SECTION OF BIOLOGY

DEMOGRAPHIC CONSIDERATION OF THE CANCER PROBLEM*

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Cancer, in its several forms, is a disease associated with age. The other major diseases of adult life also are associated with age, and the trends of each disease toward increased incidence and death rate as age increases are remarkably similar.[1,2,3] Indeed, any major disease may be used to characterize the health of a population, and diseases themselves are related in association (FIGURES 1, 2, and 3). It generally follows from these arguments that the physiologic factors that establish disease propensity are likely related, even though we may not know at this time how directly each are interrelated. Thus a logical beginning of a study of human cancer biology can be made through survey of the general pattern of the appearance of diseases by age and cause. This approach can be termed consideration of aging and disease.[4,5]

Two general assumptions provide a background for interpretation of vital statistics in terms of health:

(1) Health is defined as the counterpart of disease; or health is stated to be inversely proportional to disease; or it may be assumed that, with decay of body function, disease becomes a more likely experience. (Any one or all of the phrases describing this assumption are sufficient to support the arguments that follow. The arguments will go farther and imply that decay of body function is disease, and that decay comes about through disease experience, leading to the theory that disease begets disease in a life-long cycle.)

(2) The death rate of a population by an internal cause must reflect a measure of the functional vigor of the people who die, or we may say that the death rates compared by cause of death and age give a measure of the average health of the population concerned.

Justification of the assumptions for the interpretation of health, disease, and death rate is the fact that increasing ages within a population show progressive likelihood of the event of terminal disease. This is not the operation of a single factor of chance-of-disease-occurrence being present at any moment through life; the chance of disease is increasing when individuals of progressively older ages of life are compared. In fact, the increase in the tendency toward fatal disease is increasing in

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a logarithmic and precisely uniform way. The property of any population to become more susceptible to terminal disease by logarithmic progression of susceptibility is a striking phenomenon of animal biology. Its mathematical truth was first noted by B. Gompertz, who established in 1825 that the dwindling of the numbers of people alive, as life tables progressed to older ages, was the consequence of a uniform logarithmic worsening of the tendency to die with increasing age.[6] The general statement of this relationship is that the older a person becomes, the much more likely he is to die. Probably people of every culture are intuitively aware of the Gompertz force of mortality which, increasing with age, is

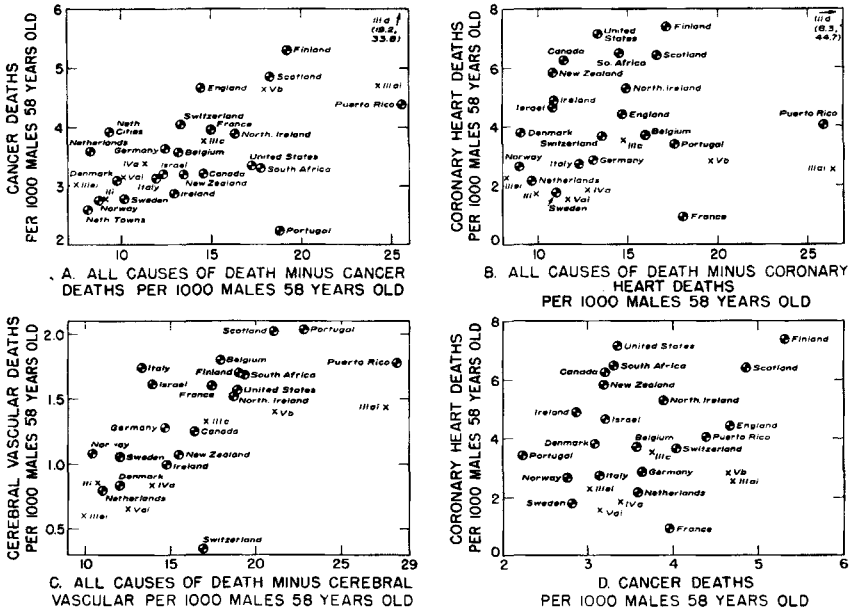

FIGURE 1. Plots of disease-death rates for 22 countries for which deaths have been compiled by age and cause of death in the *Demographic Yearbook* of the United Nations. The interassociations of the major diseases are striking and varied. The reader may select the countries he wishes to contrast. A constructive help to the argument of physiologic age and disease is the comparison afforded among similar populations such as those of Sweden, Netherlands, Norway, and Denmark as one group compared to Finland.

In this figure and those following, age is selected at the 58th year. The values given are for males only. Points on the figure 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 FIGURE 2, the measure of disease in FIGURE 1 is the incidence of disease per 1000 males at age 58 in the *general* population. FIGURE 2 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 process in that disease subgroup.

described in the graphic consideration of the age-specific death rates (FIGURES 4 to 9). During early adult life of all known populations, the rate of death has been considerably below the values that are reached progressively by the increase in the age-specific death tendency during the adult life span. Age-specific death rates differing by a factor of two are found between any group of individuals who are approximately eight years displaced in chronological age. It is a characteristic of all human populations, either male or female, from any country and, possibly, at any calendar time, that this aging-time to double the death rate is eight years' and, possibly, is precisely eight and one-half years' doubling time. No other change of body function is as well established as this precisely determined group measure of physiologic function, health, and bodily decay.

The uniformity of the doubling of the death rate leads to the conclusion that aging, on the average, is taking place at the same rate-by-time in all peoples (and so, too, in all animal populations of the same species)

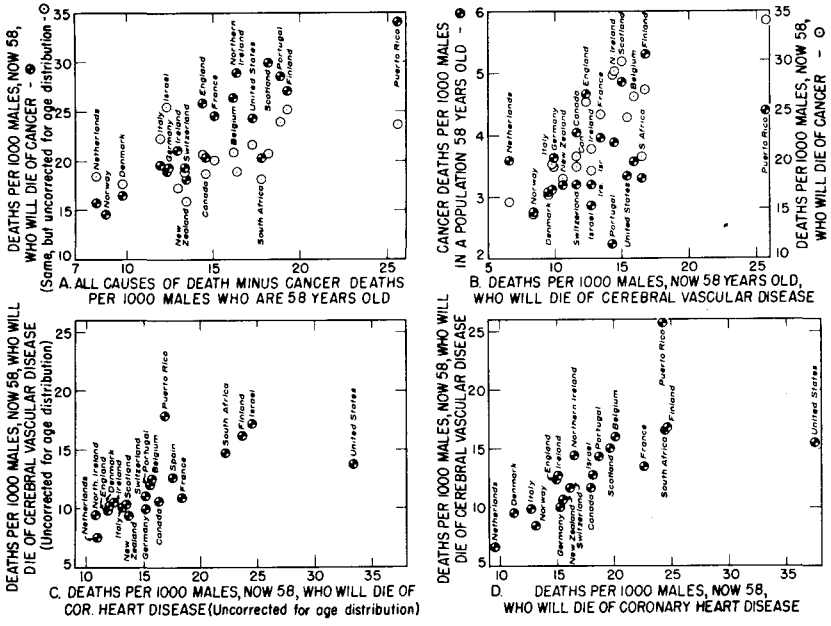

FIGURE 2. The age-specific death rates for subpopulations dying of only one selected cause of death. These are roughly estimated from the broad class-intervals of death listed by age in the *Demographic Yearbook*. These values show the associations in the tendency to develop a disease by those who will 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.

Animal populations differ from human population in that they each have characteristic times for the death rate to double (TABLE 1). This fact suggests that bodily deterioriation accumulates as a consequence of metabolic activity which, in humans, is controlled by similar metabolic "clocks." Loeb and Northrup in 1917[1] and Brody *et al.* in 1923[2] have suggested a physiologic interpretation for the function of death-rate-increase with age. Pearl, in 1927,[7] believed that the general exponential progression of the death-rate function indicated that everyone has just so much vitality, which is used up without replacement until he dies with its exhaustion. More precisely, the interpretation of Loeb, Northrup, and Brody was that, at any age, the rate of loss of vitality (as measured by the tendency to die) is proportional to the amount of the vitality that

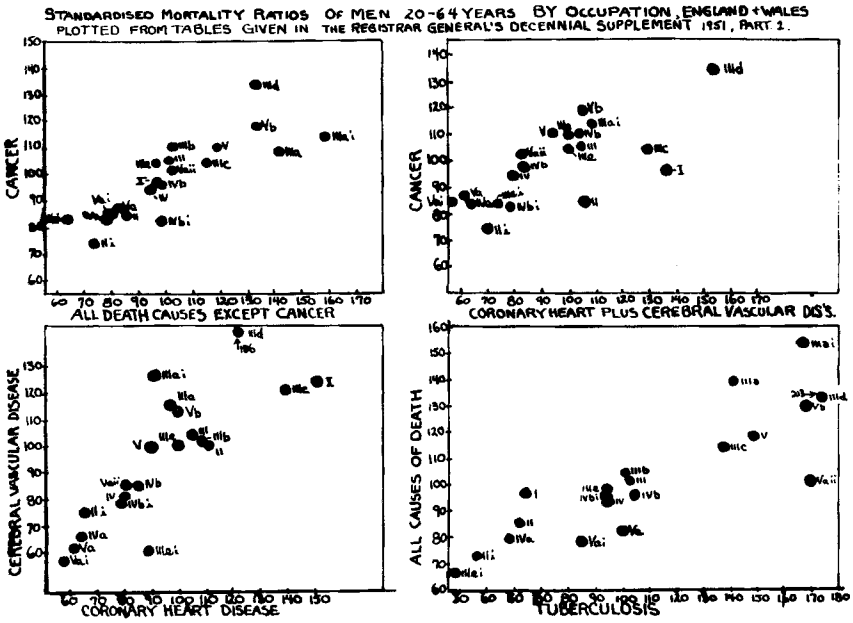

FIGURE 3. The interassociations of major diseases by occupational groups for England and Wales. The incidence values are taken from *The Registrar General's Decennial Supplement, Occupational Mortality (1951) England and Wales.* The 20 groups are: (I) professional, (II) intermediate, (III) skilled, (IV) 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)] coal-mine workers, [Va(i)] building laborers, [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.

