindhardt very generously provided population records for Denmark from the Office of the National Health Service of Denmark, Copenhagen. The death rates for Finland are from the Statistical Yearbook of Finland 1954. The population death rates of the United States are taken from the Life Table of the United States, 1949-1951.) Unfortunately, the earlier records of the population of the United States, which would have added to the force of comparison, are not available before 1900 as a tabulation for sample registry.

It is shown in the graphic records of age-specific death rates, Fig. 2, that there is no longer any tendency for the populations of the low-death-rate countries to show a progression of the death rate more intense than 8.5 years' doubling time. The important trend in these countries is that each new generation, shown as cohorts of men having the same birth dates, is experiencing less and less disease-death rate as the date of birth is later in time. Each population cohort continues to live his adult-life disease pattern as an extension of the experiences of earlier life. The current generations, which in the graph end as unfinished lines in the 1950's, have achieved a remarkable recession of the age-specific death rates compared with past experiences. There is every reason to expect that these advantages are lasting and that the current generations will remain in their favorably displaced position throughout the remainder of the life of the cohort populations. On such a basis it is easy to predict the course of disease in the present generations of Sweden, Denmark, Norway, and the Netherlands. They will follow the rows of circles extending the age-specific death rates of the indicated year of birth. These values were calculated for Sweden; the other countries of similar low death rate (Norway, Denmark, the Netherlands, and Cyprus) should be very closely comparable. The population of the United States as an average is far below the ultimate favorable expectation of longevity and youthful physiologic age that these lines predict, but the population of the United States is shifting in the same direction. Denmark, Sweden, The Netherlands, Norway, and Cyprus are at present at least six years physiologically younger than the United States and Finland; these low-death-rate countries have gained approximately 15 years of physiologic age since the middle of the nineteenth century. If the prediction is valid, by the year 1999 a man who has lived his life in any of the favorably lived countries and is by chronologic age 75 may be as young physiologically as men in the United States are today at age 60. The graphic values of Fig. 2 show a steady decline of disease tendency. The resulting death rate is characteristic of more youthful populations. This lessening of the course of disease in adult life is always accompanied and preceded by a lowering of the death rate in the early ages of life. Populations that have already lived through a period of more intense disease experience continue to age by increasing their more intensive disease tendency. Several general opinions concerning the nature of the changes in life expectancy may be made:

(a) It is again evident that the pattern of resistance to disease is established in early life. It is not possible to say how much this may depend upon the carry-over throughout life of certain habits and ways of life, but the argument is strong enough to warrant the utmost attention to the care of children, and it is not likely that optimal circumstances of growth and development and nutrition and control of childhood diseases have yet been managed for the average child.

(b) The distortion of the rate of doubling of the death-rate function which was apparent for the long-lived countries has been explained; other countries do not show the same effect because like the United States they have progressed much more slowly in their improvement of physiologic age. It is interesting to note that the distortion of the increase in the death rate's doubling time is much less in rural Sweden, where the country has always been more long-lived than the cities. These rural populations are improving relatively more slowly than the cities' populations.

(c) It has been possible to estimate the shift in the physiologic age with passing of calendar time. In Sweden the average individual born between 1855 and 1895 has gained 0.9 year for each 10 years later than 1855 they were born (or 0.09 year per calender year since 1855). It appears that since 1895 an acceleration of this gain has occurred for those who were born after this approximate date in Sweden and the Netherlands (see also Fig. 7 and the gain has increased to between 1.5 and 3.5 years of physiologic life gained for every decade by which birth was later than 1895. It is this accelerated process that seems to be associated with the great gains in resistance to disease death that are apparent in the children and youths of the low-death-rate countries. It is probably that the United States is rapidly gaining also, but if the current trend towards lower death rates in early adult life is to be seen in the United States to the same extent as is currently observed in the low-death-rate countries, it will not be as apparent until about 1965. Nevertheless, the death-rate curves for the population born in the United States in the period from 1900 to 1925 have already shown great differences in the age-specific disease rate for their entire life span, and as these people are now reaching an age when heart disease and cancer and the like are expected to develop, we may anticipate a significant reduction in the age-specific incidences of disease and the age-specific death rate (other environmental factors being equal); the reason for this is that this new generation is at a younger physiologic age for the same chronologic age than the populations that have preceded them.

VARIATION IN PHYSIOLOGIC AGE

Comparisons of age-specific disease tendency between populations and between periods of time would be useful in the examination of ranges of variation in physiologic age. Fortunately conventions and international standards for the classification of diseases seem to have been agreed upon that will make demographic data become more comparable. Comparisons of disease incidence or death rates are difficult to make at the present time, especially for the changes in physiologic age, where the problem is one of looking for small degrees of change between the decades. The following

abstract solution to the problem is made to avoid the pickle of needing absolute numbers of cases and absolute census counts in the comparisons of disease tendency. The abstraction of this problem does not use the size of the population or the fullness of the sample of cases collected for reference; it uses the distribution of the ages at death for the cause investigated and only needs a representative sample of those who die in that category of disease at that place and that time. It is constructed in this way: If for a suitable period of calendar time causes of disease deaths are grouped by age at death, then these individuals may be grouped into an abstract population of people who died from each particular cause. The number of individuals who are recorded as "alive" in the population at, for example, forty years of age are those who died at ages of forty and older and so on for all ages. The number of deaths may be constructed in the usual life-table way as the number who die in the 40th, the 41st, etc., years. It is very similar to the all-causes-of-death rate in a population life table for a given calendar year. It is an abstract population that will die from the selected cause of death and no other. It is a reasonable relative estimation if the population from which it was drawn has remained undisturbed from population movements and major fluctuations of birth or death rate, so that the distribution of ages in the population is in equilibrium with the current tendency for the population to die. However, as is usually the case, the population is not in equilibrium with its tendency to die at any age. A correction of the crude estimate of the abstract population may be made in this manner: the all-causes-of-death function for the total population and the census of the population are probably reliable; the age-specific death rates will be established. Then it is possible to construct a matching abstract population of individuals dying from all causes of death at each age and to determine the abstract age-specific death rate.

The ratio, $\dfrac{\text{the observed age-specific death rates (all causes)}}{\text{the abstract age-specific death rates (all causes)}}$, correction factor which, when multiplied by the age-specific death rates, will correct them for the distribution of ages in the population from which each disease was derived. To the extent that the subpopulation so selected is predestined by metabolism to that selected disease and recovery from the disease is unlikely, the abstract age-specific death rate is a measure of the intensity of the disease process compared to other processes of disease in the population as a whole. It may be used as a measure of physiologic age with respect to the disease concerned within a population with respect to differences in calendar time, or it may be used to compare with other abstract subpopulations of that disease type in other populations. It is not to be confused with the measure of incidence of death in a population, which as given is the rate of deaths per 1000 individuals in the population. The cases from which indicence measurements are derived may have come from the whole population or from some part of that population. The abstract measurement is for a selected population which by its selection can die of no other cause; it is an all-cause-of-death function for a population that dies only of a single cause. The abstract age-specific rate of death is a measure of the development of the metabolic process that precedes the disease-identified state; it does not, for example, predict the rate of death after a malignant process--such as cancer--has been established.

Table III

Incidence of Death, Males, Netherlands, by Age and Cause

Years of Age	All Deaths 1953 per 1000			International List B #18 Cancer Deaths 1953 per 1000			International List B #22, #26, #46b Atherosclerotic Deaths 1953 per 1000		
	C_1 Cities >100,000	C_3 Towns <5,000	$(C_1-C_3) \pm\sigma$ / C.R.*	O_1 Cities >100,000	C_3 Towns <5,000	$(C_1-C_3) \pm\sigma$ / C.R.	C_1 Cities >100,000	C_3 Towns <5,000	$(C_1-C_3) \pm\sigma$ / C.R. S.E. dif.
50-54	7.90±.30	6.00±.41	+1.90±.51 / C.R. =3.7	2.41±.16	1.26±.19	+1.15±.25 / C.R. =4.6	2.3±0.16	1.21±.18	+1.09±.24 / C.R. =4.5
55-59	12.3±.39	10.1±.57	+2.2±.69 / C.R. =3.2	3.80±.22	2.47±.28	+1.37±.36 / C.R. =3.8	3.65±.21	2.28±.27	+1.37±.34 / C.R. =4.0
60-64	19.4±.55	16.3±.77	+3.1±.94 / C.R. =3.3	5.55±.29	4.53±.40	+1.02±.49 / C.R. =2.1	6.25±.31	4.56±.41	+1.69±.51 / C.R. =3.3
65-69	30.5±.77	26.3±1.05	+4.2±1.28 / C.R. =3.3	8.10±.40	5.93±.50	+2.17±.64 / C.R. =3.4	12.4±.49	8.90±.61	+3.5±.78 / C.R. =4.5
70-74	51.3±1.2	45.6±1.54	+5.7±1.95 / C.R. =2.9	12.2±.58	9.70±.71	+2.5±.92 / C.R. =2.7	23.1±.80	19.9±1.01	+3.2±1.3 / C.R. =2.5
75-79	91.5±2.2	84.0±2.49	+7.5±3.3 / C.R. =2.3	16.9±.92	15.6±1.07	+1.3±1.4 / C.R. =0.9	43.6±1.5	37.0±1.65	+6.6±2.2 / C.R. =3.0
80-84	130.±3.7	140±4.52	-6.8±5.9 / C.R. =1.1	20.5±1.5	19.8±1.70	+0.7±2.2 / C.R. =0.3	65.4±2.6	62.8±3.0	+2.6±4.0 / C.R. =0.7

*C. R. = Critical ratio, σ = standard error of the difference

ZN-1444

Values calculated for the abstract rate of death functions are given in Fig. 3, 4, 5 for the Netherlands and for Sweden and the United States. Figure 5 and Table II give the death rates per 1000 men destined to die of cancer in Sweden in the cities and in the country in the years 1911 and 1951. There is a difference of five years in the physiologic age of cancer susceptibility for this forty-year span. Men in Sweden were four years older physiologically in 1911 than they were in 1951 with respect to the rate of cancer development in those who would die of cancer. This is in very close agreement with the previous estimate made of the tendency for the Swedish population to shift toward physiologic youthfulness Fig. 2, which is from a consideration of all causes of disease over this same period of time. (Some of these matters are discussed in greater detail in the section on cancer.) In 1911 there appeared to be little difference between the rates of development of cancer in the population of the rural and urban districts of Sweden; the abstract cancer death rate shows a slight favoring of the tendency for cancer to develop at a faster rate in the country, owing to the earlier incidence and singular abundance of cancer of the lip and skin in the rural population. In 1951 the cities of Sweden seemed to have a slightly higher abstract rate of cancer development. The abstract age-specific death rate is presented for the cities of the Netherlands, Fig. 5 and Table II; the cities of greater than 100,000 population suggest a slight increase for the interval 50 to 60 years but not at other ages. The rate of development of cancer deaths is about the same, at the present time, in the cancer subpopulations (those destined to die of cancer) of Sweden, the Netherlands, and the United States. The abstract death rate for those who die of atherosclerosis indicates a great difference between the Netherlands and the United States. The physiologic age displacement between equivalent intensities of death rate is a difference of 5 to 7 years.

