A STATISTICAL STUDY OF CANCER AMONG DIABETICS

PAUL H. JACOBSON[1]

FROM a review of the literature there are indications of a positive association between cancer and diabetes mellitus (1–7), though the evidence is open to statistical objection. It is hoped that this paper will throw some additional light on the subject, since from the statistical data presented herein cancer appears to be associated with diabetes.

CLINICAL DATA

In recent years two rather comprehensive reports based on clinical data have been published in this country. A 1934 report by Marble (3) considered the problem primarily from the point of view of diabetes while a 1944 report by Ellinger and Landsman (5) emphasized the oncological aspect. The two reports are in agreement on the fact, as stated by Marble, that "one would seem to be dealing in general with a group of diabetic patients who later developed cancer rather than with a group of patients with malignant disease who developed diabetes." In view of the relative durations of the two conditions, it is reasonable to accept this opinion. The problem, therefore, is

[1] Vital Statistics Analyst, Statistical Bureau, Metropolitan Life Insurance Company.

The work on this study was started while the author was Statistician, New York City Department of Health and Senior Assistant Sanitarian (R) USPHS, detailed to the Medical Examination Program, War Shipping Administration.

Acknowledgments are made to Mr. Louis Weiner, Chief Statistician and Mrs. Katherine Arth, New York City Department of Health for assistance in tabulating the special mortality data for New York City.

The statistics from the National Health Survey were tabulated and analyzed with the assistance and cooperation of Dr. Selwyn D. Collins, Head Statistician, Division of Public Health Methods during a temporary assignment, for which the author is indebted to Asst. Surgeon General Justin K. Fuller. Acknowledgments are also made to Miss Daisy Segal, Ralph A. Davin, and Miss Helen Aldrich for assistance in collating and tabulating these data.

The author is also grateful for helpful suggestions and criticism to Dr. Collins, to Dr. Louis I. Dublin, Second Vice-President and Statistician and Herbert H. Marks, Manager, Insurance Medical Statistics, both of the Metropolitan Life Insurance Company, to Dr. Friedrich P. Ellinger, Research Associate Director, Department of Radiology, Long Island College of Medicine, to Dr. Morton L. Levin, Director of Cancer Control, New York State Department of Health, and to Dr. Alexander Marble, Boston, Massachusetts.

basically one of ascertaining whether cancer occurs more frequently than expected among diabetics.

In the series of diabetics reported on by Ellinger and Landsman, 3.04 per cent were found to have cancer. This is not greatly different from the findings (2.56 per cent) for the group of cases reported on by Marble. On the basis of fewer cases, other authors have reported cancer to be associated with one to nine per cent of the diabetics covered in their series. In the absence of adequate data in these reports, especially of age and of period of observation, it is not possible to ascertain from them the relative frequency of cancer among these different series of diabetics. Furthermore, assuming that the clinician has satisfactorily established the incidence or prevalence of cancer among a group of diabetics, he is confronted with the problem of selecting a control group by means of which the biological significance of his findings can be evaluated. Marble, recognizing the serious objections to the procedure used for appraising his data, correctly concluded that "while certain evidence would seem to indicate that cancer is more common among diabetics, such a conclusion is open to serious criticism."

Ellinger and Landsman, on the other hand, evaluated the data for their diabetic population which had been under observation for more than one year on the basis of the 1941 cancer incidence (cases first reported in that year) in the general population of New York State (exclusive of New York City). From this comparison they concluded that "the diabetic seems to be more liable to develop cancer." Obviously, this conclusion is not tenable because of the nature of the comparison made.

A serious objection to the use of clinical data may arise from the fact that patients who attend hospital clinics may not comprise a representative sample of all diabetics in the population (8). Primarily, this may be due to two factors: (a) these diabetics may be different from others who are not under care by the very fact that they are under care and (b) some of the diabetics found to have cancer may have sought care because the coexistence of the latter condition aggravated the diabetic

symptoms. The possible bias introduced by the selection of a special population, *e.g.*, hospital patients, may be minimized or eliminated by means of a longitudinal study of the original sample. In other words, it is possible to select a sample of patients who received their first examination in a specified period of time and then to ascertain their mortality experience in subsequent years, since the effects of any bias introduced by the original selection will be reduced and eventually eliminated among those who survive.

From detailed mortality data made available by the Metropolitan Life Insurance Company, it is possible to remove most of the statistical objections to the data as previously published for the experience of the George F. Baker Clinic in Boston (3, 4, 9). These data are based on the mortality experience for the ten-year period from 1929 to 1938 among a 25 per cent sample of all diabetics examined from 1897 to 1938 and exclude diabetics who were moribund or whose death occurred within one week of first observation or hospital discharge. Unfortunately, it is not possible to determine the chronological trend of cancer mortality for these diabetics from the data as presently tabulated. However, in view of the fact that a large proportion of these diabetics were first observed from 1897 to 1928, years before the period of this mortality experience (1929–1938), and that moribunds have been excluded, it is probable that any original bias in the representativeness of the sample has been minimized. Moreover, since the data are tabulated by sex and years of life exposed to death according to attained age, the effects of variations in age, sex, and years of exposure can be eliminated from the analysis.