$$\text{Standard mortality ratios} = \frac{\text{observed deaths}}{\text{expected deaths}} \times 100.$$

has already been lost. A comparatively inverted reasoning that leads to extension of this interpretation is consideration that the change in the pattern of the death-rate-by-age function may be the consequence of disfunction, which accumulates progressively, and that the average addition of disrepair of the body in an increment of time is proportional to the amount of disrepair that has accumulated in the past.[4,5]

The body is visualized as composed of a great many functional systems (many in terms of kinds and numbers), and that an average measure of vigor of health is inversely proportional to the extent to which func-

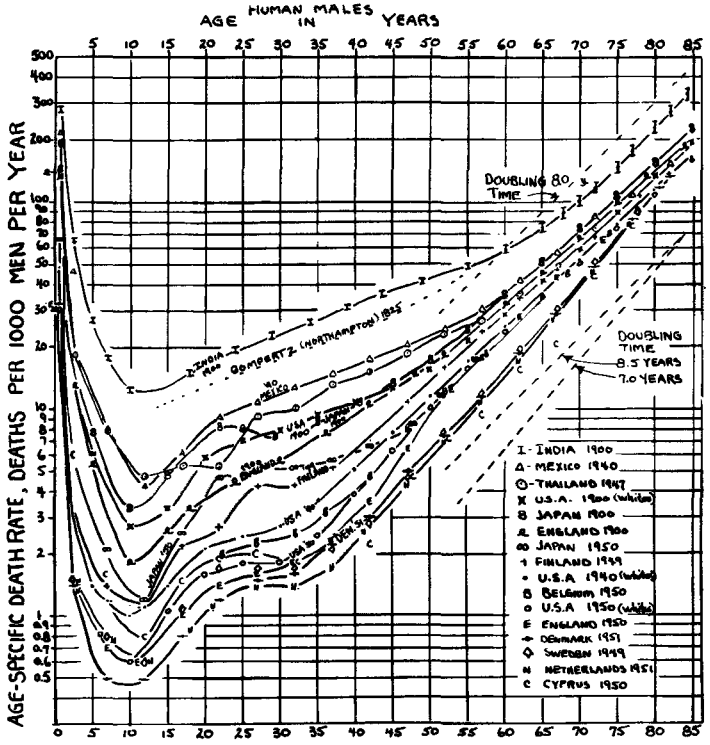

FIGURE 4. The age-specific death rate from all causes of death. Selected countries are given with examples from their immediate past. Note the reduction in disease rate throughout life and particularly in the early part of life. All countries are approaching a physiologic increase of the death rate of 8.5 years 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 rate of expression of disease-deaths at any time is a function of accumulated change 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.

tional units become disfunctionable or poorly repaired. Resistance to a disease episode or likelihood of metabolic disease can be visualized, generally, as being a function proportional to the extent of body disrepair. The increment of increase in disease rate in a population at any age always appears to be proportional to past disease experience, and if

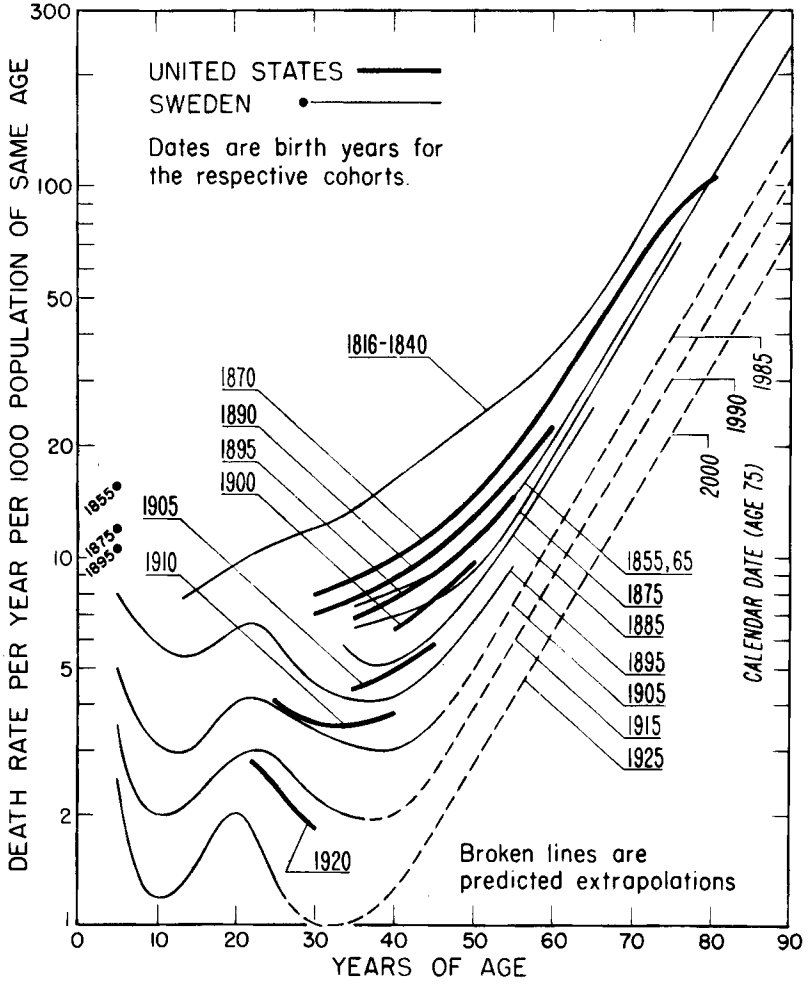

FIGURE 5. The age-specific death rates expressed as population cohorts having the approximate-same birth date. Note the common tendency for the progression of the death rates to have a slope of 8.5 years doubling time on this semilogarithmic plot. The age-specific death rates are shown to be receding 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.

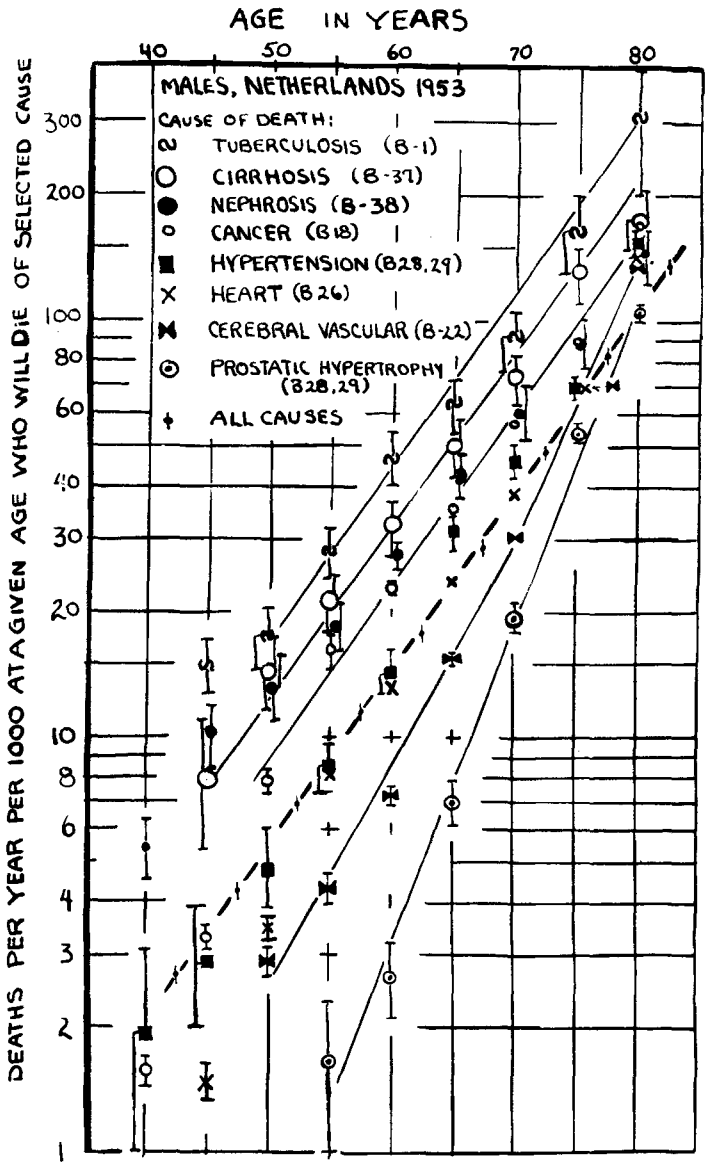

FIGURE 6. Abstract populations of the Netherlands. Each disease group dies only of the disease indicated. The function is an all-cause-of-death-function for a population that dies of only a single cause. The method of calculation is described in the text. The populations dying of tuberculosis, cirrhosis, 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-cause-of-death-function for the Netherlands. This analysis is based upon the 1953 death list of the Netherlands.

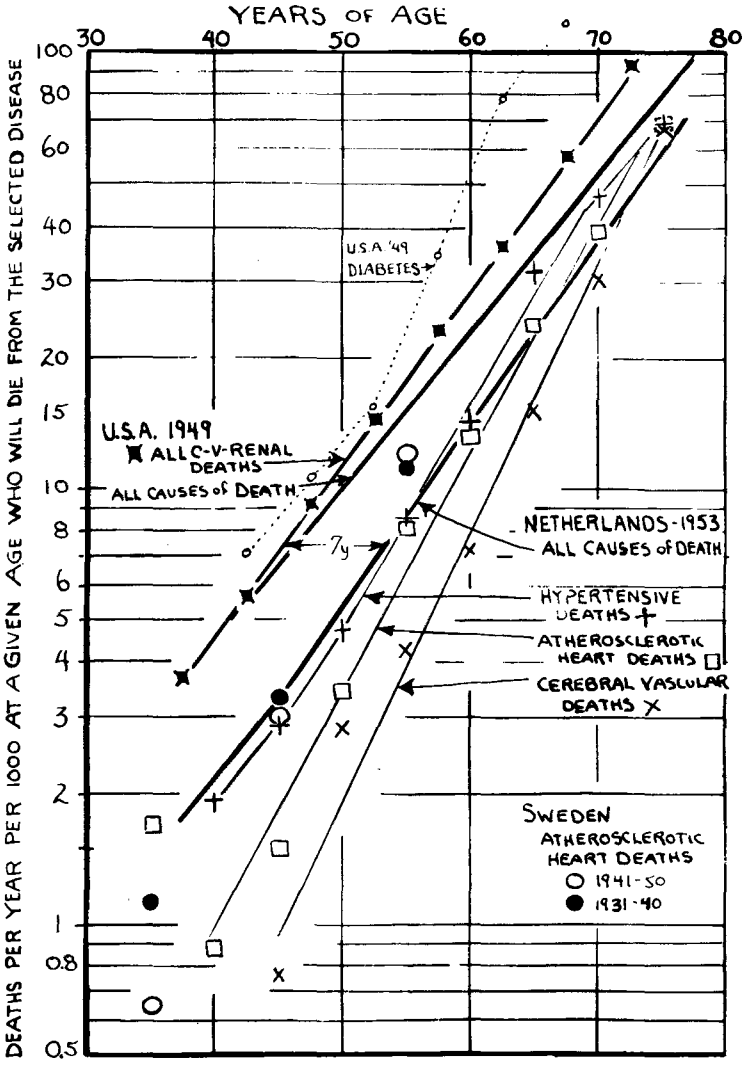

FIGURE 7. Age-specific death rates for all causes of deaths and for abstract subpopulations of the Netherlands and the United States. Physiologic age is markedly different for these two countries; it is clearly indicated by the all-cause-of-death-function. The abstract populations show the same difference in physiologic age and establish beyond doubt that the intensity of development of atherosclerotic disease is postponed by seven years in the Netherlands as 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.