Another test for differences in the physiologic ages of people may be made by using the conventional form of the incidence of death by cause, if it is possible to compare a population to a reference population that is very similar but at a lower death rate. When all causes of death are elevated in a population, the interrelationships between diseases and physiologic age are such that one disease should hasten the appearance of others and there should be a tendency for both atherosclerotic disease and cancer to be elevated. This has been tested for the population of the Netherlands to the extent that we may consider the subpopulations of cities and villages that are similar in general culture but living in somewhat different disease environments. (Doctor Van der Brink of the Central Bureau of Statistics for the Netherlands, the Hague, has kindly supplied the 1953 death lists for the Netherlands.) Table III gives all deaths, the incidence of cancer, and atherosclerotic deaths for the Netherlands by subpopulations of the cities of more than 100,000 people and towns less than 5,000 people. The large cities are diverse centers of industry and commerce; the villages and towns are the homes of people who tend the fields and the suburban homes of the large cities. The adults of these subpopulations are dying at a significantly more intense rate in the large cities than in the towns, and at the same ages the deaths from both cancer and atherosclerotic disease are elevated in the large cities compared with the towns (see Table III). It therefore appears reasonable to say that cancer and atherosclerotic disease are associated in their tendency to develop in the population of the Netherlands and that the

Table IV

Occupational Groups Selected and Segregated by Cancer Incidence, Part A
England and Wales, 1951. Males Aged 20-64

Cancer (140-205) (Observed)	(Expected)	330-334, 420, 450 Atherosclerosis		001-008 Tuberculosis		260, 290-293 Diabetes, Anemia		490-493, 500-502 Pneumonia Bronchitis		440-447 Hypertension		590-594 Nephritis		422-Other Myocardial Degeneration		
		Ob.	Ex.	Ob.	Ex.	Ob.	Ex.	Ob.	Ex.	Ob.	Ex.	Ob.	Ex.	Ob.	Ex.	
Cancer Elevated Significantly																
2568	2181	2434	2358	1158	691	66	51	1756	938	344	304	199	159	601	393	Unskilled Vb
1049	950	972	926	398	393	21	25	360	371	136	119	93	83	141	136	Transport Workers IIIb
6918	6632	6681	6688	2460	2611	157	168	2528	2677	. . .	. . .	532	562	974	1039	Skilled Workers IIIe
123	92	94	66	185	87	3	1	39	31	18	11	18	17	22	8	Armed Forces IIId
10658	9855	10181	10038	4201	3782	247	245	4683	4017	498	434	842	821	1738	1576	TOTAL
108.4 ± 1.0		101.4 ± 1.0 Not sig.		↑ 111.1 ± 1.7 Sig. elev.		100.8 ± 6.4 Not sig.		↑ 116.6 ± 1.7 Sig. Elev.		↑ 114.7 ± 5.1 Sig. elev.		102.6 ± 3.5 Not sig.		↑ 110.3 ± 2.6 Sig. elev.		100 x Ratio ± σ S. E.
Cancer Not Significantly Elevated or Depressed																
275	243	233	232	165	102	. . .	. . .	166	95	. . .	. . .	24	21	65	35	Hewers and Getters Coal IIIa(i)
136	133	108	133	77	45	. . .	. . .	84	54	. . .	. . .	13	10	17	22	Dock Laborers Va(ii)
2395	2467	2145	2536	939	901	55	60	1161	1012	304	326	181	198	410	399	Partly Skilled IVb
854	820	1128	858	410	297	30	19	322	343	141	110	88	66	107	139	Clerks IIIc
627	654	949	672	155	244	22	18	96	270	110	87	. . .	. . .	. . .	. . .	Professional I
4287	4317	4563	4431	1746	1589	107	97	1829	1774	555	523	306	295	599	595	TOTAL
99.3 ± 1.5 Not sig.		103.0 ± 1.5 Not sig.		↑ 110 ± 2.6 Sig. elev.		↑ 110.3 ± 1.1 Sig. elev.		103. ± 2.5 Not sig.		106.1 ± 4.5 Not sig.		103.7 ± 5.9 Not sig.		100.7 ± 4.1 Not sig.		100 x Ratio ± σ S. E.
Cancer Significantly Lower than Average																
376	505	355	523	73	158			77	213	. . .	. . .	30	36	66	87	Farmers II(i)
170	205	163	203	28	73			43	82	. . .	. . .	11	15	10	29	Foremen IIIe(i)
397	483	382	488	159	167			206	199	. . .	. . .	31	37	86	78	Coal Miners IVb(i)
504	600	353	616	181	213			252	252	. . .	. . .	32	48	89	102	Building Laborers Va (i)
569	688	463	725	139	239			195	291	56	93	38	54	99	119	Agricultural Workers IVa
2016	2481	1716	2555	580	850			773	1037	56	93	142	190	350	415	TOTAL
↓ 81.3 ± 1.8 Sig. lower		↓ 67.2 ± 1.6 Sig. lower		↓ 68.2 ± 2.8 Sig. lower				↓ 74.5 ± 2.7 Sig. lower		↓ 60 ± 8. Sig. lower		↓ 74.7 ± 6.3 Sig. lower		↓ 84.3 ± 4.5 Sig. lower		100 x Ratio ± σ S. E.

Table IV

Occupational Groups Selected and Segregated by Atherosclerosis, Part B

Atherosclerosis		All Cancer		Gastro-Int. Cancer		Lung Cancer		Pneumonia Bronchitis		Hypertension		Tuberculosis		Nephritis		Cancer Minus Gut Cancer		
Ob.	Ex.	Ob.	Ex.	Ob.	Ex.	Ob.	Ex.	Ob.	Ex.	Ob.	Ex.	Ob.	Ex.	Ob.	Ex.	Ob.	Ex.	
Atherosclerosis Elevated Significantly																		
↑ 1128	858	854	820	225	253	317	285	322	343	141	110	410	297	88	66			Clerks IIIc
↑ 949	672	627	654	↓ 154	204	183	230	↓ 96	270	110	87	155	244	69	54			Professional I
↑ 94	66	123	92	37	23	36	24	39	31	18	11	185	87	18	17			Armed Forces IIId
↑ 2171	1596	1604	1566	416	480	536	539	457	644	269	208	750	628	175	137	1188	1086	TOTAL
136.0 ± All sig. elev.		102.4 ± 2.6 Not. sig.		↓ 86.7 ± 4.3 Sig. lower		99.4 ± 4.3 Not sig.		↓ 71.0 ± 3.3 Sig. less		↑ 129. ± 8.0 Sig. elev.		↑ 119. ± 4.4 Sig. elev.		↑ 127.7 ± 9.7 Sig. elev.		↑ 109.1 ± 3.2 Sig. elev.		100 x Ratio ± σ S. E.
Atherosclerosis Not Significantly Elevated or Depressed																		
368	358	391	361	156	108	117	127	201	144	. . .	. . .	197	140	34	32			All Mine Workers IIIa
972	926	1049	950	290	292	373	336	360	371	136	119	398	393	93	83			Transport Workers IIIb
6681	6688	6918	6632	2113	2049	2501	2322	2528	2677	. . .	. . .	2460	2611	532	562			Skilled Workers IIIe
2434	2358	2568	2181	857	689	958	771	1756	938	344	304	1158	691	199	159			Unskilled Vb
233	232	275	243	108	76	84	86	166	95	. . .	. . .	165	102	. . .	. . .			Coal Hewers and Getters IIIa (i)
10688	10562	11201	10367	3524	3214	4033	3642	5011	4225	480	423	4213	3937	858	836	7677	7153	TOTAL
101.2 ± 1.0		↑ 108.0 ± 1.1 Sig. elev.		↑ 109.6 ± 1.8 Sig. elev.		↑ 110.7 ± 1.7 Sig. elev.		↑ 118.6 ± 1.7 Sig. elev.		113.5 ± 5.2		↑ 107.0 ± 1.6 Sig. elev.		102.6 ± 3.5 Not sig.		↑ 108 ± 1.2 Sig. elev.		100 x Ratio ± σ S. E.
Atherosclerosis Significantly Depressed																		
↓ 463	725	569	688	224	215	149	240	195	291	56	93	139	239	38	54			Agricultural Workers IVa
↓ 2145	2536	2395	2467	804	766	845	872	1161	1012	304	326	939	901	181	198			Partly Skilled IVb
↓ 481	769	640	734	193	229	235	258	336	307	. . .	. . .	258	257	45	56			Building and Dock Laborers Va
↓ 355	523	376	505	156	160	82	180	77	213	. . .	. . .	73	158	30	36			Farmers II (i)
↓ 163	203	170	205	48	65	64	75	43	82	. . .	. . .	28	73	11	15			Foremen IIIe (i)
↓ 382	488	397	483	183	149	94	171	206	199	. . .	. . .	159	167	31	37			Coal Miners IVb (i)
↓ 3989	5244	4547	5082	1608	1584	1469	1796	2018	2104	360	419	1596	1795	336	396	2939	3498	TOTAL
76.1 ± 1.2 All sig. lower		↓ 89.5 ± 1.3 Sig. lower		101.5 ± 2.5 Not sig.		↓ 81.8 ± 2.1 Sig. lower		95.9 ± 2.1 Not sig.		↓ 85.9 ± 4.5 Sig. lower		↓ 88.9 ± 2.2 Sig. lower		↓ 84.8 ± 4.6 Sig. lower		↓ 84.1 ± 1.5 Sig. lower		100 x Ratio ± σ S. E.