During the ten-year period, 1929 to 1938, 83 deaths were attributed to cancer among this sample of diabetics—or a rate at all ages combined of 5.3 cancer deaths per 1,000 years of life exposed. How does this experience compare with the cancer mortality experience of the general population? This question can best be answered by comparing the diabetic's experience with the number of cancer deaths which would have been ex-

pected among them if their cancer mortality experience had been similar to that of the general population. A number of facts must be considered, however, when selecting a suitable criterion for determining their expected cancer mortality experience. First, it should be noted that most of the diabetics in this experience were originally drawn from and eventually died in Massachusetts or other areas in the Northeastern part of the United States. Second, few nonwhites are included in this experience. Third, it is generally recognized that a major factor in the upward trend of standardized cancer mortality rates in past years was the increasing recognition and diagnosis of cancer as a cause of death. Finally, since diabetics are more likely than the general population to be under medical care, it is possible that their reported cancer mortality experience more closely approximates the true frequency of cancer as a cause of death. In view of the above, the 1940 age-sex specific cancer mortality rates for the white population in Massachusetts (10) have been used to determine the expected number of cancer

Table 1. Expected cancer mortality experience from 1929 to 1938 among a 25 per cent sample of diabetics examined at the George F. Baker Clinic in Boston from 1897 to 1938.

Attained Age Group	Males			Females			Total Expected Cancer Deaths
	Years of Life Exposed	Expected Cancer Death Rate[1]	Expected Cancer Deaths	Years of Life Exposed	Expected Cancer Death Rate[1]	Expected Cancer Deaths	
0–4	16.42	7.8	.0013	18.33	3.6	.0007	.0020
5–14	367.41	3.3	.0121	372.79	4.1	.0153	.0274
15–24	656.67	7.9	.0519	585.90	4.2	.0246	.0765
25–34	658.24	13.8	.0908	539.85	21.0	.1134	.2042
35–44	934.39	39.8	.3719	816.59	86.6	.7072	1.0791
45–54	1218.80	154.0	1.8770	1585.58	221.2	3.5073	5.3843
55–64	1652.96	415.3	6.8647	2571.99	475.8	12.2375	19.1022
65–74	1106.43	953.8	10.5531	1875.67	811.4	15.2192	25.7723
75–84	283.70	1544.1	4.3806	407.02	1334.6	5.4321	9.8127
85–89	9.26	1627.3	.1507	3.25	1407.9	.0458	.1965
All Ages	6904.28	—	24.3541	8776.97	—	37.3031	61.6572

[1] 1940 Massachusetts cancer death rates per 100,000 white population; rates for age groups 0–4 and 85–89 are those for ages 1–4 and 85 and over respectively.

deaths among these diabetics. As may be seen from Table 1, judged by this criterion 62 deaths from cancer should have occurred. Thus it is apparent that the diabetics in this sample were reported to have at least one-third more cancer deaths than expected during the period from 1929 to 1938. The evidence, therefore, appears to confirm the hypothesis that there is a positive association between diabetes and cancer.

Mortality Data

Some reports in the literature are based on data from official death records. The 1932 study by Wilson and Maher of associated causes of death as recorded on death certificates in Massachusetts revealed a positive association for cancer and diabetes (2). Do other available mortality data confirm this statistical relationship?

Mortality data are relatively easy to obtain for analysis and since they are frequently misused or misinterpreted, it is desirable to devote extensive consideration to their significance. Mortality ratios may be based on the universe of the dead (*e.g.*, 11.17 per cent of all deaths which occurred in the United States in 1940 were attributed to cancer) or on the universe of the living (*e.g.*, cancer was reported to have caused the death of 0.12 per cent of the United States population in 1940). Since the population from which deaths arise is not always known, *e.g.*, among an autopsied population, mortality ratios based on the universe of the dead have sometimes been used to ascertain the relationship between two conditions or diseases. What is disclosed by an analysis of the association of cancer and diabetes mellitus among dead persons?

Universe of Dead Persons

DATA FOR THE UNITED STATES

From a special tabulation of associated causes of death as recorded on death certificates in the United States in 1940, it is possible to determine the frequency with which cancer and other diseases are reported together with diabetes (11). As

may be seen from Table 2, which was constructed from those data, among the dead, cancer is reported for 11.6 per cent of the nondiabetics but for only 4.0 per cent of the diabetics. Even cancer of the digestive organs and peritoneum, which includes the pancreas, is reported twice as frequently for nondiabetics. As will be shown subsequently, however, these facts do not indicate that cancer and diabetes are dissociated.

THE INFLUENCE OF INCOMPLETE REPORTING OF CAUSES ON DEATH CERTIFICATES

Sole reliance on associated conditions recorded on death cer-

Table 2. Frequency of cancer and other selected diseases among diabetics and among nondiabetics at the time of death, United States, 1940.