disease is a measure of disrepair, the thought-model of aging suggests that the existence of disrepair or disfunctionable units of the body allows for the generation of further units of disfunction, and that the rate of extension of each such unit of disrepair is at a constant rate—perhaps due to a constant quality of body metabolism to extend disrepair.[4,5] The average *reproduction time* for the average kind of bodily disfunction-unit is then eight and one-half years for human populations.

While the rate of increase in disrepair is apparently the same for all

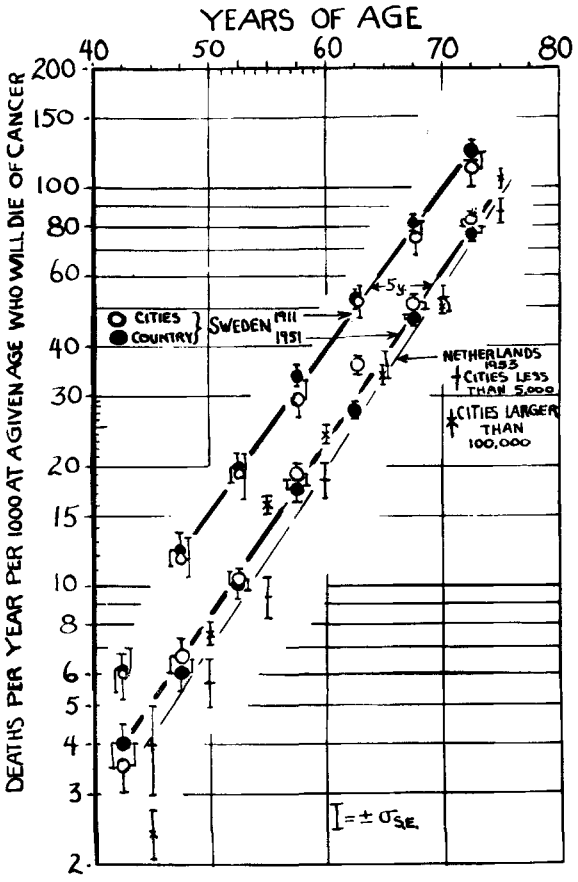

FIGURE 8. The age-specific death rates of abstract subpopulations that will die of cancer. The Netherlands and Sweden are shown by the extremes of the population subgroups of urban and rural ways of life. The cities of Sweden and the Netherlands suggest a slightly higher intensity of carcinogenesis, but only in midlife. Both rural and urban Sweden have changed by four to five 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 2, the text, and H. B. Jones.[5]

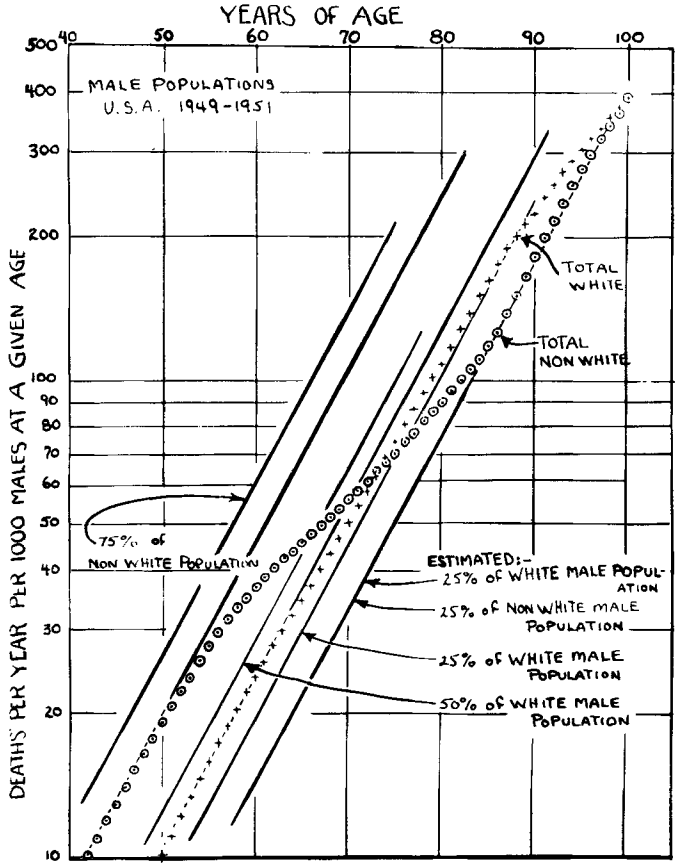

FIGURE 9, showing the inhomogeneity of the population of the United States with respect to incidence of death as a uniformly progressing change. When the death rate is relatively low, the population that supplies the deaths, at any age of low death rate, remains rather constant in internal composition 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 that survives. The United States is possibly more heterogeneous with regard to its subgroups than are some of the other countries shown in FIGURE 2. It is noted particularly that the bending-over of the curve of the population of the United States by cohort, FIGURE 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. Today the most favorably-lived is the average of the entire male population of Sweden, or of the Netherlands, or of Denmark, or of Norway.

TABLE 1

DOUBLING TIMES OF THE PROGRESSION OF THE DEATH RATE FOR THE FLY, THE MOUSE, THE GUINEA PIG, AND MAN

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

human populations, we may examine the facts that, at any age, comparisons between populations indicate that there can be great differences in the death rate from any or all causes. Comparison by incidence of death from the major diseases leads to the same general relative ranking of populations and subpopulations (FIGURES 1 to 4), and the same serial placement of countries by age-specific disease tendency may be made from the all-cause-of-death function. If population records of census, death, and cause of death could be collected upon an absolute basis, identification of great differences in health of populations probably would be established. The problem and methods of establishing an argument of differences in physiologic age and health requires special consideration.[4,5]

Use of vital records shows that the countries of the western world are decreasing their age-specific disease death rate at every age of life, and that this change has been going on progressively throughout this century. A possible explanation for this mechanism is that the association of every disease as a causative factor with every other disease is also changing in the time sequence. In this way, diseases of earlier life are being reduced, including the lowering of infectious and childhood diseases. Individuals now, from childhood on, live in a more favorable climate free of disease. Their general health remains better, and they have fewer diseases at any age in adult life, including the internal disease of adult life such as cancer, heart disease, and hypertension. All populations have not had changes to the same extent with regard to improvement of diseases of early life, and most populations and population subsamples have relatively great differences in disease experiences throughout life. As a consequence of this, and of the fact that every disease is to some extent related to every other disease, one would expect to find a positive interrelationship between the major diseases of adult life. Such positive relationships can be measured directly from disease incidence rates (FIGURES 1, 2, and 3). They can be better estimated from abstract methods of predicting disease tendency in the subgroups that are selected as susceptible to each of the major diseases. (This particular method is independent of most of the errors of population record keeping, which make for such extraordinary differences as near-absence of reported heart disease in France and an equally absurd low rate of cerebral vascular disease reported in Switzerland). Several

methods for measuring disease tendency at a comparative adult age in all countries show that all of the major diseases tend to be associated, and that there is a marked tendency for high cancer incidence or low cancer incidence to be predicted from high or low total adult death rate. Similar measureable relationships exist between any of the so-called internal diseases. These problems are more fully discussed with methods for estimating them in another paper.[5]

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 such diseases as cancer and heart disease 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 result largely from internal diseases rather than infectious diseases.

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 differences, it has been noted, are of a smaller relative range of variation than may usually be observed for arteriosclerotic disease. The following list, giving the range of variation of age by disease tendency, can be used to estimate the extent of variation in age-specific cancer tendency throughout the world today:

DIFFERENCES IN AGE OF 22 COUNTRIES OR SUBPOPULATIONS COMPARED AT AGES HAVING THE SAME DISEASE-DEATH RATE

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

Cancer, like other diseases, is probably related to specific provoking factors, the intensity of which may vary. The above list suggests that provoking factors for cancer are relatively less variant than the provoking factors for vascular disease, but nevertheless cancer varies in its tendency. The general trend estimated for cancer and all of the major diseases is a progressively less intense age-specific incidence as

calendar time progresses. Nevertheless, for lung cancer the story is quite different. Doll (1953) has presented strong evidence that lung cancer is increasing steadily throughout the world and that this increase is associated with the use of cigarettes and tobacco. In this case, a single provoking cause of cancer is on the increase, even though the general health of the populations examined here indicates a progressive improvement and, even though smoking may induce other early disease in smokers, this century's trend is toward a lower age-specific disease rate, including that of cancer.

The abstraction of the cancer deaths to give estimated death rates for those who will die of cancer leads to some interesting findings. 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. (This becomes very reasonable if we can accept either that cancer is not highly curable 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 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 a short time after the appearance of the cancerous state relative to normal life expectancy, 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 for the cancer subpopulations* of Sweden and of the Netherlands are considerably more intense than the age-specific death rates for all causes in the general population. This difference is true at 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 of Sweden or the Netherlands (FIGURES 6, 7, and 8) for, if they were, they should have given a distribution of ages similar to the distribution of average age at death from all causes in the general population. The latter circumstances would have given an abstract age-specific death rate in identical agreement with the all-cause-of-death function for the entire population. It may then be estimated that the population that will die of cancer is a rather special subgroup within the population of Sweden and the Netherlands, and that, possibly, the entire population may not have a basic tendency for cancer to develop, just as the similarly abstracted subpopulations of those who will die of tuberculosis, or cirrhosis, or diabetes always all have much more intense age-specific death rates for those who will die of these diseases than the average death rate of the population from all causes. These subpopulations of very unhealthful people involve limited

*Male; female population not analyzed.