100 = Average Mortality Ratio of Population

Significance Test is for Deviation from 100

male population of the towns and villages has a physiologic age 2.2 years younger than the males in the large cities.

Further differences in disease-development rate as an indication of physiologic age are apparent in the occupation groupings of subpopulations of England and Wales (The Registrar General's Decennial Supplement, Occupational Mortality 1951). The first test for differences in physiologic age within the population of England and Wales is made by grouping the subpopulations that are available into classes in which cancer is either significantly higher or significantly lower than the average for the population subgroups that are segregated; and similarly they are re-sorted according to whether atherosclerotic disease is significantly elevated or not. The results are observed in Table IV. The regrouping shows that all the major diseases follow the trend of cancer and that they also follow the trend of atherosclerosis. This is of course in disagreement with many of the subgroups, which show a preferential elevation of one particular disease, but it does show that on the average in these populations there is a tendency for all the diseases of internal origin to be associated at either a higher or lower intensity than the average of the population in a way that suggests a displacement of the physiologic time scale. The population of the armed forces of England and Wales is of primary interest; it has the highest incidence of all the major causes of death, and this population is possibly an example of the argument that diseases tend to facilitate the growth of disease states. The displacement toward more intense death tendency is equivalent to this population's being 5 years older in physiologic age than the average male of that chronologic age and 10 years older than the more favorably lived subpopulations, for example the farmers and building laborers. The associated trend of diseases in the English population may be observed in the scatter-diagram relationships given in Fig. 8a, b, c, d, and Fig. 9a, b. The interassociations of cancer and other disease in general, of cancer and artherosclerosis, of cerebral vascular disease and coronary heart disease, and of all diseases and tuberculosis indicate that diseases all tend to be associated in these subpopulations. These populations of occupational groups are discussed in later sections.

The final illustration of differences in physiologic ages of populations is prepared from the compilation of death rate by age, sex, and cause prepared by the Demographic Staff of the United Nations (Demographic Yearbook 1952-1954). (The preceding analyses were made from the official publications of each country concerned, but for general population statistics the Demographic Yearbook is a remarkable international collection of uniformly assembled population data.) Incidence of death and major causes of death by male sex at age 58 have been calculated for the 22 countries that are listed in the Demographic Yearbook; these are given in Table V and in Fig. 9 and 10. These calculations will not correspond precisely to the usual values given by the life tables of the various countries because they have been estimated from the broad class intervals of the groupings in the yearbook. Disease incidence rates per 1000 males are given for age 58. This age is for the class interval 45 to 64 years of age and the age 58 was selected to represent this class interval, as the median death of the class interval would occur at approximately this age. In addition to the conventional incidence rates, a calculation was made for each disease as the abstract death rate of the disease for age 58. Unfortunately this is subject to considerable error because it is

made from only two class intervals, the 45-to-64 age group and those 65 and older. It is estimated, from comparisons of these roughly made abstract death rates with ones more suitably calculated from complete life-table listings, that the error here is within a range of plus or minus 19% . Since the difference between the countries is much greater than the range of error of the estimated abstract death rate, this rough value will still be very useful. The reader will recall from an earlier discussion that the incidence rate of a disease death is the fraction of the total population that die of a stated cause in a given time and that the abstract death rate is an estimation of the rate of development of that disease to death in that fraction of the population which dies of that selected disease. The abstract death rate concerns the physiologic age of the population developing a specific disease; its usefulness here is in part due to the fact that it is not subject to the errors of subtle differences in the classification of deaths or the tabulation of the death by cause, which might affect international classifications of incidence rate in the Yearbook. Both the crude abstract death rate and the abstract death rate corrected for age distribution of the population from which it was derived are listed. The reader must regard these as very tentative estimations if he wishes to use them for other purposes. The abstract death rates given in Fig. 3, 4, and 5 and in Table II were prepared from regular listings of death by cause and should be reliable.

The class interval of the death lists given in the Demographic Yearbook, age 45 to 64, gives an opportunity to observe displacements of physiologic age in those countries with respect to the average trend. The more the physiologic age is advanced the more the incidence of disease will be elevated in this group and the more the abstract death rate will be elevated. The single class 65 and older may not be used in the same way, as all the individuals in this age range will die of disease during the class interval. Estimation of these functions for 22 nations are given in Table V and in Fig. 9, and 10. A very similar ranking of death rates was found in the 25-to-45-year age-class interval for these same nations, but they are not presented.

A comparison of the rate of death due to cancer, coronary heart disease, or cerebral vascular disease compared with all other causes of death shows -- as plotted in the Fig. 9 and 10 --that there is an unmistakable trend for each of these diseases to be elevated when the general death rate is also elevated and that the rates of development of disease (the abstract death rates) are also related between the diseases. There are some exceedingly interesting exceptions to the average trend, such as the reported low incidence rate of cancer in Portugal, the relatively low rate of death from coronary heart disease in France, and the near absence of cerebral vascular disease in Switzerland. Each reader will probably wish to make comparisons of his own choosing between countries that he can contrast. One of the most constructive contrasts -- of the argument of differences of physiologic age -- is the remarkable difference between Finland and the three other Scandinavian countries, Norway, Sweden, and Denmark. Each of the four major causes of death is elevated in incidence and rate of development of the disease as though Finnish males are similar to other Scandinavian males in disease pattern but are at a different stage of development of physiologic time; the discrepancy in physiologic time is eight years and is one of the greatest differences observed between populations.

Table V

Deaths per Year per 1000 Males at Age 58
by Country and Cause of Death

International Brief List 6th Revision

Causes		Netherlands 1951			Israel 1950		
		A	B	C	A	B	C
All Causes		. . .	11.8	11.8	. . .	15.5	15.5
Cancer	B 18, 19	18.4	15.7	3.58	25.5	18.9	3.2
Heart	B 26	10.9	9.5	2.16	24.5	18.1	4.65
Cerebral Vascular	B 22	7.6	6.6	0.79	17.2	12.7	1.61
Hypertension	B 28, 29	10.8	9.4	0.19	. . . . .		0.38
Diabetes, Nephritis	B 20, 38	15.6	13.6	0.33	. . . . .		0.34
Tuberculosis	B 1, 2	28.5	24.7	0.42	. . . . .		0.88

International Brief List 5th Revision

		Norway 1950			Denmark 1949			Sweden		
		A	B	C	A	B	C	A	B	C
All causes		. . .	11.5	11.5	. . .	12.8	12.8	. . .	13.0	13.0
Cancer	15, 16	. . .	14.7	2.75	17.7	16.5	3.08	22.3	22.0	2.8
Heart	24	. . .	13.1	2.63	12.0	11.2	3.80	14.1	13.9	1.86
Cerebral Vascular	22	. . .	8.4	1.08	10.2	9.5	0.84	9.5	9.4	1.05
Diabetes, Nephritis	18, 33	. . .	14.55	0.49	14.9	16.0	0.54	21.9	21.6	0.42
Tuberculosis	6, 7	. . .	25.1	0.65	27.9	29.9	0.37	20.0	19.7	0.65

A, the death rate per 1000 men age 58 destined to die of cancer, etc., uncorrected for the distribution of ages in the population.

B, the death rate per 1000 men age 58 destined to die of cancer, corrected for

Table V

International Brief List 6th Revision (cont.)

	New Zealand 1950			Canada 1950			France 1950		
	A	B	C	A	B	C	A	B	C
All		16.6	16.6		17.7	17.7		19.0	19.0
C: B18, 19	15.9	18.1	3.19	18.7	20.3	3.20	20.1	24.6	3.95
Ht: B26	13.7	15.5	5.83	16.4	17.9	6.25	18.4	22.6	0.94
CV: B22	9.3	10.6	1.07	10.6	11.6	1.25	10.9	13.4	1.60
Hyp: B28, 29	14.1	16.0	0.77	13.4	14.7	0.70	20.8	25.4	0.09
D, N: B20, 38	14.4	16.4	0.35	13.6	14.9	0.54	16.1	19.8	0.39
TB: B1, 2	33.3	37.8	0.80	31.2	34.2	0.70	36.3	44.2	1.88

International Brief List 5th Revision

	Italy 1950			Ireland 1949			Germany 1950		
	A	B	C	A	B	C	A	B	C
All		15.0	15.0		15.8	15.8		16.0	16.0
C: 15, 16	22.3	19.6	3.12	17.3	21.1	2.86	19.3	19.3	3.63
Ht: 24	13.2	12.7	2.72	12.4	15.0	4.88	15.2	15.2	2.85
CV: 22	10.1	9.8	1.74	10.5	12.7	1.00	9.9	9.9	1.28
D, N: 18, 33	37.1	36.1	0.52	13.8	16.7	0.56	22.2	22.2	0.49
TB: 6, 7	39.0	38.0	1.11	39.6	48.1	1.63	32.8	32.8	1.21

the distribution of ages in the population of that country.

C, the incidence of death per 1000 men age 58 by the indicated cause. All death rates are per year; age 58 and not the mid-year interval.

Values for the rate of death per 1000 to die of a cause are estimated from the broad class intervals of numbers of death by age and cause compiled in the Demographic Yearbook, United Nations. These are crude and are estimated to have a range of deviation from true values of ± 19 percent, columns A and B above. Some precise values of the death rates of abstract populations destined to die of a selected cause are given in Fig. 3, 4, and 5 and in Table VII.

Table V

International Brief List 6th Revision (cont.)