Disease and International List Number	Diabetics		Nondiabetics	
	Number	Per Cent	Number	Per Cent
Total, Known and Defined	33,653	100.0	1,357,456	100.0
Cancer, All Sites, All Forms (45–55)	1,348	4.0	157,015	11.6
Cancer of Digestive Organs and Peritoneum (46)	753	2.2	72,002	5.3
Tumors, Non-malignant and Unspecified (56, 57)	115	0.3	6,542	0.5
Tuberculosis (13–22)	804	2.4	59,642	4.4
Pneumonia and Influenza (33, 107–109)	2,152	6.4	92,546	6.8
Ulcer of Stomach or Duodenum, Appendicitis, Hernia, Cirrhosis of Liver, *etc.* (117, 121, 122, 124)	892	2.6	44,681	3.3
Intracranial Lesions of Vascular Origin (83)	3,474	10.3	119,776	8.8
Diseases of the Heart (90–95)	12,339	36.7	385,273	28.4
Other Diseases of the Circulatory System (96–103)	3,353	10.0	28,763	2.1
Biliary Calculi, *etc.* (126, 127)	261	0.8	7,773	0.6
Diseases of the Pancreas (128)	101	0.3	842	0.1
Nephritis (130–132)	4,267	12.7	107,355	7.9
All Others	4,547	13.5	347,248	25.5
Ill Defined and Unknown (199, 200)	5,353	—	20,807	—
Grand Total	39,006	—	1,378,263	—

Source: Primary and secondary causes of death as reported in "Vital Statistics of the United States, 1940, Part I," Bureau of the Census, U. S. Department of Commerce, Washington, Government Printing Office, 1943, pages 570–623. Deaths attributed to ill-defined and unknown causes are here assigned to their associated cause.

tificates is usually a risky matter. Less than thirty years ago, only one-third of all certificates filed in the United States Death Registration Area reported more than one morbid condition (related and overlapping conditions and diseases included). While great improvement has been made in the completeness of reporting contributory and associated causes, it is worth noting that as recently as 1940 only a little more than one-half (55.4 per cent) of the death certificates filed in the United States reported more than one cause (12).

If this is true for deaths from all causes, may we expect a smaller proportion of secondary causes reported on death certificates for which the deceased were known to have a cancer or diabetes mellitus? Are certifying physicians less likely to report a contributory or an associated cause for deaths for which the primary cause is known to be an acceptable "killer" —a major disease or condition?

The importance of the above cannot be overstressed. For example, if some of the cancer deaths tabulated for nondiabetics were due to failure of physicians to report diabetes mellitus as a contributory or an associated condition when it actually existed, then the reported frequency of cancer was decreased among diabetics.

What effect, if any, incomplete reporting may have had on the data presented in Table 2 cannot be determined. That not all diseases and conditions known to have existed prior to death are reported on death certificates may be seen from analysis of unpublished data for a selected sample of 6,938 white deaths reported in New York City proprietary and municipal hospitals in 1937–1939 and 1941 (13).

Among the 6,938 deceased persons there were 1,280 diagnosed as having cancer, but only 1,216, or 95.0 per cent, were so reported on their death certificates. Also, there were 533 deceased persons who had been diabetic, but only 407, or 76.4 per cent, of the death certificates reported diabetes mellitus. Omissions in varying proportions are also evident for other conditions and diseases.

Equally pertinent is the fact that significantly fewer diabetics are reported on death certificates among persons for whom cancer is reported. Among these persons (1,216 for whom cancer was recorded on their death certificate), there were 57 who had been diabetic but on only 35, or 61.4 per cent, of the certificates was diabetes mellitus recorded as a contributory or an associated condition.

If we may assume (though without any justification) that these figures approximate the extent of under-reporting of diabetes on death certificates from all sources in the United States (including voluntary hospitals, private physicians attending persons who die at home, *etc.*), we can correct the cancer frequencies presented in Table 2 to allow for the effects of incomplete reporting. Adjusted on this basis, cancer is found to be associated with 5.0 per cent of the diabetics (instead of 4.0 per cent) and with 11.6 per cent of the nondiabetics (not affected by correction).

No doubt there are many reasons why all diseases and conditions are not reported on death certificates, including the fact that the condition may not have contributed to death. And it is probable that physicians are less likely to report contributory and associated causes when a major disease or condition is the primary cause of death. Regardless of the reasons for these omissions, however, contributory and associated causes reported on death certificates are probably not yet sufficiently complete to warrant critical studies of associated causes of death solely on the basis of data from death certificates.

NEW YORK CITY SPECIAL MORTALITY DATA

The New York City special mortality data (13) provide an efficient means of determining the relative association of cancer and diabetes at the time of death. These data, for white persons only, classified according to sex, by selected age groups, are presented in Table 3.

It is interesting to observe from this table that at the time of death cancer is less frequently reported among diabetics than

among nondiabetics; the rate per one hundred for all ages combined among males is 12.3 for diabetics and 18.4 for nondiabetics, and among females it is 10.3 and 19.8 respectively.

Granted that cancer is less frequently found among diabetics than among all other persons at the time of death, does this

Table 3. Cancer among diabetics and among nondiabetics at the time of death, white population, deaths reported in proprietary and municipal hospitals, City of New York, 1937–1939 and 1941.[1]