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 (TABLE 2). However, this cancer subpopulation is at nearly the same age-specific death rate as these same cancer groups in Sweden and in the Netherlands (TABLE 2 and FIGURES 6, 7, and 8). This suggests that the subpopulations that die of cancer are far more similar among the three countries than are the outward averages of total disease rates for the entire populations of these countries. Considering the very wide spread of differences that have been noted internally in populations,[5] it seems possible that such cancer subpopulations, among countries of subgroups, may indeed have a number of common disease-determining factors and similar disease-rate tendencies in spite of the possible gross dissimilarities of the parent groups. It is suggestive that a special population is susceptible to cancer and that, in general, it has a higher age-specific death rate than the total populations of Sweden and the Netherlands. Using a compilation of tumor incidence in Sweden for the years 1911 and 1912 prepared by Gunner Nystrom, it is possible to examine the tendency to develop cancer over a period of nearly one half of a 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, of course, are 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, using the abstract age-specific death rate method, which is not sensitive to the average errors of imperfect vital statistic records and of pathologic classifications. The results are listed in TABLE 2 for all tumors, by rural districts, by urban areas, and by carcinoma of the stomach. These results are for the Swedish male, and comparable values are given calculated from the death lists and census for the year 1951. The abstract age-specific death rate from cancer has shifted in intensity over the past 40 years. The rate of development into cancer of those who died of cancer in 1911 was as great as that of the Swedish male today who develops cancer, the latter being five years older. 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 examining further, it is an advantage to select a form of cancer, cancer of the stomach, which may have remained as a similar 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:

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

TABLE 2

COMPARISONS OF MALE DEATH RATES; 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	
Netherlands 1953		1.35	1.71	2.65	4.20	6.95	11.3	17.7	28.2	48.4	82.0	
United States 1949		2.42	3.66	5.55	8.67	13.4	19.7	28.9	43.9	63.0	92.0	
Abstract cancer death rates. Deaths per year per 1000 at given age who will die of cancer.												
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	112.0	124.0	
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	76.2	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	83.0	130.0	
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	78.0	114.0	
Netherlands, 1953												
All	d/1000		1.1	2.0	4.5	10.0	18.5	27.8	45.0	74.0	130.0	
Cities >100,000	d/1000		0.6	1.5	5.6	10.2	19.5	28.5	46.0	81.0	145.0	
Towns< 5,000	d/1000		1.3	2.8	4.0	8.0	12.5	25.0	41.0	66.0	120.0	
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	106.0	228.0		
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	70.6	138.5		

(2) In both 1911 and 1951 there are no significant shifts relative to rural and urban populations of Sweden as to either the incidence death rate from cancer of the stomach or the abstract death rate for those who die of cancer of the stomach. This is important, as over the 40 years there has been a redistribution of the population of Sweden favoring urbanization.

(3) Cancer of the stomach has prominent symptoms that will aid in the diagnosis.

(4) If cancer of the stomach is related to food habits, there are many factors of custom that will have tended to keep these habits somewhat similar over the period of time. It is observed that age-specific comparison of the development rate of cancer of the stomach in 1911 to 1912 and in 1951 shows a marked difference interpreted as a change of physiologic age by 5 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 *incidence* of cancer of the stomach in the Swedish population, for whatever reliability these statistics may have, they are:

Males, aged 45 to 64 $0.92 \pm .03$ deaths per 1000 in 1911 to 1912.
Males, aged 45 to 64 $0.68 \pm .08$ deaths per 1000 in 1953.

The interpretation of stomach-cancer incidence values, in line with the argument that has been presented, is that this single type of cancer has become less prevalent 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 4-to-5 year change in the age-specific physiologic age, so that the Swedish male of these ages is today physiologically 4 to 5 years younger than he would have been had he been at 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 that has also been attributed (in this text) to an increase in the general vigor of the average person. It has been argued that this gain in health has been associated with the general diminution of diseases over the past century.

Demographic Considerations of Populations Already Having Cancer

From the progression of the death rate from all causes, we have seen that the death rate becomes doubled in human populations every eight and one-half years of increase in age, and physiologic argument is presented that such change with age reflects basic metabolic decay of body function. It is not surprising that the age-specific incidence of development of cancer in the general population follows the same mathematical function of increase in incidence intensity with increase in age, approximately doubling every eight and one-half years.[1,2,3,5] In an earlier section it was also explained that the character of the death-rate in-

crease with age can represent fundamental change, leading to development of the cancer state. In spite of the increase of the death rate with age, the death rate for the population at large is relatively low, even in the higher reaches of old age, as compared to the death rates that can be seen in selected groups where selection is based upon individuals already having malignancy. Thus the death rate for populations already having malignancy is in the range of 100 deaths per 1000 individuals per year to rates approaching 2000 deaths per 1000 individuals per year. The average human malignancy, such as carcinoma of the breast, has death rates that approximate 200 to 400 deaths per 1000 per year. Most of these death rates would be seen in the general population only if the population were well over 70 years of age. It can be shown that these death rates both characterize cancer and tend to characterize certain classifications of cancerous disease. It is a remarkable fact that the death rate for all kinds of cancer remains nearly fixed from the moment when cancer is identified, so that the individual having cancer has a constant and characteristically high death rate for the entire duration of his disease. Thus if cancer survival studies are examined in the method of FIGURE 10, a straight-line relationship will be observed between the logarithmic scale of survival and the linear measure of time duration of the disease. Those familiar with the calculus and with such problems as decay of isotopes will immediately be able to recognize the straightness of this line as indicating that the death rate is the same at all times after the establishment of the cancer state. Only mammary cancer groups are shown in FIGURE 10, but the same relationships hold for every cancer described in the following sections of this paper, with the exception of the disease polycythemia vera, which does not show this phenomenon. All of the remaining cancers, then, show a characteristic death rate, and the interpretation of this may be extended further by stating that usual circumstances that lead to worsening or progression of a disease lead to signs of that worsening. If, then, we consider the progression of cancer as attributable mainly to the intergrowth of cancer masses in the body, the death rates in the various cancer groups should become more intensive as time of the duration of the disease increases. This circumstance is never seen in human cancers. The death rate early in the disease is strikingly similar to death rates in the middle course or at the end of the disease, so that the person having cancer, while he has a high death risk, does not decrease his chance of survival by having already lived some time with his disease. There is abundant evidence, however, for a terminal phase of cancer, and the death rate of this phase is in the range of 1000 deaths per 1000 individuals per year.

In contrast to human cancers, transplanted cancers in experimental mice kill the animal with death rates that progressively increase after time of transplantation, so that the death-rate-progression function in cancerous mice is a very satisfactory replica of what is known of the

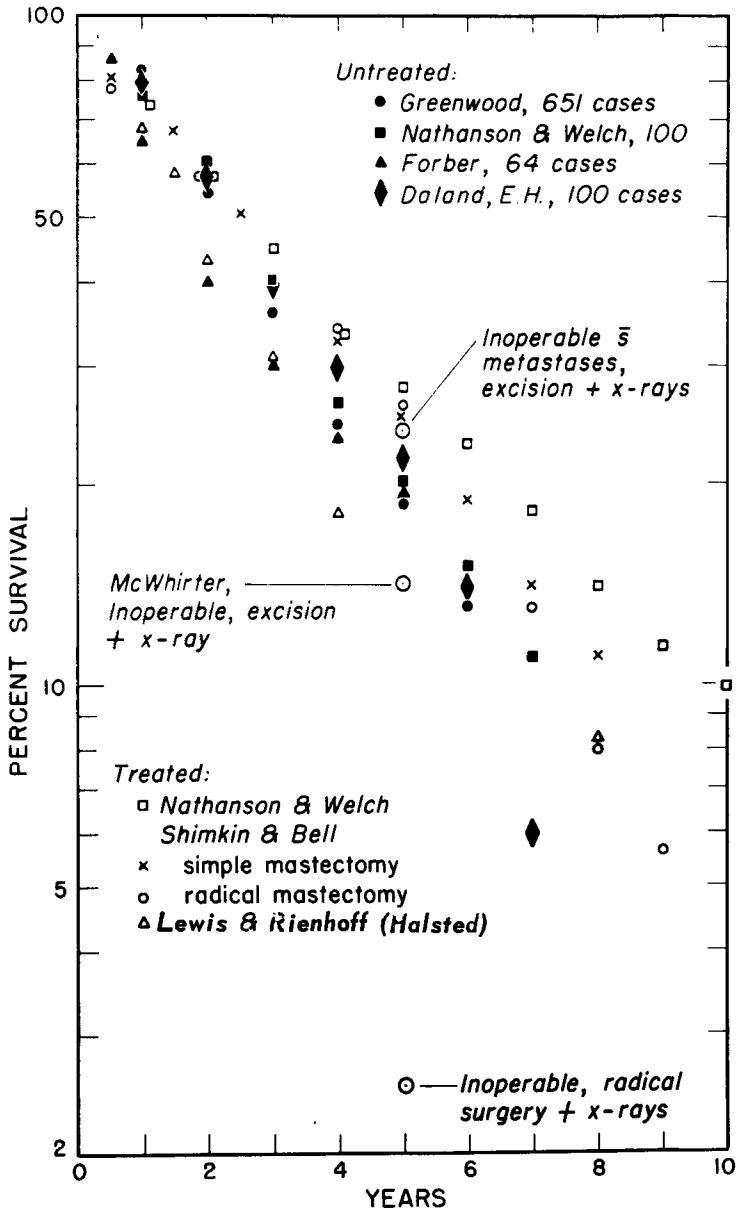

FIGURE 10, showing the percentage of survival of treated and untreated cancer cases followed up to 10 years. The scale of survival is logarithmic. Time is adjusted to read years from treatment and, in the untreated series, years from reported onset, or years from first contact with the physician reporting. All cases fit a straight line having a halftime between 2 to 2.5 years. It may be seen from inspection of the figure that approximately 50 per cent of the patients in all of the series remain at 2 to 2.5 years; 25 per cent remain at 4 to 5 years; and 12.5 per cent remain at 6 to 7.5 years. There is no significant difference in the survival tendency of any of the cases reported on this graph.

increase in the transplanted tumor tissue in the mouse. Death frequently occurs when tumors have grown so that preponderance of the body mass is measurably tumor.