	England and Wales 1950			North Ireland 1950			United States 1950		
	A	B	C	A	B	C	A	B	C
All		19.1	19.1		20.2	20.2		20.5	20.5
C: B18, 19	20.6	25.8	4.66	18.9	28.9	3.88	21.6	24.3	3.34
Ht: B26	11.9	14.9	4.44	10.8	16.5	5.3	33.4	37.4	7.15
CV: B22	9.8	12.3	17.6	9.4	14.4	1.52	13.7	15.4	1.57
Hyp: B28, 29	12.5	15.7	0.64	. . .	. . .	0.77	16.7	18.8	1.16
D, N: B20, 38	17.0	21.3	0.35	. . .	. . .	0.33	17.6	19.9	0.65
TB: B1, 2	36.7	46.0	1.22	. . .	. . .	1.47	33.9	38.2	0.90

International Brief List 5th Revision

	Switzerland 1950			Belgium 1950			Finland 1949		
	A	B	C	A	B	C	A	B	C
All		17.3	17.3	. . .	19.7	19.7	. . .	24.5	24.5
C: 15, 16	18.3	19.3	4.04	20.8	26.3	3.57	25.1	27.0	5.3
Ht: 24	15.2	16.1	3.66	15.7	20.1	3.69	23.7	24.6	7.4
CV: 22	11.0	11.6	0.35	12.5	15.9	1.80	16.2	16.7	1.7
D, N: 18, 33	21.5	23.8	0.66	13.9	17.7	0.70	31.9	32.9	0.51
TB: 6, 7	31.6	33.3	0.99	38.2	49.9	1.70	37.4	38.5	3.3

Table V

International Brief List 6th Revision (cont.)

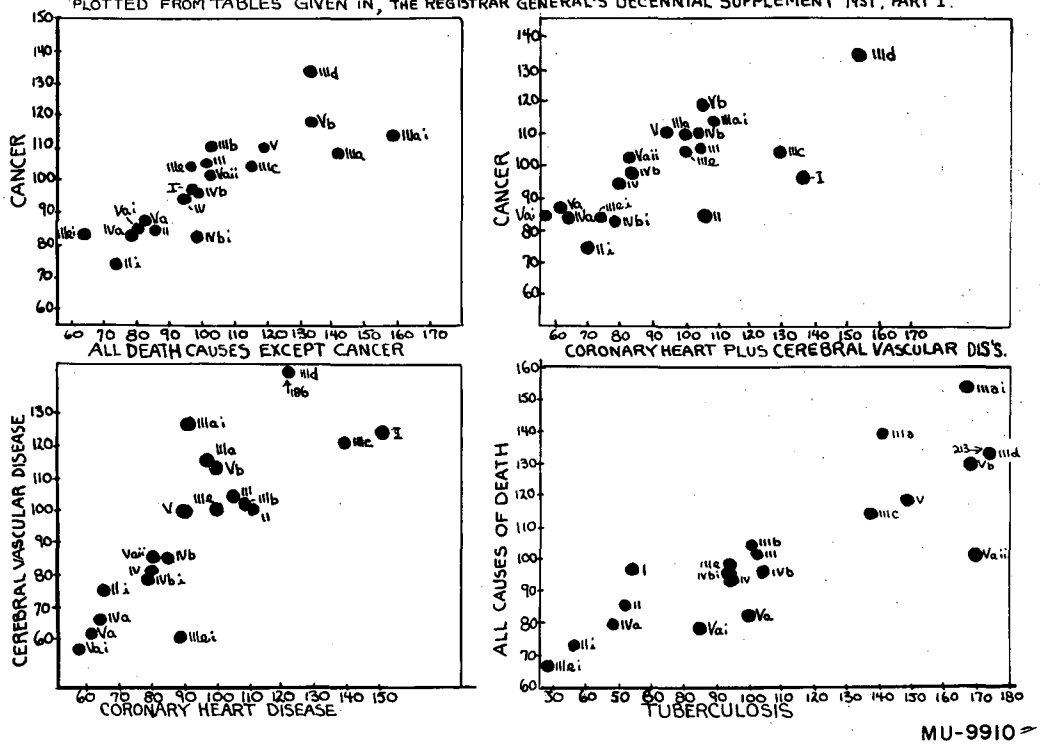
	Union of South Africa (Europeans) 1946			Scotland 1951			Puerto Rico 1940		
	A	B	C	A	B	C	A	B	C
All	. . .	21.0	21.0	. . .	23.0	23.0	. . .	30.0	30.0
C: B18, 19	18.1	20.3	3.30	20.7	29.9	4.85	23.6	33.9	4.38
Ht: B26	22.2	24.4	6.47	13.5	19.6	6.42	16.9	24.2	4.07
CV: B22	14.7	16.5	1.68	10.3	15.0	2.02	17.9	25.7	1.78
Hyp: B28, 29	14.2	16.2	0.71	14.2	20.6	0.49	22.1	31.5	1.2
D, N: B20, 38	. . .	. . .	. . .	18.6	27.1	0.37	. . .	. . .	. . .
TB: B1, 2	34.3	38.3	0.86	36.2	52.7	1.27	35.8	51.2	5.67

International Brief List 5th Revision

	Spain 1950			Portugal 1949		
	A	B	C	A	B	C
All	18.3			. . .	21.0	21.0
C: 15, 16	22.0			24.0	28.5	2.23
Ht: 24	17.6			15.6	18.6	3.41
CV: 22	12.6			12.0	14.3	2.04
D, N: 18, 33	13.6			41.3	48.9	0.72
TB: 6, 7	39.1			40.0	48.0	3.50

Fig. 8. The interassociations of major diseases by occupational groups for the Countries of England and Wales. The incidence values are taken from The Registrar General's Decennial Supplement, Occupational Mortality (1951) England and Wales. The 20 groups are: I-Professional, II-Intermediate, III-Skilled, IV-Partly Skilled, V-Unskilled, IIIa Mineworkers, IIIb Transport Workers, IIIc Clerical Workers, IIId Armed Forces, IIIe Others in III, IVa Agricultural Workers, IVb Others in IV, Va-Building and Dock Laborers, Vb-Others in V, II(i) Farmers, IIIa(i) Hewers and Setters of Coal, IIIe(i) Foremen and Overlookers, IVb(i) Coalmine Workers, Va(i) Building Laborer, Va(ii) Dock Laborers. When one disease is elevated it is likely that all diseases are elevated. The variations indicate a great range in physiologic age even though all individuals are at the same chronologic age. Standard Mortality Ratios = $\frac{\text{observed deaths}}{\text{expected deaths}} \times 100$

STANDARDISED MORTALITY RATIOS OF MEN 20-64 YEARS BY OCCUPATION, ENGLAND + WALES
PLOTTED FROM TABLES GIVEN IN, THE REGISTRAR GENERAL'S DECENNIAL SUPPLEMENT 1951, PART 1.

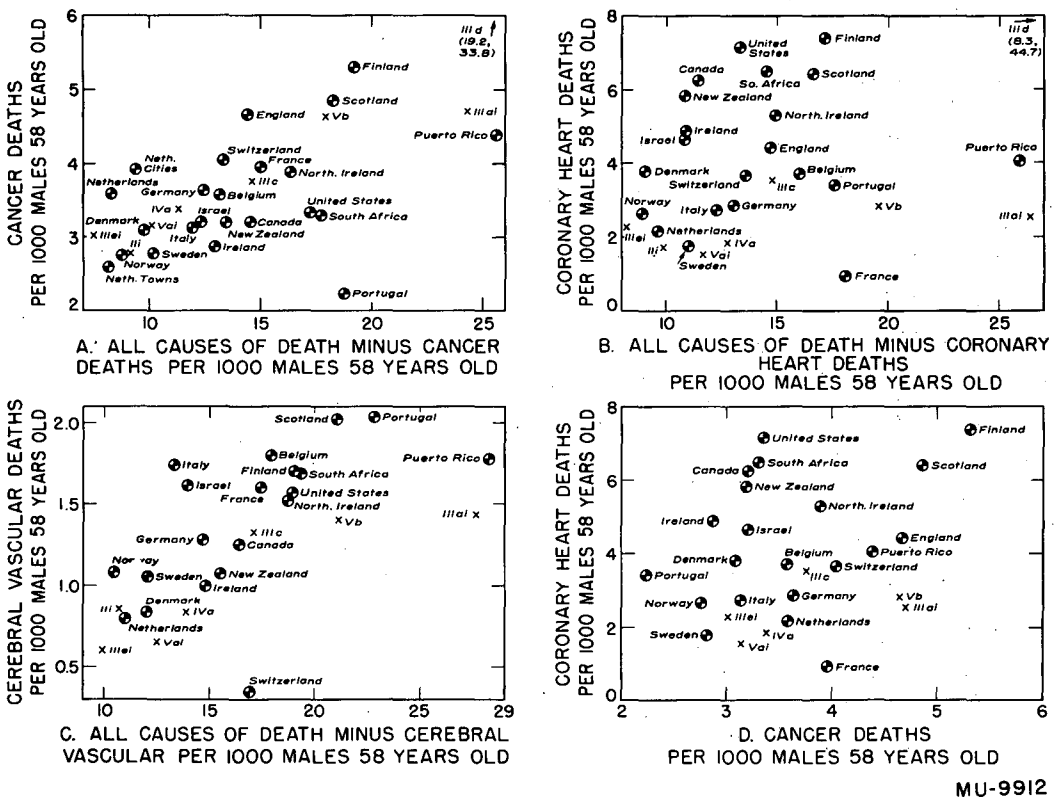


MU-9910

Fig. 9. Plots of disease-death rates for 22 countries for which deaths have been compiled by age and cause of death in the Demographic Yearbook, United Nations. The interassociations of the major diseases are striking and varied. The reader may select the countries he wishes to contrast. A constructive help to the argument of physiologic age and disease is the comparison afforded between the similar populations such as Sweden, Netherlands, Norway, and Denmark as one group compared to Finland.