Age in Years	Males		Females	
	Diabetics	Nondiabetics	Diabetics	Nondiabetics
	TOTAL DEATHS			
0– 4	0	636	0	446
5–14	1	34	1	45
15–24	1	69	0	83
25–34	7	138	6	196
35–44	3	273	16	331
45–54	23	523	50	441
55–64	73	756	123	618
65–74	71	644	102	553
75 and Over	24	332	32	287
All Ages	203	3,405	330	3,000
	NUMBER OF DEATHS WITH CANCER			
0– 4	—	5	—	0
5–14	0	2	0	0
15–24	0	6	—	1
25–34	0	11	0	13
35–44	1	32	2	68
45–54	2	118	8	123
55–64	11	210	12	200
65–74	9	175	12	137
75 and Over	2	67	0	53
All Ages	25	626	34	595
	PER CENT OF DEATHS WITH CANCER			
45–54	8.7	22.6	16.0	27.9
55–64	15.1	27.8	9.8	32.4
65–74	12.7	27.2	11.8	24.8
75 and Over	8.3	20.2	0	18.5
All Ages	12.3	18.4	10.3	19.8

[1] Excludes deaths due to accidental causes and others certified by the medical examiner's office.

fact indicate that diabetes is dissociated from cancer? Some persons have erroneously reached this type of conclusion on the basis of associated conditions among the dead. The classical example found in the literature involves the association of cancer and tuberculosis (14). By means of autopsy data, the frequency of active tuberculosis in persons dead of cancer and those dead of other causes including tuberculosis was compared. On the basis of a negative relationship between cancer and tuberculosis, it was concluded that tuberculosis was antagonistic to the development of cancer. That the noncancerous group did not constitute a valid control group was shown in a subsequent study, wherein it was revealed that the frequency of active tuberculosis in persons dead of heart disease was as low as in the cancer death group (15). In other words, it is not sufficient to show that a condition is less frequently associated with another at the time of death, but rather that it is less frequently associated with it than it is with other diseases and conditions.

In order to apply this principle to the relationship between cancer and diabetes, the New York City special mortality data

Table 4. Cancer associated with selected conditions at the time of death, white population, 25 or more years of age, deaths reported in proprietary and municipal hospitals, City of New York, 1937–1939 and 1941.[1]

Condition	Number with Condition		Number with Cancer					
			Observed		Expected[2]		Ratio[3]	
	Males	Females	Males	Females	Males	Females	Males	Females
Diabetes Mellitus	201	329	25	34	48.3	80.7	.52	.42
Tuberculosis (All forms)	136	65	13	8	27.4	12.6	.47	.63
Syphilis	88	29	13	3	20.2	6.9	.64	.43
Cardiovascular-Renal Disease	925	905	28	20	210.2	206.4	.13	.10

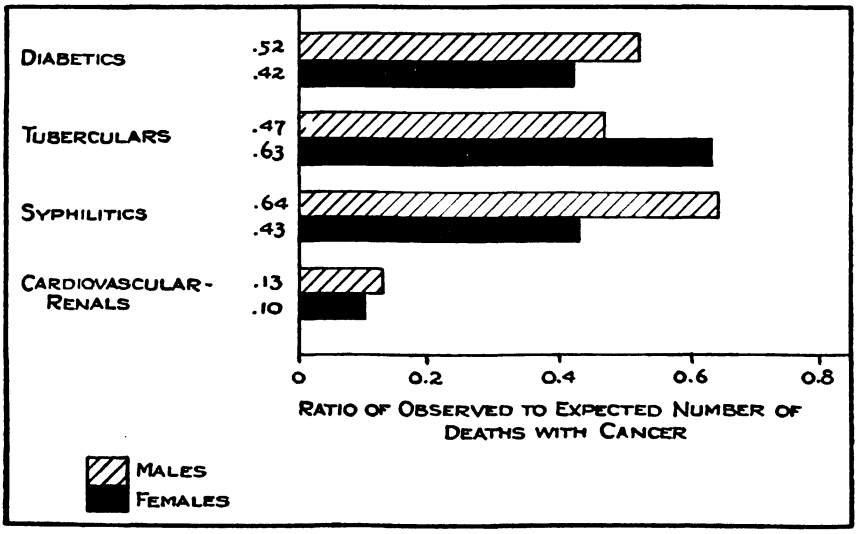
[1] Excludes deaths due to accidental causes and others certified by the medical examiner's office.
[2] Based on the age-sex specific proportionate frequency of cancer as a cause of death among all deaths in the sample applied to the age distribution of deaths in each diagnostic-sex group.
[3] Ratio of observed to expected number of deaths with cancer.

have been used to set up four diagnostic groups: (a) diabetes mellitus, (b) tuberculosis (all forms), (c) syphilis, and (d) cardiovascular-renal diseases. Tuberculosis (2) and syphilis (16) were set up since cancer is generally recognized to be associated with these conditions. The relationships between these conditions and the control group, the cardiovascular-renal diseases, will, therefore, serve as a check on the findings for cancer and diabetes.

A comparison of the expected and observed frequency of cancer among males and females for these groups is given in Table 4. Since the "expected number" was derived from the age-sex specific proportionate frequency of cancer as a cause of death among all deaths[2] in the sample applied to the age distribution of deaths in each diagnostic-sex group, the influence of age differences has been eliminated from the data.

As may be seen from these data, cancer is associated with diabetes mellitus among the dead to relatively the same extent as it is with syphilis and with tuberculosis. Cancer is, however,

Fig. 1. Cancer associated with selected conditions at the time of death, white population, 25 or more years of age, deaths reported in proprietary and municipal hospitals, City of New York, 1937–1939 and 1941.