In human cancer, no counterpart of growth of experimental transplants in the mouse is observed, and the argument is advanced for the tentative theory that the causes of death in human cancer have less to do with the extensive growth of cancer than they do with some other explanation of the metabolic state in cancer.

A form of logarithmic analysis such as that presented in FIGURE 10 has been used to summarize a representative selection from basic papers in the literature of cancer survival in the various cancer disease groups studied. These groups are listed in the following tabulation in terms of disease, source, and death rate by logarithmic analysis. Death rate is given in terms of deaths per 1000 individuals per year. The method is sensitive to cancer classifications that have mixed survival rates when the survival rates are different by a factor of 2. The method is also sensitive to detect fractions of the population that have "normal" survival rates or rates of survival that are definitely slower than the death rate given by a factor of 5. The method, in fact, is so sensitive that 5 to 10 per cent of individuals in a cancer population approximating a normal death rate could be detected in a series of follow-ups of 100 cases. It is rare to find individuals in a tumor follow-up classification who comprise even a small group having a normal death rate.

Breast Cancer

Perhaps no form of cancer has received more attention than cases of cancer of the breast, of which there are records of considerable usefulness as early as 1910

Nathanson and *Welch*[8,9,10,11,12] in 1937 summarized statistics of cancer survival in a paper that directly infers a great difference in the survival tendency of treated and untreated cancer cases, with a marked improvement of the survival tendency of those having treatment. Several logical points for statistical control of this series were overlooked. The collection of case material for breast cancer and other cancers reported by Nathanson and Welch was such that time is measured from the onset of cancer. Any case dying before the initiation of treatment became a part of the untreated series. Cases that died during treatment, or closely following treatment, were discarded because of the possible effect of the severity of treatment.

Exponential analysis of this material is not sensitive to these errors, and it can be shown at once in the examination of FIGURE 10 that the death rate of both the untreated cases reported by Nathanson and Welch and the treated cases die at the same rate, namely 280 deaths per 1000 individuals per year for the entire time of the duration of cancer. The

two series are displaced by an error in considering the origin of the comparison as the onset of the disease; and, in the treated series, the population is adjusted to 100 per cent survival at the end of treatment, which gives the treated series, at any year of duration of the disease, a year's "head start" in which no deaths occur. No part of either series suggests a hidden group having a significantly lower death rate than the average for the group.

Daland's[13] untreated group is also shown in FIGURE 10. The survival rate of his untreated group is 300 deaths per 1000 individuals per year. Fractionation of material presented by Nathanson and Welch shows that death rate in cancer is only slightly influenced by age, and that the death rate for cases below 40 in the Nathanson and Welch series is 270 deaths per 1000 individuals per year, whereas, over 40, it is 220 deaths per 1000 individuals per year.

Lewis and *Rienhoff*[14] in a follow-up including the original Halsted series in the tradition of the Halsted treatment of breast cancer may be broken down in two ways:

(1) If it is considered a single homogeneous group of cancers, the death rate for the entire series is 365 deaths per 1000 individuals per year. However, the Halsted, Lewis, and Rienhoff series is so large in numbers that a more precise fractionation of survival tendency may be made. This indicates that of those with metastasis present at the time of treatment, 33 per cent have a death rate of 163 deaths per 1000 per year, and 67 per cent have a death rate of 1000 deaths per 1000 individuals per year.

(2) In the Lewis and Rienhoff group seen initially without evidence of metastasis, 10 per cent of the group appears to have a normal survival rate of less than 20 deaths per 1000 per year. Of this group, 54 per cent have a death rate of 129 deaths per 1000 per year, and 36 per cent have a death rate of 576 deaths per 1000 per year.

A follow-up of a large series of cases treated in England shows 100 per cent dying at 404 deaths per 1000 per year. Greenwood's analysis[15] shows that women from 25 years to 44 years have a 25 per cent higher death rate than those from 45 to 75. These are respectively 480 deaths per 1000 per year and 330 deaths per 1000 per year. The treated cases of Greenwood show that of those having metastasis to lymph nodes, 40 per cent die at a rate of 700 deaths per 1000 per year; 60 per cent die at a rate of 250 deaths per 1000 per year. No low death rate group is present among the cases followed who initially showed lymph-node involvement. Greenwood's grade 1 cases who were without axillary involvement at the time of treatment show a death rate of 32 deaths per 1000 per year for the entire group. This rate is probably not significantly different from the death rate of a normal population that might have been similarly drawn at that time.

TABLE 3

	Type of cell Broder's classification	Number of patients traced	Per cent	Per cent dying at "normal" rate	Per cent dying accelerated rate	Death rate, half time, years	Per cent of total having normal life expectancy
With	I	12	0.3	43	57	3.2	1.72
metastases	II	261	6.5	28	74	2.6	1.90
Average age	III	1288	32.0	9	91	2.6	2.81
51 years	IV	2473	61.2	8	92	1.9	4.92
	Total	4034	100				

% of patients with metastases having life expectancy equal to average population **11.35**

Without	I	423	18.7	100	0	—	16.0
metastases	II	526	23.3	0	100	20.0	12.5
	III	763	33.7	50	50	3.5	17.5
	IV	551	24.3	36	64	3.5	9.0
	Total	2263	100				

% of patients without metastases having life expectancy equal to average population **55.0**

Calculated from Harrington (Mayo Clinic)
Second National Cancer Conference, Vol. I, p. 252

Survival and death rates can be calculated from this follow-up to 20 years for this large series of surgically treated cases. Fractionation of these groups by the exponential method of determining homogeneity of death rate and the death rate is shown above.

Harrington lists his patients by whether metastasis was detectable at operation and the pathology of the cancer by cell type according to Broder's classification. Grades 1 and 2 are borderline and least grades of malignancy. Grades 3 and 4 are those commonly held as malignant in mammary carcinoma and are the most abundantly seen in those cases already showing metastasis at operation. The percentage of cases with metastasis or without metastasis falling into each of Broder's classifications is given. For each of Broder's classifications, either with or without metastasis, the follow-up has been fractioned into the percentage dying identifiably at a rate that would be characteristic of a normal population and a percentage dying at an accelerated rate. Those that die at an accelerated rate have a rate that is characteristically the same as those shown for the treated or untreated cases of mammary carcinoma shown in FIGURE 10; namely, death rates of half-times of 2 to 3 years and death rates from 200 to 300 deaths per 1000 per year.

The numbers having normal life expectancy in the groups studied by Harrington, either with or without metastasis, are listed in the last column as a percentage of the group having normal life expectancy. The sum of this column with metastasis present indicates that of all those seen with metastasis, 11 per cent will have normal life expectancy. Of those seen without metastasis, 55 per cent will have normal life expectancy.

The Harrington study is a strong argument in favor of the contention that cures are possible for treated cancer cases. However, these cures, at the most are 11 per cent of those already showing metastasis, and the tabulation shows that there is a rapid decline of the percentage of cases having normal life ex-

pectancy as Broder's grade of malignancy increases, leaving the proof for this relatively small effect upon the sureness of the pathologic grading and the ability of the Broder's classification alone to establish malignancy in mammary carcinoma.

Cases seen without metastasis also establish a strong argument that cancer may be cured if caught early. However, grade 1 without metastasis uniformly shows normal life expectancy. This also suggests that grade 1 mammary carcinoma, especially without metastasis, is possibly a disease entirely different from the usual mammary carcinoma. Grade 2 without metastasis is very similar to grade 1, uniformly showing a death rate only slightly elevated compared to the normal population. Considering the ranges of differences in physiologic ages within the American population, these individuals are not provably different from the normal population in death rate. Grades 3 and 4 show progressively fewer cases having normal death rate, 50 per cent and 36 per cent respectively, and those that die at an accelerated rate do so at a rate characteristic for malignant mammary carcinoma.

Proof of the curability of cancer in such a series should require a concept of provability of malignancy, and this requires objective tests other than the Broder classification.

The *Small* and *Dutton*[17] series is summarized as follows:

(1) Nonradical treatment, including those who are untreatable, among those less than 50 years of age: 65 per cent have death rates in excess of 1000 deaths per 1000 per year; 35 per cent have death rates of 161 per 1000 per year. Among 50- to 70-year-old females, 62 per cent have a rapid death rate exceeding 1000 deaths per 1000 per year; 38 per cent have a death rate of 173 per 1000 per year. In the group over 70 years of age, 28 per cent exceed in death rate 1000 deaths per 1000 per year; 72 per cent have a death rate of 230 deaths per year.

(2) Radical mastectomy in women less than 40 years of age: 100 per cent have death rates of 165 per 1000 per year. In 41- to 50-year-old females, 100 per cent have a death rate of 115 deaths per 1000 per year. In 51- to 60-year-old females, 100 per cent have a death rate of 133 deaths per 1000 per year. In 70-year-old females, 100 per cent have a death rate of 145 deaths per 1000 per year. The follow-up of this material extends to 20 years; and while it does not show that there is a significant group within any of the treated cases who have death rates low enough to be within the "normal" range, the death rates for this entire series include individuals who would be in the normal range of death rate had they been in their 80th to 90th year of age. It is a tempting analogy to draw the comparison between the death rate of groups from mammary cancer with the death rates of the upper ages of the life span. They are indeed of similar intensities, and relatively little difference is seen in the death rate of the case of mammary carcinoma regardless of age.