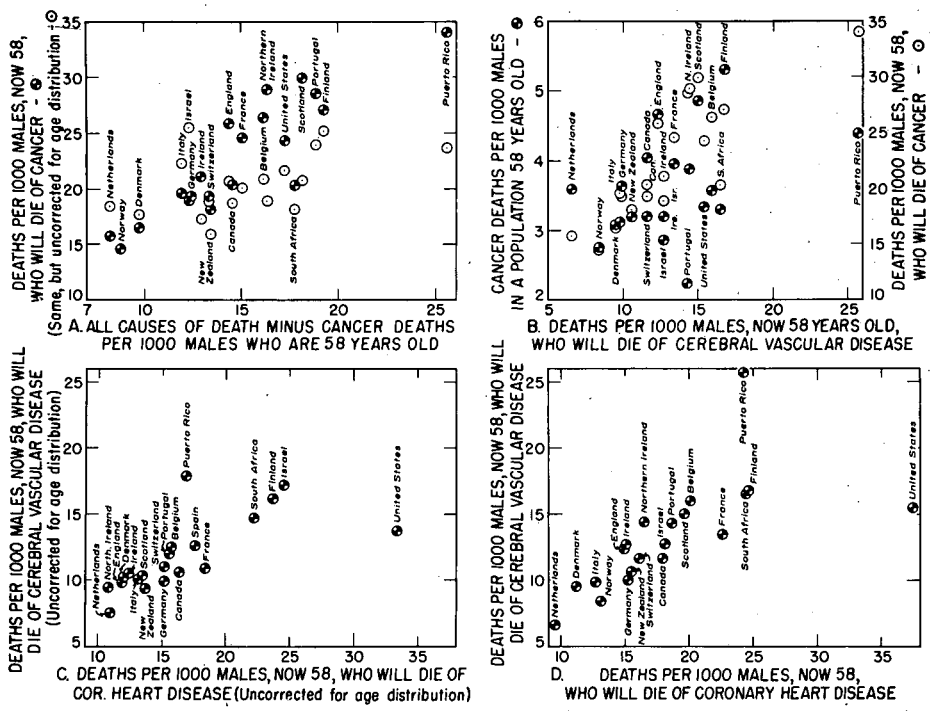
In this figure and the following ones age is selected at the 58th year. The values given are for males only. Points on the figure that are designated by Roman numerals are for selected subgroups by occupation for England and Wales. It is noted that the internal variation within such a country is the same as the differences between countries, and that there are the same relationships between the diseases.

In contrast to Fig. 10, the measure of disease in Fig. 9, is the incidence of disease per 1000 males at age 58 in the general population. Figure 10 is the abstract death rate of the subpopulations that die of a selected disease and no other; this is a measure of the intensity of the disease processs in that disease subgroup.


CANCER DEATHS PER 1000 MALES 58 YEARS OLD
A. ALL CAUSES OF DEATH MINUS CANCER DEATHS PER 1000 MALES 58 YEARS OLD
CORONARY HEART DEATHS PER 1000 MALES 58 YEARS OLD
B. ALL CAUSES OF DEATH MINUS CORONARY HEART DEATHS PER 1000 MALES 58 YEARS OLD
CEREBRAL VASCULAR DEATHS PER 1000 MALES 58 YEARS OLD
C. ALL CAUSES OF DEATH MINUS CEREBRAL VASCULAR PER 1000 MALES 58 YEARS OLD
CORONARY HEART DEATHS PER 1000 MALES 58 YEARS OLD
D. CANCER DEATHS PER 1000 MALES 58 YEARS OLD

MU-9912

Fig. 10. The age-specific death rates for subpopulations dying of only one selected cause of death. These are roughly estimated from the broad class intervals of death listing by age in the Demographic Yearbook. These values show the associations in the tendency to develop a disease by those who will develop that disease. In certain circumstances where the subpopulations of a country are in greatly differing proportions in incidence of a disease, this method allows the relative development of the disease process in only those individuals who are susceptible to that disease.


DEATHS PER 1000 MALES, NOW 58, WHO WILL DIE OF CANCER - ●
(Same, but uncorrected for age distribution - ○)
A. ALL CAUSES OF DEATH MINUS CANCER DEATHS PER 1000 MALES WHO ARE 58 YEARS OLD
CANCER DEATHS PER 1000 MALES IN A POPULATION 58 YEARS OLD - ●
DEATHS PER 1000 MALES, NOW 58, WHO WILL DIE OF CANCER - ○
B. DEATHS PER 1000 MALES, NOW 58 YEARS OLD, WHO WILL DIE OF CEREBRAL VASCULAR DISEASE
DEATHS PER 1000 MALES, NOW 58, WHO WILL DIE OF CEREBRAL VASCULAR DISEASE
(Uncorrected for age distribution)
C. DEATHS PER 1000 MALES, NOW 58, WHO WILL DIE OF COR. HEART DISEASE (Uncorrected for age distribution)
DEATHS PER 1000 MALES, NOW 58, WHO WILL DIE OF CEREBRAL VASCULAR DISEASE
D. DEATHS PER 1000 MALES, NOW 58, WHO WILL DIE OF CORONARY HEART DISEASE

MU-9919

Another way of saying this is that the intensity of the development of diseases and the pattern of diseases would be very similar if one compared for the year 1950 men of Finland at age 50 with men of Sweden, Norway, or Denmark who are 58 years of age. This is a very great difference, and it argues strongly for believing such variations in disease rates to be determined by the physiologic age with regard both to the development of internal disease and to resistance to externally imposed disease.

Not only is it apparent that each of the three leading causes of adult deaths--heart disease, cancer, and cerebral vascular disease--is related by a measure of relative abundance of disease type. They are also related by measures of the rate of evolution of any disease state. In these ways each disease is related to every other disease. This is quite understandable for coronary heart disease and cerebral vascular disease, since both are considered categories of atherosclerotic disease. (The abstract death rate shows that a very precise relationship exists between the rates of development of cerebral vascular disease and coronary heart disease for those people in the various countries who are susceptible to these diseases. See Fig. 10 c and d). Elevation of the incidence of coronary heart disease is generally accompanied by an elevation of cerebral vascular disease, but the relationship is not as regular as the comparisons of the rate of development of this disease in susceptible groups. France has a very greatly reduced incidence rate of coronary heart disease; Switzerland has a phenomenally low incidence rate of cerebral vascular deaths. Comparing such differences by the abstract disease rates, we may see that for those individuals who do develop these forms of atherosclerosis the rate of development is comparable with other nations, and this suggests that the differences observed in the incidence rates of atherosclerotic diseases in France and Switzerland may be due to the freedom from diseases in large subpopulations of these countries, but that a specific subpopulation is more similar to the other nations. The more usual trend, however, is an agreement between the measure of incidence of a disease and the measure of the rate of development in those who are susceptible to that disease. This can be seen in the low disease rates of Norway, Sweden, Denmark, and the Netherlands, and in the higher disease rates of the United States, Scotland, South Africa, Finland, Belgium, and Puerto Rico. For all the nations it appears that coronary heart disease develops sooner and to a greater intensity by age 58 than does cerebral vascular disease (see Fig. 10c and d). The United States is an exaggerated exception, showing that the level of coronary heart disease is nearly 50 percent greater than would be expected on the basis of the rate of development of cerebral vascular disease at age 58. Puerto Rico (Fig. 10) is the only country in this collection having the same rate of development of cerebral and coronary atherosclerotic disease, both of which are at a high level.

The differences between countries and nations given in Table V and Figs. 9 and 10, strengthen the argument of differences of physiologic age between the countries, but they also indicate that there must be other dissimilarities between these countries which have favored the development of one disease more than another.

For the purpose of advancing the argument of differences in physiologic age, the reader must not use plots such as Fig. 10d, in which the corrected abstract death rate of cerebral vascular disease is compared with the corrected abstract death rate of coronary heart disease. Both these measurements are corrected by the same factor; if the factor is in error the relationship would seem stronger than it actually is. The relationship of atherosclerotic disease is, however, probably more correctly estimated in Fig. 10c than in Fig. 10d; Fig. 10c alone is acceptable as an argument for differences in physiologic age.

INTERNAL HOMOGENEITY OF POPULATIONS WITH REGARD TO SUBPOPULATIONS, PHYSIOLOGIC AGE, AND TENDENCY TOWARD DISEASE

Takin as a whole the population of the world is exceedingly different, as the various national, social, occupational, and geographically separated groups of men have been shown to vary. The range of differences present at the mid-point of the twentieth century covers a span of 20 years' variation in the average physiologic ages of populations. Cyprus at the low extreme has 9.3 deaths per 1000 men at age 58 per year; the Virgin Islands at the other extreme has 48 deaths per 1000 men at age 58 per year. Atherosclerotic disease shows the greatest variation in tendency to develop, cancer tendency varies by less than half of the range of atherosclerosis. These are estimated as the range and plus or minus one standard deviation from the mean; two standard deviations account for the variation among the countries of the middle two-thirds of the range of physiologic ages by diseases.

Difference in physiologic age (22 countries)

Disease	Total Range	Two Standard Deviations
Cancer	9.3 years	3.1 years
Coronary heart	25 years	8 years
Cerebral vascular	20 years	7 years

Within a population such as Denmark, Sweden, and to some extent the Netherlands there are ample evidences that there are striking differences between the average individual who has lived in the country and the one who has lived in the cities (see regular death lists and life table of these countries and also Tables II and III and Fig. 5). City populations are dying at a faster rate than the more rural groups. At any age of life these populations are different by a fixed proportion. In spite of differences in the death rates of population samples, the rate of progression of the tendency to die remains the same at about 8.5 years' doubling time, and in the cities there is a constantly higher proportion of individuals dying of disease at any age. The constancy of the slope of the physiologic doubling of the death rate--which also is approximately the same for all the countries, regardless of their general disease rate--suggests that progression of physiologic change to disease states is not, in these populations, altered in time schedule. A multiple-stage process of physiologic aging is visualized in which the progression from step to step is according to a precise clock which must be related to some average property of body metabolism; however, these environmental factors may induce some extra steps in aging which had not already

Table VI

Selected Extremes of the Occupational Subgroups of England and Wales
(death rate per 1000 individuals per year, males only)

		All Causes	Cancer	Coronary Heart	Cerebral Vascular	Hypertension	Diabetes Nephritis	T. B.
Va(i)	Building laborers	13.2	3.14	1.54	0.65	. . .	. . .	1.12
IIIe(i)	Foremen	10.5	3.02	2.28	0.60	. . .	. . .	0.51
IVa	Agricultural workers	14.7	3.38	1.85	0.83	. . .	. . .	0.51
IIi	Farmers	11.6	2.76	1.74	0.85	. . .	. . .	0.53
IIId	Armed Forces	53.0	19.2	8.3	6.1	2.8	3.0	29.0
IIIc	Clerical workers	18.4	3.75	3.55	1.32	0.62	0.48	1.80
Vb	Unskilled	22.5	4.64	2.85	1.40	0.62	0.43	2.1
IIIa(i)	Hewers, getters of coal	29.0	4.7	2.55	1.44	. . .	. . .	2.82

been taken, or they may be visualized as acting to increase or lower the threshold of change into disease, in which case they may prove to be reversible. Aside from the large characteristic differences that are a part of each of the populations, certain general relationships of disease tendency may be outlined:

1. The death rate in the country is generally more favorable than in the cities. (See general population statistics reports for Denmark and Sweden.)
2. The death rate in the small towns is more favorable than in the large cities. (See general population statistics reports for the Netherlands.)
3. Hammond and Horn[6] have shown that a subpopulation selected in the United States on the basis of the status of smoking or nonsmoking gives great subpopulation differences, with the smoking population dying from all causes of death at any age approximately twice as fast as nonsmokers.
4. Married men at nearly all ages are dying less rapidly than are either single men or widowers or divorced men. (See general population statistics reports for Sweden and Denmark.)
5. The occupational groups of England and Wales clearly indicate a constant increase in the tendency to die with progressing age in the various groups, the worst of which are the armed forces and the most favorably inclined the men in agricultural occupation and the building laborers.