[2] Excludes deaths due to accidental causes and others certified by the medical examiner's office.

associated with the cardiovascular-renal diseases to a significantly lesser extent than it is with diabetes. These relationships are readily seen in Figure 1, which presents the ratios of observed to expected number of deaths with cancer for these four groups.

Since cardiovascular-renal diseases are not thought to be correlated with cancer, the frequency of cancer among persons dead of these diseases does constitute a valid means for evaluating the association of cancer with diabetes. Judged by this criterion, the data appear to indicate that cancer is positively associated with diabetes.

UNIVERSE OF LIVING PERSONS

DATA FOR THE UNITED STATES

Wilson (17) takes a different approach to this problem but with comparable results. If we are interested in ascertaining the relative frequency with which conditions occur in pairs at the time of death, then a universe of dead persons is a proper one to use. If, on the other hand, we wish to reason in regard to the functioning state of an individual, we must study a population of living persons. Since we intend to determine relationships in order to ascertain whether one condition is predisposing or antagonistic to another, we should use a universe of living persons.[3]

Wilson found for mortality from cancer and diabetes dissociation in the universe of the dead (17) and association in the total population (2). It is not possible to relate the New York City special mortality data to a living population, for reasons similar to those which occur in regard to an autopsied population. The 1940 mortality data for the United States and 1930 data for New York City, therefore, will be used to investigate the latter finding.

The 1940 population of the United States was 131,669,275 and, from Table 2, deaths were as follows: cancer—158,363;

[3] Wilson has termed the use of a universe of dead persons for this purpose the statistical fallacy of "observational selection."

diabetes mellitus—39,006; and with both causes—1,348. If we assume that the two causes of death fell independently upon the total population, the expected number of deaths from both cancer and diabetes is 46.9—(158,363) × (39,006) ÷ 131,669,-275. Thus, the reported number of deaths with both conditions was 29 times more frequent than expected.

An even greater ratio is derived from 1930 data for New York City (18). Among an estimated population of 6,954,700 persons, deaths were reported as follows: cancer—8,125; diabetes —1,784; and with both causes—74, or 35 times the expected number (2.1).

Would association be disclosed if the expected number of deaths was calculated specific for age, sex, and color? This may be done for the United States by applying the 1940 age-sex-color specific cancer death rates for the United States (10) to the comparable distribution of deaths charged to diabetes (19). From these computations, the expected number of deaths with both diabetes and cancer is found to be 210. Since 1,348 deaths were reported with both conditions, cancer and diabetes were reported jointly 6.4 times more frequently than might be expected on the assumption that the two conditions caused death independently. Similarly, the 1930 data for New York City give a ratio of 6.4 (11.53 deaths expected in contrast to 74 reported).[4]

Thus it is evident that available mortality data indicate that cancer and diabetes mellitus are positively associated as causes of death.

Morbidity Data

Would comparable results be obtained if as is more logical morbidity rates were used, rather than mortality rates, to evaluate the relationship of the two conditions?

[4] From Massachusetts data for a ten-year period (1902, 1912, and 1920–1927), classified by age and sex, Wilson (2) reported a ratio of 64, which is ten times greater than the ratios found for the United States and for New York City. Analysis of the Massachusetts data appears to indicate that the reported frequency of deaths from both cancer and diabetes was extremely high; cancer was reported for 34 per cent of the diabetics in contrast to 3.5 per cent and to 4.1 per cent for the United States and for New York City respectively, and to 10 to 12 per cent for all known diabetics at the time of death (Table 3).

There is no report of morbidity data in regard to cancer among diabetics available in the literature. Collection of such data involves costly, time-consuming efforts of a large organization regardless of whether the data be amassed by means of a continuous reporting system, a canvass or an intensive diagnostic investigation of a representative group of the population. The author was thus fortunate in obtaining access to unpublished prevalence data on diabetes mellitus, cancer,[5] and other conditions, which were made available by the National Health Survey (20, 21).

DESCRIPTION OF DATA

The survey data are based on schedules taken in 83 cities for 703,092 households, comprising 2,502,391 individuals, distributed so as to give a fairly representative sample of the urban population in the United States during the winter of 1935–1936. In addition to other related social and economic information obtained by interview with the housewife or other responsible member of each household, morbidity data were requested concerning: (a) illness keeping a person from work, school, or other usual activity on the day of the canvass; (b) illness which had disabled a person in the above sense continuously for seven days or more during the twelve months preceding the date of the canvass, including all hospitalized cases and all confinements; (c) all fatal cases during the past twelve months regardless of the duration of disability, and (d) all other handicapping diseases and conditions of a chronic nature.

The prevalence data used herein have been limited to the white population (includes a small percentage with color unknown but excludes Mexicans residing in California and Texas), 25 or more years of age, canvassed in the National Health Survey—a total of 1,310,051 individuals.

CANCER AMONG DIBETICS

There were 2,912 males and 5,278 females reported as di-

[5] Cancer was defined in the National Health Survey according to its definition in the 1938 revision of the International List of Causes of Death.

Table 5. Cancer prevalence among all persons and among diabetics, classified by age and sex, white persons,[1] 25 or more years of age. The National Health Survey, 1935–1936.