Harrington[18] of the Mayo Clinic, Rochester, Minn., in an extraordinarily well-kept follow-up, accounts for 4,034 patients traced who originally were treated when metastasis was already present. Altogether, 2,263 cases in his series were treated without detectable metastasis at the time of treatment. Each of these two groups are broken down into pathologic grades by Broder cell-type classification. The four groups of the

Harrington follow-up have been reanalyzed by exponential analysis. The results are presented in TABLE 3. In grades 3 and 4 with metastasis, 91 and 92 per cent respectively of these populations are dying at death rates of 255 and 363 deaths per 1000 per year respectively. The low death rate groups are largely seen in Broder's grades 1 and 2, where 43 per cent and 28 per cent are individuals having "normal" death rates. For those without metastasis, grade 1 without metastasis uniformly shows a normal death rate. Grade 2 without metastasis uniformly shows a slightly higher than average normal death rate, 35 deaths per 1000 per year. This is not the death rate commonly observed in cancer populations. Grade 3 and grade 4 without metastasis show 50 per cent and 64 per cent having death rates of 200 deaths per 1000 per year, and the remaining 50 per cent and 36 per cent have normal death rates. The death rates of populations of mammary cancer where the grade of malignancy is established are exceedingly high compared to the normal population. The low death rates observed in the above groups are associated with borderline grades of malignancy. It is also possible that those cases caught in grades 1 or 2, or those in general caught without metastasis, are those caught early in the course of disease and hence "cured." Unfortunately the background of material which, in other series, has comprised a control population, does not exist for these recent series which have led the investigators involved to regard these forms of cancer as of established malignancy. It is equally possible to say that these may be different kinds of cancers with different prognoses.

Miller and *Pendergrass.*[19] With regard to earliness of treatment and contrast to size of tumor, Miller and Pendergrass have been able to show that survival at the fifth year is greatest among those who had smaller tumors at the time of initial treatment in addition to the good prognostic sign of lack of lymph node involvement. In their series of cases reaching surgery, where the tumor size was less than 50 mm., 247/524 cases, or 47 per cent survived for five years, but of the tumors under 50 mm. that were also under two weeks in duration of the disease, 42 survived out of 66, or 64 per cent. The difference, which is only probably significant, bears out the idea that smallness in size, as a measure of a slowly progressing disease, is associated with favorable prognosis. This would be an argument for early detection.

Shimkin et al.,[20,21] in one of the most critically constructed examinations of survival in mammary cancer, have followed two series. Series 1 were all cases who had previously been treated for mammary cancer and in whom mammary cancer had recurred. These cases were divided into three groups: 147 that had radical mastectomy originally; 86 that had simple mastectomy initially; and 28 that had simple mastectomy originally and were reoperated upon by radical operation and subsequently followed. The survival populations in the Shimkin series are plotted in FIGURE 10. In both the group that originally had simple mastectomy and

the group that had radical mastectomy, survival rate is the same, being 276 deaths per 1000 per year in both groups. In this case an analytical argument can be constructed to the effect that, for those who subsequently have recurrence of their mammary disease, the death rate is the same whether they had radical operation or a simple form of mastectomy. The smaller series of 28 cases in the Shimkin analysis appears to have a more favorable death rate, but examination shows that this group is constructed in terms of time from initial treatment. In this case, retreatment has been initiated; and when this group is recalculated so that death rate is calculable from the time of retreatment, the treated recurrence group shows no significant difference from the death rate of the other two recurrence groups. Shimkin's series 2 are those known initially to have had radical operation and to have died of or with breast cancer. Of these, 75 cases were in stage 1 at initial operation, and these have a death rate of 280 deaths per 1000 per year. Altogether, 157 cases are at stage 2, and the follow-up death rate is 395 deaths per 1000 per year. A total of 140 cases at stage 3 at initial operation had a death rate of 460 deaths per 1000 per year. The Shimkin analysis presents a totally uniform and elevated death rate for those with persistent or recurring mammary cancer.

Nohrman,[22] in a study of 1,042 cases in which 294 were operated at stage 1 without evidence of metastasis, found that 47 per cent had death rates similar to normal rates, and that 53 per cent had death rates of 131 per 1000 per year. Altogether, 473 cases were operated at stage 2, at which time there was microscopic evidence of metastasis. Of these cases, 10 per cent in the 10-year follow-up suggest a normal death rate, but the follow-up is not sufficiently complete to be certain. Ninety per cent of the cases are dying at 230 deaths per 1000 per year. Two hundred cases were originally observed with generalized advanced metastasis and were classed inoperable. The death rate of this group is 1,150 deaths per 1000 per year, and this death rate is probably characteristic of patients in the terminal stage of illness.

Nyström[23] lists untreated cases as well as treated cases in a population of Sweden in 1911, 1912, and 1913. The untreated group was set aside for the same reason that excluded the treated groups in other series. These cases comprised the individuals who refused operation or who had already advanced to an inoperable state. It is remarkable that the death rate in this group is still 60 per cent of 330 deaths per 1000 per year; and 40 per cent of 190 deaths per 1000 per year as analyzed by logarithmic means. In this case a further refinement of analysis may be made, for the total pool of patient material is recorded. Moreover, the numbers available to be treated or left untreated are tabulated, as well as the duration of time from initial symptoms to treatment and from treatment to death, or, in the untreated group, from onset to professional contact to death. This closed group shows that the longer the cancer

patient lives, the more it becomes likely that he will be seen in medical consultation, and that, the longer he lives, the more likely it will be that he will receive medical treatment. Those that are left untreated are those that have become untreatable. In consequence of a peculiar sampling of patient material as time from the onset of cancer progresses, there is more and more likelihood that the patient will become a member of the treated group, and less and less likelihood that he will remain in the untreated group. As a consequence of this phenomenon, the distribution of durations of life among untreated patients is not characteristic of what might have been seen if the cancer patients had been left untreated. In most methods of constructing death rates for cancer populations, the untreated cases are considered an independent sample; but if the untreated cases are corrected for the shrinkage of the membership as a result of cases removed by treatment, it is possible to make a guess concerning the natural death rate of cancer cases. When the Nyström series is calculated in terms of deaths per death risk, it appears that the death rate of the untreated mammary carcinomas in terms of deaths per unit of the population untreated at any time may be as low as 88 deaths per 1000 per year. This rate is constant for any period of duration of mammary cancer. This raises the crucial question concerning treatment of breast cancer and, indeed, of all other forms of cancer treatment, for in all the history of medical research, there exists no control series for cancer treatment. It is obviously possible that the high death rates reported in "untreated" series of Greenwood,[15] Nathanson and Welch,[8,9,10,11,12] Daland,[13] and others have exactly the same biasing factors foreshortening the natural distribution of duration of disease in the untreated groups by taking off those who live long enough to be treated. It is a reasonable possibility that the natural duration of cancer in patients at large and in those who are in terminal state is considerably greater than is now supposed, and that these cases may, indeed, have a longer life expectancy than when they undergo the treatment by surgery and treatment by radiation.

In summarizing population groups known to be afflicted by mammary cancer, all follow-up groups show uniformly high death rates when the grade of cancer is of established malignancy. Favorable survival percentages are a function of various admixtures of bordering grades of pathologic types for which there is no provable concept that treatment has altered the course of the disease. It is not possible to make a certain evaluation of the fact that cancer may be arrested if "caught early." If early treatment leads to cure, series of cancers reported are already far past the point of early cure, or the populations are metabolically characterized by a high death rate.

Cancer of the Bladder

Whitmore.[24] Twenty per cent of cases having a simple total cystectomy

have a normal death rate, while 80 per cent have a death rate of 770 per 1000 per year. Of those having radical cystectomy, 100 per cent have a death rate of 770 per 1000 per year. No criterion of cancer is established in the 20 per cent having normal death rate.

Cancer of the Cervix

Lynch.[20] Five-year survival of 55 per cent.

Nathanson and *Welch.*[8,9,10,11,12] Treated cases, 55 per cent dying at 230 deaths per 1000 per year; 45 per cent at 630 deaths per 1000 per year. Untreated cases, 1000 deaths per 1000 per year. Because of the method of selection of untreated cases, the death rate in the untreated group may really be no greater than in the treated group.

Greenwood.[15] Among untreated cases, 35 per cent had a rate of 563 deaths per 1000 per year, and 65 per cent a rate of 1600 deaths per 1000 per year, based upon 1,749 cases.

Kottmeier.[26] In 5,569 cases in Sweden, adequately large samples followed from 1915 to 1943 show that approximately 16 per cent in 1915 had a death rate similar to that of normal women. This percentage increases progressively, being 26 per cent of the normal rate in 1930 and 44 per cent of the normal rate in 1943. At no period of time is there any abrupt change in the fraction having a normal death rate in the treated cases. The Nyström[23] tabulation for Sweden for the years 1911, 1912, and 1913 shows a uniformly high death rate for all cases, being greater than 600 deaths per 1000 treated or untreated. In the Kottmeier series, the majority of the cases have accelerated death rates that remain unchanged every year, half being 530 deaths per 1000 per year and approximately half greater than 1000 deaths per 1000 per year. It is not possible to derive a criterion of initial malignancy in the sizeable fraction that has a normal death rate in the Kottmeier series. These are either cases of carcinoma of the cervix that were cured, or are cases with a milder type of disease than is usually reported. The transition has occurred gradually. Hopefully, but not probably, they represent a cancer cure.

Fibrosarcoma

Nathanson and *Welch.*[8,9,10,11,12] One hundred per cent death rates, 191 deaths per 1000 per year.

Cancer of the Esophagus

Greenwood.[11] One hundred per cent death rates, 1100 deaths per 1000 per year.

Nathanson and *Welch.*[8,9,10,11,12] One hundred per cent, 960 deaths per 1000 per year—all categories of treatment; 100 per cent, 960 deaths per 1000 per year—untreated. The apparent reference to improvement with treatment in the Nathanson-Welch paper is due to the different time scale for the treated and untreated series explained earlier.