In each of the above groups it appears that the tendency toward disease at any age is some constant displacement of the age-specific death rate, so that the slope or the doubling time remains nearly constant, and between the various subpopulations there are very great differences in physiologic age.

The occupational subgroups of England and Wales* show that within a nation of even small geographic boundaries, very large differences in the intensity of disease and, of course, physiologic age may exist. Internal ranges of differences in disease tendency are as great as the variations between countries. See Table VI and Figs. 8, 9, and 10. The death rates of extremes of the subpopulations of England and Wales have been converted into the same form of death rate for males age 58 as in Table V for the 22 countries, and these extremes of the population of England and Wales are plotted lightly in Fig. 10a, b, and c in comparison with the spread of death rates observed between countries. The range of differences is of the same order of magnitude, suggesting that the various nations or countries may be composed of various proportions of subgroups and that the country may be characterized by a dominantly abundant class or some average of several classes. The death rate for the occupational groups of England and Wales is given in terms of the Standardized Mortality Ratios, SMR, which is:

$$\text{SMR} = \frac{\text{observed number of deaths at a given age}}{\text{expected number of deaths at a given age}} \times 100.$$

The expected number of deaths is estimated from the pooled population sample.

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*From the Registrar General's Decennial Supplement for England and Wales, Occupational Mortality Report of 1951.

The SMR is functionally related to the differences between the death rates of the subpopulation and the pooled population, and it is a convenient measure of physiologic age. The higher the SMR value the higher the death rate at that age and the greater the physiologic age. Figure 8 shows that the pattern of disease tendency between the various subgroups of the population of England and Wales is exceedingly similar to the relationships seen between disease abundances on a global basis. When all causes of death are elevated, cancer is also elevated, tuberculosis is elevated, and atherosclerotic disease is elevated; see Fig. 8 and 10. England is an example of the internal spread of population differences in physiologic age that are possible to visualize as a pattern that must apply to some extent to every country.

In examination of the population of the United States one finds considerable evidence for variability in physiologic age. Figure 6 is an enlarged scale of the age-specific death rates for the last part of adult life. White males and nonwhite (essentially Negroes) indicate that the progression of the death rate is not the precisely regular progression that it has been described to be, but that in the upper ages it has a progressive bending over to lower age-specific rates than would be predicted as an extension of the death rate characterizing the death rate in mid-adult life. This is evidence of an extreme degree of variation in physiologic age within these groups and especially within the Negro population. It has been seen that each of the various subpopulations has a characteristic age-specific death rate. In the entire population these will each contribute deaths, and as long as the relative numbers of the various subpopulations remain similar the observed progression of the death rate of the entire population will remain as regular as each of the contributing parts, and since they all have the same doubling time of death tendency, no change in the average death rate for the population will be observed unless a significant amount of one of the subpopulations which is contributing heavily to the deaths of the whole population begins to be consumed much more than the other subpopulations. A very slight tendency of this sort is observed in the population of white males, but it occurs to a striking extent in the nonwhite male population. As estimated 75% of the Negro population at any adult age is dying 4 times as fast as the remaining 25%. The white population shows a much lesser variation in the rate of death tendency; one-half of the white male population at any age is indicated to be 50% higher in death rate than is the average of the population, another 25% of the white males is at an equal step lower than the more disease-prone subgroup, and there is an estimated 25% of the white population that is as favorably placed with regard to tendency to survive as the more healthful subgroup of the Negroes. The most healthful average group in the United states (25% of both whites and nonwhites) is at the same position as is the average of the long-lived countries such as Sweden, Norway, etc. This of course suggests that the long-lived countries may have similar subgroups even farther displaced in a favorable direction in physiologic age. The age range of the subgroups of whites estimated in this way is approximately 8 years, or equal to the internal differences seen in the ranges of occupational groups of England and Wales. The nonwhite data indicate that the range of physiologic ages may be at least 17 years and perhaps more. These evidences of differences do not suggest that there are any racial factors that have made them appear, but it is suggested that they have come into existence through the interaction of environment and disease effective from early life.

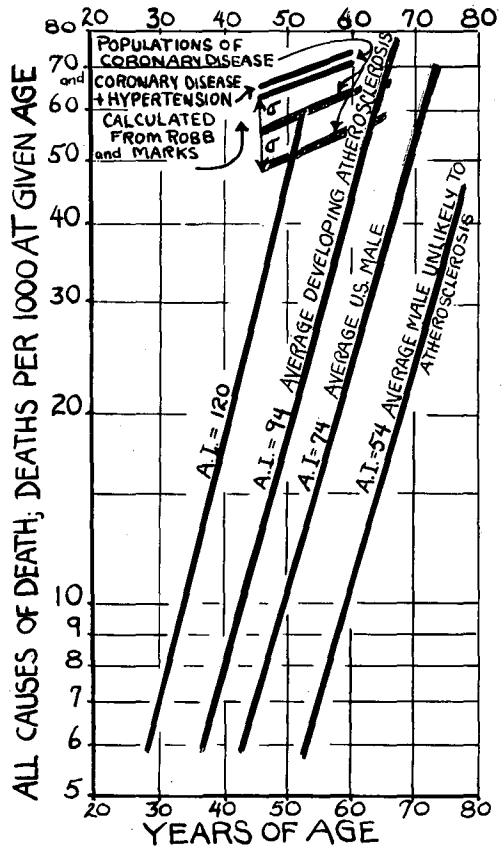
The current death rate of nonwhite children has reached a much more favorable position of less intense disease, but it is still considerably higher than the average for white children of the same age; this predicts that there will continue to be a high death rate of the average adult nonwhite male of the United States for at least another thirty years.

III MAJOR-DISEASE GROUPS

1. Atherosclerosis

Gofman and Tamplin and his associates have been able to make a theoretical construction of how the differences between the death rates of those individuals who die of coronary disease have come about. Their estimation is based upon the assumption that atherosclerotic deposits grow throughout life at a rate that is proportional to a function of the level of the atherosclerogenic lipoproteins of the blood and the duration of the elevation of these classes of lipoproteins. Gofman has given predictions of the fraction of the lumen of the coronary artery closed by atherosclerotic process as an objective prediction of the incidence of death from coronary heart disease for the American male, and on this basis has compiled tables for prediction of incidence of coronary heart deaths by age and by serum lipoprotein level. From his table of values for the increase in coronary heart deaths, and on the assumption that other causes of death are the same as for men at the same age in the general population, subpopulations of males by serum lipoprotein level have been computed and are presented according to age-specific death rate in Fig. 11. It is observed that these predicted subgroups are very similar in relative progression of the death rate to others that have been examined. The displacements of physiologic age may be relatively great over the possible range of serum lipoprotein. Lipoprotein level is indicated as the A. I. or Atherosclerotic Index; this is a measure of lipoproteins giving atherosclerogenic weighting to different classes of lipoproteins. Also given in Fig. 1 is an estimation of death rate by age of men who have already developed coronary artery disease. These rates were calculated from survival rates quoted by Robb and Marks[11]. The death rate of men with coronary artery disease already established is not significantly higher than the probable values for such a population on the basis of probable lipoprotein level. As has been noted by Jones et al.,[7] and Gofman,[3, 4] early coronary disease is much more likely associated with the higher elevations of serum lipoproteins. Figure 11 is also a clue to the greater range of physiologic age associated with the development of atherosclerosis than with the other major diseases. The average American man who has a low serum lipoprotein, A. I. = 54, is estimated to be in the same favorable position with regard to the death rate at adult ages as the estimated best 25% of the population of the United States. However, is such a population existed that could be followed with regard to death rate it would be predicated that awing to the interaction of disease mechanisms and the interassociation of disease incidence the death rate of this estimated population having an "ideal" lipoprotein metabolism should be even more favorably placed at lower death rates.

Fig. 11. Death rates of the subpopulations having various tendencies to develop atherosclerosis. The lines are constructed from Gofman's estimation of chances of development of coronary-heart-disease death at various lipoprotein burdens. All other causes of death are assumed to be the same as the general population of the United States. The subpopulation that already has coronary heart disease is indicated as constructed from the life values given by Robb and Marks. The A. I. is a weighted measurement of two classes of serum lipoproteins. The figure indicates that the subpopulation having high levels of atherosclerogenic lipoproteins will be consumed by coronary heart disease much more rapidly than the subpopulations having lower-than-average developmental rate of atherosclerosis. The well-known association of early death from atherosclerosis with very high concentrations of the atherosclerogenic classes of lipoproteins is logical from the high death rates of the individuals with disturbed lipoprotein metabolism.



ALL CAUSES OF DEATH U.S.A. MALE POPULATION 1949; COMPARED WITH THREE SUB-POPULATIONS IN WHICH ATHEROSCLEROTIC DISEASES ARE ESTIMATED FROM LIPOPROTEINS AND OTHER CAUSES OF DEATH ARE ESTIMATED AS UNCHANGED.

MU-9913

Smoking

The recent report by Hammond and Horn[6] on the association between smoking cigarettes and a higher tendency to disease is a striking example of the contrasts that may be encountered in the physiologic age of subpopulations. As noted earlier, there is a tendency for the smoking group to die nearly twice as intensely at any age as the nonsmokers, and the physiologic ages are 8 years apart at the same chronologic age. Thus it is indicated that the difference between these two groups is as great as the previously estimated range of physiologic age of the men in the United States Fig. 6, and as great as the range of physiologic ages for the occupational groups of England and Wales. It is of course important to resolve the question whether or not the accelerated death rate is due to smoking. Should it be--and there is good likelihood that it is--then smoking might account for a great deal of the internal variation of disease tendency in the population of the United States and it might also account for the general discrepancy in death rates between the United States and longer-lived countries.