Age (Years)	Males						Females					
	Total			Diabetics			Total			Diabetics		
	Number in Survey	With Cancer		Number in Survey	With Cancer		Number in Survey	With Cancer		Number in Survey	With Cancer	
		Number	Proportion		Observed	Expected (4)×(5)		Number	Proportion		Observed	Expected (10)×(11)
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
25–34	176,610	27	.000153	167	0	.03	200,845	68	.000339	215	0	.07
35–44	170,610	95	.000557	352	2	.20	180,911	233	.001288	555	2	.71
45–54	138,194	233	.001686	651	4	1.10	138,119	391	.002831	1,215	8	3.44
55–64	81,843	372	.004545	848	7	3.85	89,064	449	.005041	1,649	12	8.31
65–74	43,466	399	.009180	675	4	6.20	52,309	371	.007092	1,289	14	9.14
75–84	14,385	191	.013278	206	1	2.74	18,734	219	.011690	335	1	3.92
85–99	2,036	21	.010314	13	0	.13	2,925	37	.012650	20	0	.25
Total— 25–99	627,144	1,338	—	2,912	18	14.25	682,907	1,768	—	5,278	37	25.84

[1] Includes a small percentage with color unknown but excludes Mexicans residing in California and Texas.

abetic among urban white adults, 25 or more years of age, included in the National Health Survey. Cancer was recorded for 18, or 0.6 per cent, of these diabetic males and for 37, or 0.7 per cent, of these females. These data by age according to sex are shown in Table 5.

Inspection of the data in the separate age groups reveals that the diabetic individuals were reported to have more cancer than the general population included in the survey up to age 65 among men and up to age 75 among women, but less at the older ages.[6] This relationship can be readily observed from Figure 2, which presents the reported cancer prevalence rates by sex and age groups from 35 to 84 years of age.

It may also be seen from Table 5 that for all ages combined the observed number of individuals with cancer exceeds the expected among both male and female diabetics; the ratio of observed to expected number of cases with cancer is 1.26 among males and 1.43 among females. However, the findings for males may be due to chance sampling, but those for females and for both sexes combined are statistically significant.[7]

There is evidence from the data, therefore, that cancer was reported more frequently than expected among diabetics. May we conclude that cancer is associated with diabetes or can this finding have resulted from some bias in the data?

For example, it is possible that respondents who are sufficiently cooperative to report one illness (condition or disease)

[6] This observation raises a question concerning the meaning of the heterogeneity in the data by age. The possibility that there is a relationship with age in the association between cancer and diabetes as well as between cancer and other conditions may be noted from other data (2). It would be difficult, however, to draw such a conclusion from the National Health Survey data since it is very unlikely that they are sufficiently accurate or representative for older persons. Primarily this results from the fact that persons absent from their household for one month or longer who were in homes for the aged or the incurable were excluded from the survey. Also, persons who had gone from their household to an institution for the care of disease anytime previously (and were still there) were included in the survey if reported by the family respondent, but obviously the record obtained was incomplete. These facts would appear to be especially important in the case of older persons with diabetes and/or cancer. Finally it is unlikely that respondents passed 70 years of age supplied accurate and complete information.

[7] The respective probabilities of obtaining deviations from the expected number as great or greater than those observed due to chance are .19 for males, .02 for females, and .01 for both sexes combined.

Fig. 2. Cancer prevalence rates among white diabetics and among all white persons, 35 to 84 years of age, included in the National Health Survey, 1935–1936.

are more likely to report all known associated or contributory conditions. If this were actually true, the data would reveal a greater association than really existed for any pair of conditions.

Another bias which may exist could result from the fact that diabetics are more likely to be under medical care than other persons in the population.[8] As such, therefore, the known prevalence of cancer among diabetics could more closely approximate the true prevalence. In other words, if a cancer develops, it is more likely to be diagnosed since the diabetic is more frequently and more thoroughly examined.

In order to give due consideration to the possible effects of these two biases, it is necessary to ascertain the prevalence of cancer among a control group of nondiabetics who also might be more likely to be under medical care than the general popu-

[8] This bias could be kept to a minimum but not necessarily eliminated even in an intensive diagnostic survey since the diabetic could supply a more complete history of existing conditions and he would thus reduce the chances of an existing cancer being overlooked.

lation. The condition selected for this purpose could not be related to or associated with diabetes mellitus nor with cancer, and a relatively large number of cases had to be available for study. Nondiabetics with sinusitis was the control group selected since it most closely approximated these requirements.

CANCER AMONG NONDIABETICS WITH SINUSITIS

A total of 12,622 white adults, 25 or more years of age, was reported in the survey as having sinusitis but not diabetes mellitus. Among these persons, 11, or 0.2 per cent, of the males and 10, or 0.1 per cent, of the females were reported as having cancer. These data by age according to sex are shown in Table 6.

As may be seen from that table, for all ages combined the observed number of individuals with cancer exceeds the expected among males but it is less than the expected among females (and among both sexes combined). The ratio of observed to expected number of cases with cancer is 1.29 for males

Table 6. Cancer prevalence among nondiabetics with sinusitis, classified by age and sex, white persons,[1] 25 or more years of age, the National Health Survey, 1935–1936.