Lip Cancer

Nathanson and *Welch.*[8, 9, 10, 11, 12]

Lower lip, treated,	100%,	141	deaths per 1000 per year.
Upper lip	65%,	87	" " " " "
	35%,	990	" " " " "
Untreated cancer of the lip	100%,	725	" " " " "

Cancer of the Tongue

Nathanson and *Welch.*[8, 9, 10, 11, 12]

	40%,	278	deaths per 1000 per year.
	60%,	1700	" " " " "

Cancer of the Antrum[8, 9, 10, 11, 12]

	41%,	221	deaths per 1000 per year.
	59%,	1400	" " " " "

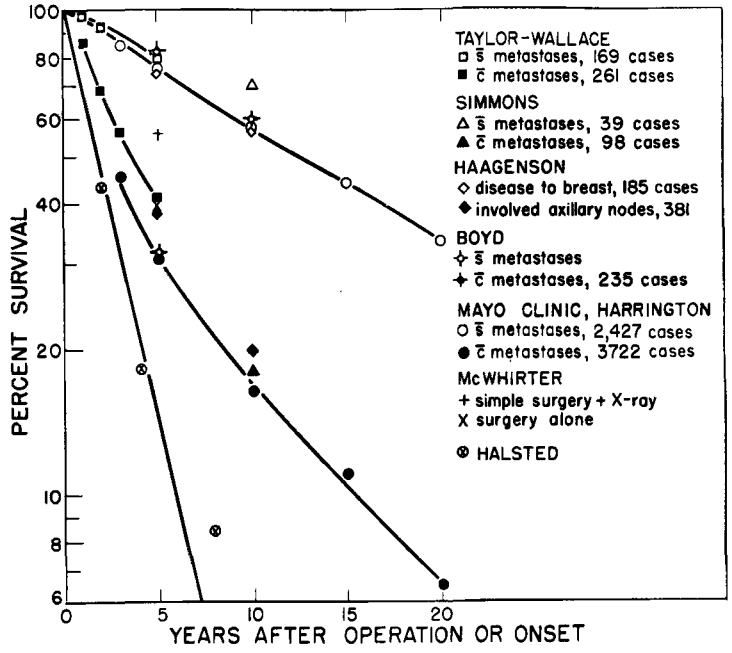

FIGURE 11, showing the survival of treated cases of mammary carcinoma considered as a sample of the series reported by cases having no detectable metastasis at initial treatment and those with metastasis at initial treatment. Throughout the literature of mammary carcinoma survival, five-year survivals in excess of 40 per cent include those cases seen at initial treatment without metastasis. The majority of cases treated with metastasis follow closely to the line of Halsted (see FIGURE 10). A special consideration of the Harrington cases is made in TABLE 3.

Cancer of the Larynx[8,9,10,11,12]

100%, 580 deaths per 1000 per year.

Leukemia, Hodgkin's Disease, Lymphoma

Lawrence.[28] Chronic lymphatic leukemia, 100%, 238 deaths per 1000 per year.
Chronic myelogenous leukemia, 100%, 510 " " " " "

Nathanson and *Welch.*[8,9,10,11,12]
Lymphatic leukemia, 100%, 340 deaths per 1000 per year.
Myelogenous " 100%, 340 " " " " "

Shimkin.[21] Hodgkin's Disease.
Males, 100%, 347 deaths per 1000 per year.
Females, 100%, 299 " " " " "
The difference between males and females is significantly established.

Nathanson and *Welch.*[8,9,10,11,12]
Lymphoma, 100%, 300 deaths per 1000 per year.
Hodgkin's Disease 100%, 345 " " " " "

Melanoma

Pack and *Livingston.*[29] Males, 100%, 364 deaths per 1000 per year.
Females, 100%, 250 " " " " "

Allen and *Spitz.*[30] Males, 100%, 470 deaths per 1000 per year.
Females, 100%, 270 " " " " "

Nathanson and *Welch.*[8,9,10,11,12] 100%, 230 deaths per 1000 per year.

Osteogenic Sarcoma

Nathanson and *Welch.*[8,9,10,11,12] 100%, 375 deaths per 1000 per year.

Prostatic Carcinoma

Colston.[31] 100%, 192 deaths per 1000 per year, with radical operation.
100%, 300 " " " " " , with orchiectomy.
Note: Small series not statistically different.

Thompson.[32] Seven years' follow-up, 100%, 410 deaths per 1000 per year, orchiectomy treatment.

Bumpers.[33] Seven years' follow-up with 1000 cases, radium, 100%, 320 deaths per 1000 per year.
Untreated cases, 100%, 500 deaths per 1000 per year.

Nathanson and *Welch.*[8,9,10,11,12]
Treated, 100%, 530 deaths per 1000 per year.
Untreated, 100%, 700 " " " " "

Nesbit and *Baum*.[34] With orchiectomy of those who did not have metastasis at time of treatment, 100 per cent, 240 deaths per 1000 per year. Those with metastasis having orchiectomy, 315 deaths per 1000 per year.

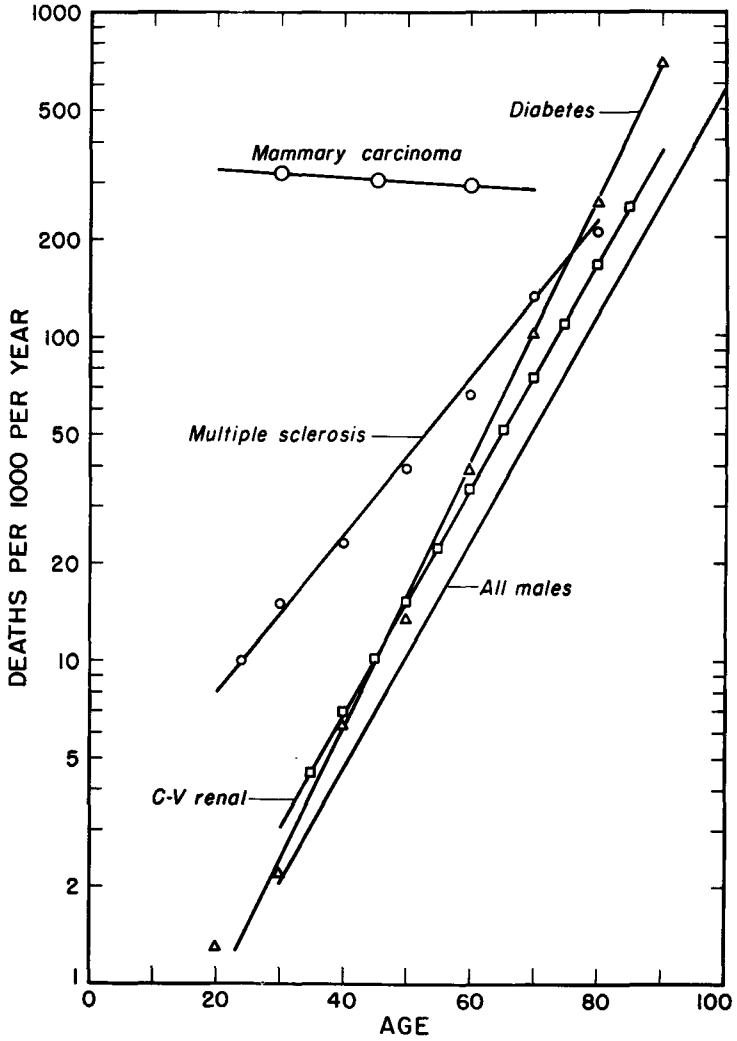

FIGURE 12, showing the survival of cases treated radiologically from the British Empire Cancer Campaign, according to stage of progression of the disease at time of initial treatment. The slope of the survival populations is somewhat steeper, indicating a slightly more rapid death rate in those who are initially seen at the advanced stage 3, compared to the earliest stage 1. There is also a slight difference between cases reported from Great Britain and groups in the United States, the British populations tending to have a slightly longer surviving time. The reason for this is not known, but it can be expected to lie within the populations concerned as much as within the method of treatment.

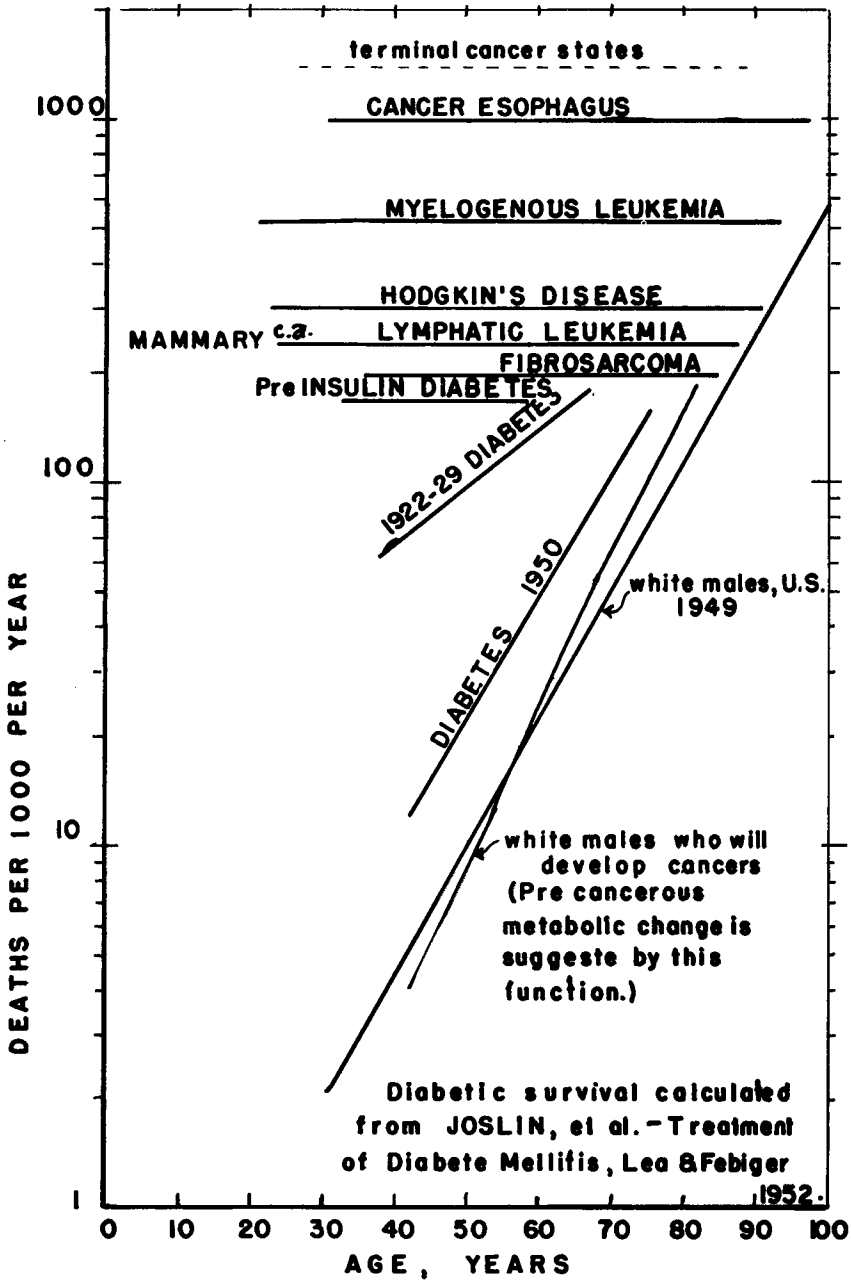

FIGURE 13, showing survival of cancer populations in deaths per 1000 per year, as compared to survival of other populations of identified disease groups and other populations at large.