Cancer and the Subpopulations Dying of Cancer

Considerable evidence has been presented that cancer incidence and the total disease rate are interrelated. It has also been shown that there are differences between countries and subpopulations with respect to either the incidence of cancer or the rate of development of cancer. These were noted to be of a smaller relative range of variation than may usually be observed for atherosclerotic disease. Cancer, like other diseases, is probably related to specific provoking factors, the intensity of which may vary. The general trend estimated for cancer and all the major diseases is a progressively less intense age-specific incidence as calendar time progresses. Nevertheless, for lung cancer the story may be quite different. Doll[2] has presented strong evidence that lung cancer is increasing steadily throughout the world, associated with the use of cigarettes and tobacco. In this case a single provoking cause is on the increase, even though the general health of the populations examined here indicates a progressive improvement.

The abstraction of the cancer deaths to give estimated death rates for those destined to die of cancer leads to some interesting estimations. This measurement may be taken to be an estimation of the rate of development of the cancer process for the average of the population concerned.*

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*This is reasonable if we can accept either that cancer is not cured or that if it is cured the cure rate is not a function of age; a second fact that makes it possible to examine the abstract age-specific death rate as the rate of average carcinogenesis is the fact that the death rate of those who die of cancer becomes greatly elevated with respect to the average death tendency of the average person. In this way the average cancer death occurs but a short time after the appearance of the cancerous state, and thus the rate of death by cancer is in early equilibrium with the number of cases of cancer that are formed and hence in equilibrium with and a measure of the average process that converts the normal state to the cancer state.

The abstract age-specific death rates from cancer in Sweden and the Netherlands are considerably more intense than the age-specific death rates for all causes in the general population. This difference is true to all ages, and from this fact it may be estimated that the individuals who die of cancer are not generally identifiable with the average population; for if they were, they should have given a distribution of ages similar to the general population, which would have given an abstract age-specific death rate in closer agreement with the all-causes-of-death function for the entire population. It may then be estimated that the population destined to die of cancer is a rather special subgroup within the population and that possibly the entire population may not have a total tendency for cancer to develop, just as the similarly abstracted populations of those destined to die of tuberculosis, or cirrhosis, or diabetes, all reveal a more intense death rate than the average of the population and involve limited numbers. For cancer deaths in the United States the estimated abstract age-specific cancer death rate indicates a cancer population that is dying at about the same general rate as the average population is dying of all causes of death. However, this cancer population is at nearly the same age-specific death rate as these same cancer groups in Sweden and in the Netherlands: see Table II and Fig. 3, 4, and 5. This suggests that the subpopulations that die of cancer are far more similar among the three countries than are the outward averages of these countries. Considering the very wide spread of differences that have been noted internally in populations, it seems possible that such cancer subpopulations may indeed have a number of common disease-determining factors and similar disease-rate tendencies between countries or groups in spite of the possible gross dissimilarities of the parent groups. Tendency toward cancer was followed over a long interval of recent time by use of the technique of abstract death rates applied to the tumor incidence in Sweden for the years 1911 and 1912 prepared by Gunnar Hystrom; there it is possible to examine the tendency to develop cancer over a period of nearly a half-century. The Nystrom listing is a comprehensive report for tumors in the whole of Sweden by age and sex, by district, and by pathologic classification. General comparisons are of course subject to the problems of lack of death-certificate documentation, and changes in the classifications of the various tumors, and there is apparent in the listing of the Nystrom report an absence of a number of neoplastic diseases that are separately given in current death lists. However, examination of the tendency toward death by cancer has been completed with the abstract age-specific death rate method, which is not sensitive to the average errors of imperfect records, and the results are listed in Table II for all tumors, by rural districts, by urban cities, and by carcinoma of the stomach; these are for the Swedish male and comparable values are given for the year 1951. The abstract age-specific death rate from cancer has shifted in intensity over the past forty years; the rate of development into cancer for those who died of cancer in 1911 was as great as that of the Swedish male today who is four years older and who will also develop cancer. The trend is quite unmistakable that the cancer physiologic age was not as young in 1911 as it is today at the same chronologic age. In further examination it is an advantage to turn to a selected form of cancer that may have remained as an unchanging classification over the period of time and for which environmental factors may be estimated. Cancer of the stomach is the only good choice that may be made, for these reasons:

(a) The apparent pathologic classification has remained much the same.

(b) In both 1911 and 1953 there are no significant differences between the rural and urban populations of Sweden as to either the incidence death rate of cancer of the stomach or the abstract death rate--this is important, as over the forty years there has been a redistribution of the populations, favoring urbanization.

(c) It has prominent symptoms that aid in the diagnosis.

(d) If cancer of the stomach is related to food habits there are many factors of custom that will have tended to keep these similar over the period of time.

It is observed that the difference between the development rates of cancer of the stomach in 1911-12 and in 1951 is also more intense than a difference of physiologic age of 4 years, and that the Swedish male in 1911 was more prone to the early development of this form of cancer. If the reader wishes to compare the incidences of cancer of the stomach, for whatever reliability they may have, they are, for males aged 45 to 64, 0.92 ± .03 deaths per 1000 in 1911-12, and 0.68 ± .08 per 1000 males in 1951. The interpretation of these facts in line with the argument that has been presented is that this single type of cancer has grown less likely and is developing among those who are susceptible to it less rapidly today than in 1911. This change in tendency toward cancer could be explained as a change in the age-specific physiologic age of 4 to 5 years, so that the Swedish male of these ages (45 to 64) is today 4 to 5 years younger than he would have been had he been the same chronologic age in 1911. This difference is the same as was observed in the lowering of the tendency to die from every cause of death, which has also been attributed to an increase in the general vigor of the average person (male). It has been argued that this gain in health has been associated with the general diminution of diseases over the past century.

IV. THE ONSET OF DISEASE AND LIFE EXPECTANCY

It has been argued that diseases are interrelated and that each disease episode takes away some of the vigor of body function that resists disease. The fact that the resistance to diseases in general has been increasing over a period of time when general diseases at all ages have been abating leads to some wonderment as to when the process of generation of disease may have begun. A consideration of the changes in the age-specific death rates for any age and calendar year indicates that there has been a general lowering of the death rates at any age with each passing decade for as far as we can usually trace the population record and be satisfied that the structure of the enviornmental population has remained reasonably comparable. There is a suggestion, however, that the change in the death rate of the twentieth century had its beginning as a relatively great increase in the health of the children, which was marked by a lowering of the childhood mortality rate, and that only recently has as great a shift been observed in the adult population. Figure 7 shows how these trends may be followed with respect to age and calendar time. The population of Sweden is shown with respect to a graphic plot of the death rate at 5 years vs the death rate of the same population at 50 years for

the same calendar date. On the same graph are indicated the cohorts of the populations of Sweden, the Netherlands, Denmark, Finland, the United States, and England, but covering an age span of 45 years of difference in calendar time from date age 5 to date age 50. The changes in the death rate appear to follow a more regular pattern when the comparison is made by cohort over a difference of 45 years than the similar trend for the death rates of 5 to 50 years of a population by calendar time. This is some further argument that the pattern for health may be fixed to a great extent in early life, even if it is altered by other modifying factors throughout life. The current high death rate of the male population of Finland is apparently largely related to factors that were associated with high death rate in the period of childhood.

Strict attention to the literalness of the mathematical logic that has been used as a method of analysis of changes that accompany aging indicates the following scheme: Aging begins by the action of unfavorable factors of the environment. Possibly some of the changes are of internal origin, such as genetic constitution, but these are not detectable as average trends for whole populations. The internal balance of metabolism progresses by physiologic time through a succession of changes that are related to the environmental vectors of disease in that each physiologic misfortune may add another sequence of deterioriation of the total functional capacity of the body, but from whatever changes are induced the average person will continue to increase his deterioriation as measured in physiologic units by a rate of increase of deterioriation proportional to the amount of deterioration that he already possesses. This argues that owing to random action of incurrence of diseases, little or big, there must always be a few exceptional individuals who may escape the general experience of disease just as by coincidence there are likely to be a number who will have been exposed to an unfortunate combination of disease experiences. When the general disease rate is high in childhood it is quite possible that a relative minority of the children are transformed into a low-vitality group, which accounts for much of the higher-than-predicted death rate that is seen prior to adult life. This argument has been outlined earlier in the text. In a similar chance-determined way, even under otherwise uniform circumstances, there will always be some who have escaped certain average experiences, just as there are older adults who may have not had the common diseases of childhood. However, a more likely factor, which adds in general to the state of health of certain people, is possibly the fact that they have by chance been exposed to coincidentally favorable factors in childhood in place of inhabitation, occupation, and physical activity, which have made them less likely to accumulate extra steps in the average aging process. No period of life is to be suspected to have a greater effect than the childhood period; any deterioriation that is suffered in this period is -- according to the argument -- likely to accentuate the aging process. It must be kept in mind that damage, aging, and disease and vigor are all abstract words which describe physiologic units of resistance to death, and which may or may not be obvious in gross appearance. It seems possible that as the process of disease is becoming lessened throughout each generation and from one successive generation to another and that as on the average 5 to 15 years have already been gained in physiologic time and there are internal differences within populations of as great an amount of physiologic time, there is an enormous difference in

Table VII

Death rates in various countries at mid-life in comparison to physiologic age (all causes of death)

Country	Date	Age in years		
		50-54	55-59	60-64
Cyprus	1953	6.7	9.5	12.8
Iceland	1950	6.7	10.5	22.7
Norway	1952	6.9	10.2	15.9
Netherlands	1953	6.9	11.3	17.5
Sweden	1951	7.1	11.8	19.0
Denmark	1953	7.4	12.1	18.5
Palestine (Moslems)	1944	8.8	10.9	22.1
New Zealand (European)	1953	8.8	14.9	23.7
Israel (Jewish)	1953	8.9	13.7	21.2
Channel Islands	1951	9.2	15.8	22.9
Switzerland	1952	9.3	14.9	22.6
Western Germany	1952	9.8	15.3	23.4
		10.2 [a]		
England and Wales	1952	10.4	17.4	27.5
Italy	1951	10.5	15.5	22.7
Canada	1952	10.6	16.3	24.5
Northern Ireland	1953	10.8	16.6	25.8
Portugal	1952	11.3	16.9	24.8
Scotland	1953	11.6	20.4	30.3
France	1952	12.0	17.7	25.6
Japan	1952	12.0	18.8	28.7
Nicaragua	1950	12.2	14.5	21.7
United States	1951	13.2	20.0	28.5
Finland	1952	13.7	22.3	33.5
		15.3 [b]		
Argentina	1947	16.4	24.2	34.7
Jamaica	1951	17.9	17.7	37.1
Chile	1940	22.3	31.2	40.7

Table VII (cont.)