Age (Years)	Nondiabetics with Sinusitis					
	Males			Females		
	Number in Survey	With Cancer		Number in Survey	With Cancer	
		Observed	Expected (2) × (Column 4 of Table 5)		Observed	Expected (5) × (Column 10 of Table 5)
(1)	(2)	(3)	(4)	(5)	(6)	(7)
25–34	1,691	1	.26	2,485	0	.84
35–44	1,847	4	1.03	2,187	7	2.82
45–54	1,084	3	1.83	1,294	1	3.66
55–64	523	2	2.38	770	1	3.88
65–74	243	1	2.23	355	1	2.52
75–84	59	0	.78	72	0	.84
85–99	5	0	.05	7	0	.09
Total—25–99	5,452	11	8.56	7,170	10	14.65

1 Includes a small percentage with color unknown but excludes Mexicans residing in California and Texas.

but it is not statistically significant.[9] These findings compared with those for diabetics are shown in Figure 3. Since cancer was not more frequently reported than expected among nondiabetics with sinusitis, it is improbable that the survey data are biased by the extent of cooperativeness of respondents.[10] It is also doubtful whether the data are materially biased by the fact that diabetics may know of a greater proportion of existing cancers than do the general population.

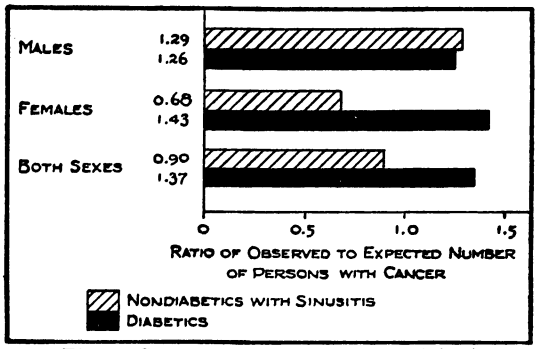


Fig. 3. Cancer prevalence among diabetics and among nondiabetics with sinusitis, white persons, 25 or more years of age, included in the National Health Survey, 1935–1936.

Judged by the reported cancer prevalence among the total survey population, the findings from the National Health Survey indicate that cancer is more prevalent than expected among diabetics but not among persons with sinusitis. Moreover, since the total population consists of persons with various conditions, some of which may be associated with cancer even as diabetes appears to be, it would be more valid to evaluate the significance of the data for diabetics by means of the cancer prevalence among nondiabetics with sinusitis. Unfortunately, the population and cases for that group are too small to permit such analysis. It should be noted, however, that the reported cancer prevalence rates, standardized for age on the basis of the age distribution of all persons included in the survey, are more than twice as great among diabetics than among nondiabetics with sinusitis (2.09 times greater among males and 2.98 among females).

[9] The probability of obtaining a deviation from the expected as great or greater than that observed is .24 for males.

[10] Theoretically, nondiabetics with sinusitis constitute an excellent control group for evaluating the data in regard to cancer among diabetics. While this would be true in the case of an intensive diagnostic survey, it is questionable whether sinusitis would be as completely reported as diabetes in the presence of cancer.

VALIDITY OF THE DATA

The physicians or hospitals reported to have attended cases of illness were requested to confirm or change the family diagnoses. In addition, copies of death certificates for fatal illnesses were obtained in order to verify statements of cause of death. However, only a small proportion (26.3 per cent) of all reported diagnoses could be checked in this manner due primarily to two factors: (a) not all persons included in the survey had had a medical attendant during the year covered by the survey; and (b) not all physicians could or did supply the requested medical information.

It would not be consistent to use the physician's reports (or statements of cause of death from death certificates) where available and the family's reports in other cases; for this and other reasons, the family respondent's statements only have been used in tabulating the data presented herein. How reliable are the diagnoses given by the family respondents?

First, it should be noted that for those statements which could be compared, an agreement of about 90 per cent (between the family's and the physician's statements was found in terms of classifications of diagnoses into 15 to 30 groups. The extent of agreement of two of the three diagnostic groups used in this study was approximately similar to the average for all diagnoses, cancer, 89.4 per cent and sinusitis, 90.4 per cent; while for the third, it was above the average, diabetes mellitus, 96.2 per cent. Second, for several cases of disagreement, it was evident that the physician was not familiar with the condition mentioned by the family, primarily due to the fact that he was not the physician who treated the patient for the particular illness but also partly because of inadequate medical records in the physician's office or hospital. Thus, it is probable that the diagnoses used herein are reasonably accurate.

Were all diabetics and persons with cancer reported? From experience with data from various surveys, it is reasonable to expect that various known diagnostic conditions would be under-reported in varying degrees. Comparison of the data on

diabetics with those obtained from the Massachusetts survey during 1929–1931 would seem to indicate the essential completeness of the National Health Suvey data (22).

The same degree of completeness in reporting of cancer is not evident from the data. This no doubt results primarily from two factors: (a) many respondents will not supply the information in regard to cancer even when known; and (b) others are not aware of the existing cancer or of the fact that the tumor which is known to exist is malignant. Or, how else account for the fact that for those tumors which were not specified as malignant by the family respondent, an agreement of only 60 per cent was found for those statements which could be compared and that for 28 per cent of these reported instances of disagreement the physician specified the tumor as malignant?