Diethylstilbesterol, 100 per cent of those without metastasis at time of treatment have 165 deaths per 1000 per year. Diethylstilbesterol, those with metastasis, 100 per cent, 570 deaths per 1000 per year.

Diethylstilbesterol plus orchiectomy—for those initially without metastasis, 255 deaths per 1000 per year; those with metastasis, 300 deaths per 1000 per year.

The untreated group initially without metastasis is 100 per cent, 510 deaths per 1000 per year; and those with metastasis, 620 deaths per 1000 per year.

Rectal Cancer

Pack and *Livingston.*[29] Surgery or surgery plus X rays, 1000 deaths per 1000 per year. Untreated, 990 deaths per 1000 per year.

Nathanson and *Welch.*[8,9,10,11,12]

Treated, 100%, 530 deaths per 1000 per year.
Untreated, 100%, 1000 " " " " "

Lee.[35] 100%, 450 deaths per 1000 per year. No difference in death rate from groups age 45 to age 70.

Greenwood.[15] Untreated, 46%, 577 deaths per 1000 per year.
54%, 1600 " " " " "

Lockhart-Mummery.[36] 100%, 400 deaths per 1000 per year. Note: Lockhart-Mummery dropped out of the series deaths other than cancer in deriving his figures on mortality. The above death rate is corrected on the basis that death from intercurrent disease is at a rate as high as death from cancer in cancer of the rectum. The corrected death rate is twice as high as would be obtained directly from Lockhart-Mummery's paper.

Cancer of the Vulva

Nathanson and *Welch.*[8,9,10,11,12] 100%, 240 deaths per 1000 per year.

Cancer of the Vagina

Nathanson and *Welch.*[8,9,10,11,12] 45%, 198 deaths per 1000 per year.
55%, 867 " " " " "

Carcinoma of the Stomach

Walters, Gray and *Priestley.*[37] Carcinoma of the stomach given by Broder's
Grade 1, 100%, 31 deaths per 1000 per year, treated
Grade 2, 100%, 108 " " " " " "
Grade 3, 100%, 238 " " " " " "
Grade 4, 100%, 290 " " " " " "

All cases with metastasis at the time of treatment, 100 per cent, 345 deaths per 1000 per year. Note: This series, of low Broder's

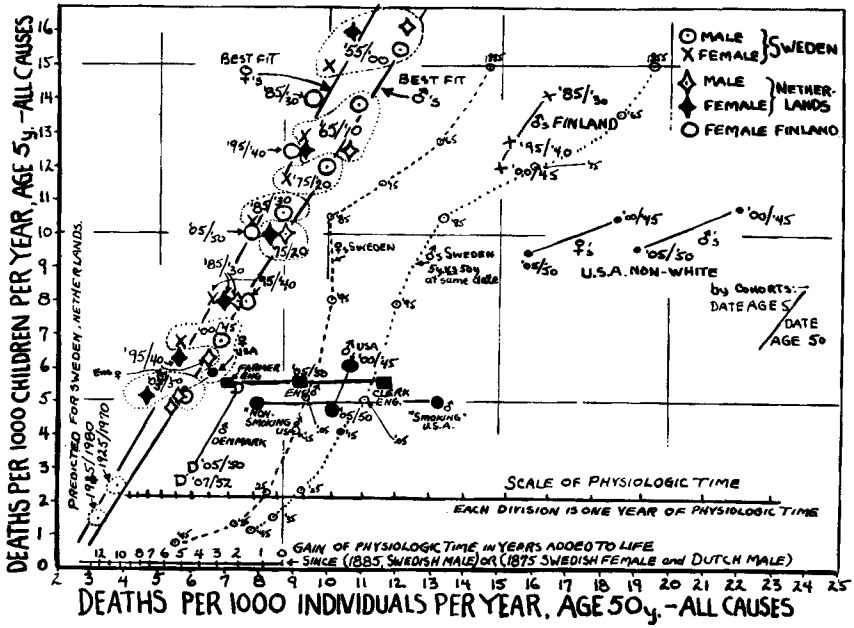

FIGURE 14, showing factors of health throughout life and childhood health. The patterns of death rate intensities of populations appear to be established early in life. Death rates of all ages have been diminishing steadily since the early nineteenth century. Death rates at 5 years and at 50 years are 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 woman in Finland is at the same position she would be 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 are, therefore, 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 on the basis of the childhood disease experiences also, were they known.

grades of pathologic type, is associated with death rates much more like the normal population.

Greenwood.[15] Untreated, 100%, 890 deaths per 1000 per year.

Cancer of the Thyroid

Lahey.[38]*	Papillary adenosarcoma	43	deaths per 1000 per year.
	Adenoma	69	" " " " "
	Malignant papillary carcinoma	70	" " " " "
	Cystadenoma	62	" " " " "
	Fibrosarcoma	223	" " " " "
	Alveolar adenosarcoma	256	" " " " "
	Small cell carcinoma	330	" " " " "
	Giant cell carcinoma	360	" " " " "

Discussion

With the few exceptions noted, all of the groups of cancer types comprise elevation of the death rate as contrasted with death rates in the population at large. Death rate of groups with cancer maintain the same death rate throughout the disease, and the death rate does not advance with duration of the disease. This finding is also apparent in the calculations of Greenwood,[15] who showed that the death rate of his untreated cases of cancer was essentially the same at every interval after establishment of cancer. This fact can lead to some speculations as to the nature of the biology of human cancer. First, it can be inferred that the events taking place in the precancerous period that are responsible for the evolution of the cancer state show a "growth" phenomenon, and that the likelihood of the establishment of a cancer condition is growing by a doubling of the probability that it may occur every eight and one-half years. Having occurred, every kind of human cancer does not worsen the probability of terminal illness of the disease as the disease progresses, all forms having a fixed and high death rate. This suggests that, following the establishment of the cancer state, some other event occurs, probably definable in metabolic terms, and that this final event is the one that causes the terminal illness. This final event is happening at any time, *at random*. Part of the random nature of such events could be explained on the basis of scattered metastases randomly encroaching upon body function. However, only a fraction of cancer follow-up suggests that death is due to recurrence of the cancer in an advanced state. Cancer populations are also characterized by a high rate of death from intercurrent disease. The high rate of death from intercurrent disease is equally as great as the rate of death from cancer itself. While it is not possible to establish a general metabolic basis of cancer as a disease, current evidence certainly suggests this as one of the possibilities. A

*Estimated from five-year survival only.

reason why a half century of search for cures of cancer has been meager in expected findings may be that the population that shows cancer may be already aged from the standpoint of intact metabolic function, so that cancer is only one of the manifestations that occurs in this diseased population. The evidence for cancer cure lies in a few special studies where it is not possible to defend, through biological controls, a differentiation between mild diseases that are slow-growing or nonmalignant and between small growths that are malignant but caught early.

Early evidence for the responsiveness of cancer to treatment is based on untreated cases that comprised a sort of control. For the most part, it has been shown that crude analysis of the populations involved by the exponential method of establishing the death rate gives a death rate largely identical and undistinguishable from the death rate of the treated series of cancer. It has been pointed out that a larger error existed in the Nathanson and Welch review of cancer treatment in that treated cases were displaced in time and gave rise to an apparent constant improvement in survival compared to the untreated cases. The Nathanson-Welch review of treated and untreated cancers of all kinds in re-evaluation shows that improvement obtained in the cases of treated cancer vanishes when the error is corrected.

A much more serious dilemma in the cancer-treatment problem arises in consideration of the fact that all of the so-called controls for such cancer series as do exist are controls in which the untreated series competes for cases with the treated series, so that the cases of longer duration tend to be put into the treated series. No certain mathematical means can eliminate these ancient errors. It has been suggested that the untreated cases are perhaps longer-lived than the treated cases, and the evidence is strong enough to warrant full attention to this part of the cancer problem, for not only is there complete uncertainty of the efficacy of cancer treatment today, but there is also the possibility that survival tendency is less with treatment. It is most likely that, in terms of life expectancy, the chance of survival is no better with than without treatment, and there is the possibility that treatment may make the survival time of cancer cases less.

In this entire survey of death rate of cancer groups with or without treatment, the criterion of death rate is the only one that has been used. Nothing written here has concerned the place of devices of cancer therapy in relief of pain and the removal of mechanical hindrances. Furthermore, it is quite obvious that cancer growths are frequently obstructive and that, unless the tissue mass is reduced, life itself may terminate abruptly. Such circumstances cannot be evaluated in cancer statistics of survival taken in a broad sense.

In the first section of this paper, an argument was presented for a relativistic basis of disease aging and internal disease. Cancer tendency is shown to be associated with prior disease experience in the population

of the world. It is also associated with a criterion of healthfulness in that poor health marked by high death rate from general causes is associated with high cancer rate. The sum of factors that have made for tendency of disease expressions of all kinds has been dropping steadily throughout the past century, and, associated with a decline of disease in general, age-specific incidence of general cancer appears to be on the decline by age-specific comparisons of individuals. The populations within a country that die of cancer appear to have a more characteristic distribution of ages than do the populations from which they are derived. This suggests that rather characteristic circumstances lead to cancer tendency and that cancer is perhaps not an average disease for the whole population. There is hope that identification of carcinogenic factors might lead to an eradication of cancer on a prophylactic basis. Decrease in age-specific death rate for the internal diseases and for cancer is occurring at such a marked rate that the future incidence of cancer may be surprisingly low when children who are growing up today become adults in the next decade. The strong association between childhood death rate as a measure of disease experience and adult death rate predicts that cancer will continue to diminish over the next several generations since childhood disease rates have dropped to very encouraging low levels. This may be a measure of improved general health, and the childhood disease experience can be expected to diminish further.

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