Country	Date	Age in years		
		50-54	55-59	60-64
Thailand	1947	23.4	26.9	36.1
Mexico	1940	24.4 24.7 [c]	30.4	41.8
British Honduras	1946	25.7	29.4	68.9
Virgin Islands	1940	27.7	48.2	43.2

[a] This rate, in the 50-54 age group, is equivalent to 5 additional years of physiologic age relative to Cypress and Iceland.

[b] This rate, in the 50-54 age group, is equivalent to 10 additional years of physiologic age relative to Cypress and Iceland.

[c] This rate, in the 50-54 age group, is equivalent to 15 additional years of physiologic age relative to Cypress and Iceland.

Death rates are given per 1000 population per year; the above values of rates are for males.

physiologic ages of the average persons in different populations. (As a guide to physiologic age, death rates by age for a representative sample of the world populations are given in Table VII.) It is likely that there can be average further gains in the direction of better health at every age. It was indicated that the average trend to a lesser intensity of internally developing disease may have added to the life span another 5 to 10 years of useful life for the generation of individuals now reaching adult age, in addition to the gain apparent in adults over the past 50 years.

The tendency to develop all the major diseases of adult life is seen to be steadily diminishing when people of the same age are compared throughout a century of calendar time for the subpopulations of the western world. If the tendency to develop these diseases of internal origin may be taken as a measure of general intactness of body function, then the physiologic ages of the populations of body function, then the physiologic ages of the populations of the world are becoming more youthful at every chronologic age.

SUMMARY

An argument for a theory of aging has been presented. It states that the tendency toward further disease experience is at a metabolic rate determined by accumulated disease experience of the past. It implies that there is a common trend of aging among a very large number of bodily-function compartments and that the extension of disease by any one single experience is probably limited by some considerations of boundaries of the system affected, but that following the episode, physiologic progression of aging will be an increment more intense--remaining so indefinitely--because of the addition of another increment of damage.

Evidence and theory suggest that the process of aging is irreversible, but this information is derived from populations in which no specific effort was made to reduce such metabolic deterioriations as obesity, fat metabolism etc.

Increments of physiologic deterioriation may be incurred at any age, but the earlier they occur in life, the more serious their consequences may be because of the logarithmic progression of the aging process.

There are several reasons for believing that high infancy and childhood death rates--as a measure of extent of disease episodes in early life--fix the basic pattern of aging throughout life and may account for nearly the entirety of the current longevity of Sweden, Norway, and the Netherlands--and some other countries--in this case acting together with a relative absence of environmental hazards of adult life.

Theory and evidence state that childhood experiences are the most important factors determining survival tendency of adult populations. Adult environment is also important.

The theory also states that while certain diseases affect limited systems of the body, the general disease tendency is enhanced by any disease processes. This is shown to have strong supportive evidence in comparisons of disease rates in various countries and subpopulations of countries.

In general, cancer, cerebral vascular disease, coronary heart disease, nephrosis and diabetes, hypertension, and tuberculosis are all interrelated in such a way that an increase in the factors of decay into disease associated with one of them will also influence the common tendency toward all diseases. This is in spite of the fact that certain provocative causes may enhance a given disease relatively greatly.

The theory states that all diseases whose incidence rates increase with age are interrelated.

It is established that at the mid-point of the 20th century there are differences in physiologic ages between nations and subpopulations of nations that cover a range of at least 20 years in age difference--if these populations are compared at ages when they would each have the same tendency to develop disease.

Special enviornmental hazards are discussed with respect to their nature, and abundance in adult life, and effect upon the life span.

Differences between populations in age-specific disease-death rates are established and are used as arguments that physiologic ages of disease susceptibility may be greatly different. It is argued that any of the common diseases may be used as a guide to physiologic age, but that the most significant test of physiologic age is probably the incidence rate of death from all causes. This function is logical because of the interassociations of disease mechanisms, and it is least likely to be disturbed by factors which provoke specific disease responses.

An abstract approach to the problem of physiologic age is presented. It is the grouping of deaths for any of the major causes of death into a special subpopulation of individuals who die of that cause alone. It is independent of completeness of tabulations of death records, and in many circumstances it may be used to estimate the intensities of the physiological factors of decay which underlie that disease process. It is useful in making relative comparisons between populations differing in time and location. When the abstract age-specific death rate is much higher at all ages than the all-causes-of-death rate of the general population from which the abstract population is selected, then it is likely that the disease concerned is not an average disease tendency of the population but that it is confined to a rather well-described subpopulation in which disease process is proceeding much more intensively than in the population as a whole. Examples of such disease populations are those dying of tuberculosis, cirrhosis, nephrosis, diabetes, and cancer.

The various subpopulations that die of cancer appear to show individual differences in cancer-physiologic age, but as a group they are much more similar in physiologic age than are the general populations with which they are associated. This is an argument that suggests that the circumstances of cancer may be related to rather specific causes similar from one country to another.

Cancer appears to be a disease to which only certain individuals are prone. It is not an average disease tendency of the populations of Sweden and the Netherlands. In this respect it more closely resembles tuberculosis, cirrhosis, and nephrosis as diseases affecting discrete and short-lived subpopulations.

Changes in physiologic age are to be observed with respect to specific disease tendency. There are many examples that lead to a conclusion that atherosclerotic diseases are developing on relatively great ranges of displacement of time schedule. It appears that physiologic age of cancer susceptibility is also able to change. Thus the age of susceptibility to cancer has become 4 years older for the man in Sweden in the period from 1911 to 1951. This is true for the sum of all cancers and for a specific comparison, cancer of the stomach.

Atherosclerosis and hypertensive disease appear to be more nearly than cirrhosis and cancer--average diseases or perhaps average tendencies of

BIBLIOGRAPHY

1. S. Brody, The Kinetics of Senescence, J. Gen. Physiol. 6, 245-257 (1923).

2. R. Doll, Bronchial Carcinoma, Incidence and Aetiology, Brit. Med. J. 4835, 521-527; 4835, 585-590 (1953).

3. J. W. Gofman, H. G. Jones, T. P. Lyon, F. T. Lindgren, B. Strisower, D. Colman, and V. Herring, Blood Lipids and Human Atherosclerosis, Circulation 5, 119-34 (1952).

4. J. W. Gofman, F. Glazier, A. Tamplin, B. Strisower, and O. de Lalla, Lipoproteins, Coronary Heart Disease and Atherosclerosis, Physiol. Rev. 34, 589-607 (1954).

5. B. Gompertz, On the Nature of the Function Expressive of the Law of Human Mortality and on a New Mode of Determining Value of Life Contingencies, Phil. Trans. Royal Soc. (London) (1925) pp. 513-585.

6. E. C. Hammond, and D. Horn, The Relationship Between Human Smoking Habits and Death Rates, J. Am. Med. Assn. 155, 1316-1328 (1954).

7. H. B. Jones J. W. Gofman, F. T. Lindgren, T. P. Lyon, and B. Strisower, Lipoproteins in Atherosclerosis. Am. J. Med. 11, 358-380 (1951).

8. J. Loeb and J. H. Northrup, On the Influence of Food and Temperature on the Duration of Life, J. Biol. Chem. 32, 103 (1917).

9. G. Nystrom, Statistiska Undersökningar Utförda På Uppdragg Av Svenska Cancerföreningen, Kraftsjukdomarne I Severige Svenska Tryckeriaktiebolaget, Stockholm (1922).

10. R. Pearl, The Rate of Living, Knopf, New York, 1928.

11. G. P. Robb and H. H. Marks, What Happens to Men Disabled by Heart Disease, The Association of Life Insurance Medical Directors of America, Press of Recording and Statistical Corporation, New York City, 1954.

12. H. Simms, Logarithmic Increase in Mortality as a Manifestation of Aging, J. Gerontol, Nontech. Suppl. 1 (1946).

13. A. R. Tamplin, B. Strisower, O. F. deLalla, J. W. Gofman, and F. W. Glazier, Lipoproteins, Aging and Coronary Artery Disease. J. Geront, 9, 404-411 (1954).

Demographic Sources

H. H. Van Gelderen, Preschool Child Mortality in the Netherlands. Stenfert Kroese, Leiden (1955).

Demographic Yearbook, United Nations (1952) (1953), Fourth Issue, 1952, Sixth Issue, 1954. Statistical Office of the United Nations, New York.

Sveriges Officiella Statistik, Dödlighets och Livslängdstabeller, 1900-1951, Statistiska Centralbyran, Stockholm.

Sundhedsstyrelsens Medicinalstatistiske Kontor (National Health Service of Denmark) various publications of death lists 1900 to 1953 Dødsårsagerne i Kongeriget Danmark I Kommission Hos. H. Hagerup, København.

Statistisk Årsbok För Finland (1950-1954) (Statistical Yearbook of Finland) The Central Statistical Office, Helsinki.

Death lists of the Netherlands, B1, C1, C2, C3, International list 6th revision for 1953, Unpublished; provided through the kindness of Doctor Van der Brink of the Centraal Bureau voor de Statistiek, Den Haag.

The Registrar General's Decennial Supplement, England and Wales, 1951, Occupational Mortality, Part I, Her Majesty's Stationery Office, London, 1954.

United States Life Tables and Death Lists, 1910 to 1951. U. S. Dept. of Health, Education and Welfare, National Office of Vital Statistics. United States Government Printing Office.