In view of the above, it appeared advisable to analyze the data on tumors to assure the validity of the findings in regard to cancer. From such analysis, a significantly greater number of observed cases of tumors (other than those specified as malignant) than expected is found among both male and female diabetics; the ratio of observed to expected is 1.93 for males and 2.29 for females.[11]

Since there is no *a priori* reason to expect an association between benign tumors and diabetes, part of this observed excess of tumors not specified as malignant may be due to the fact that diabetics know of a greater proportion of existing tumors than do the general population and part to the fact that some of these tumors were malignant. From this analysis, therefore, no evidence is produced to contradict the finding that cancer is more prevalent than expected among diabetics.

It should also be noted that the data do not appear to be biased by variations in the findings by place of residence (broad groupings) of persons included in the survey. No significant differences in the cancer rates among diabetics and among non-

[11] In view of the inclusion of nasal polyps and polypoids with tumors, the finding of more observed cases of tumors (other than those specified as malignant) than expected among nondiabetics with sinusitis does not appear to be significant to the present analysis.

diabetics with sinusitis are revealed from an analysis of the data for males and females, 60–69 years of age, classified for those residing in the Northeast, Central, and other areas of the United States.

Explanation for Excess Prevalence of Cancer Among Diabetics

A greater prevalence of cancer among diabetics than among nondiabetics might be explained by the fact that the pancreas is the primary site in which the excess malignant tumors arise. This hypothesis appears to be supported by Marble's data in which carcinoma of the pancreas constituted 13 per cent of all cancers among a group of 10,000 diabetics (3) and also by data reported on by McKittrick and Root in which 32 per cent of the cancers were of the pancreas among a group of 2,179 diabetics (23), in contrast to 3 to 5 per cent for the total population in the United States (24). Also, Ingelfinger (25) has stated that "Although a definite causal relation between diabetes and pancreatic cancer cannot be established, the two conditions coexist frequently enough for any suggestion of a diabetic state to intensify suspicion of pancreatic cancer if the clinical picture is otherwise suggestive." In contrast, however, Ellinger (5) and Hanssen (7) found no abnormal frequency of cancer of the pan-

Table 7. Cancer of the pancreas among diabetics and among nondiabetics at the time of death, white population, deaths reported in proprietary and municipal hospitals, City of New York, 1937–1939 and 1941.[1]

Sex	Cancer of the Pancreas as Per Cent of				Ratio of Observed to Expected[2] Number of Deaths	
	Deaths From All Causes		Total Cancer Deaths			
	Diabetics	Non-diabetics	Diabetics	Non-diabetics	Diabetics	Non-diabetics
(1)	(2)	(3)	(4)	(5)	(6)	(7)
Males	0.99	0.79	8.0	4.3	1.23	0.99
Females	0.61	0.70	5.9	3.5	1.43	1.01
Both Sexes	0.75	0.75	6.8	3.9	1.32	1.00

[1] Excludes deaths due to accidental causes and others certified by the medical examiner's office.

[2] Based on proportionate frequency of cancer of the pancreas as a cause of death among all male (or female) deaths in the sample applied to all male (or female) deaths in each group.

Table 8. Prevalence of cancer of digestive organs and peritoneum and of other cancers among diabetics and among non-diabetics with sinusitis, classified by age and sex, white persons,[1] 25 or more years of age, the National Health Survey, 1935–1936.

Age (Years) by Sex	Cancer of Digestive Organs and Peritoneum Among						Other Cancers Among			
	All persons in survey		Diabetics		Nondiabetics with Sinusitis		Diabetics		Nondiabetics with Sinusitis	
	Number	Proportion	Observed	Expected (3)×(Columns 5 and 11 of Table 5)	Observed	Expected (3)×(Columns 2 and 5 of Table 6)	Observed	Expected (Columns 7 and 13 of Table 5)–(5)	Observed	Expected (Columns 4 and 7 of Table 6)– (7)
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Males										
25–34	12	.000068	0	.01	0	.11	0	.01	1	.14
35–44	27	.000158	1	.06	0	.29	1	.14	4	.74
45–54	88	.000637	2	.41	1	.69	2	.68	2	1.14
55–64	155	.001894	2	1.61	0	.99	5	2.25	2	1.39
65–74	137	.003152	0	2.13	0	.77	4	4.07	1	1.46
75–84	58	.004032	1	.83	0	.24	0	1.90	0	.55
85–99	3	.001473	0	.02	0	.01	0	.11	0	.04
Total, 25–99	480	—	6	5.07	1	3.10	12	9.16	10	5.46
Females										
25–34	10	.000050	0	.01	0	.12	0	.06	0	.72
35–44	42	.000232	0	.13	0	.51	2	.59	7	2.31
45–54	80	.000579	2	.70	0	.75	6	2.74	1	2.91
55–64	113	.001269	4	2.09	1	.98	8	6.22	0	2.90
65–74	100	.001912	4	2.46	0	.68	10	6.68	1	1.84
75–84	58	.003096	0	1.04	0	.22	1	2.88	0	.62
85–99	9	.003077	0	.06	0	.02	0	.19	0	.07
Total, 25–99	412	—	10	6.49	1	3.28	27	19.36	9	11.37

[1] Includes a small percentage with color unknown but excludes Mexicans residing in California and Texas.

creas among their diabetics who had cancer. It is thus of interest to analyze the data presented herein to ascertain the prevalence of cancer of the pancreas among diabetics.

First, let us examine the New York City special mortality data (13). As can be seen from columns 2 and 3 of Table 7, no real difference is apparent in the frequency of cancer of the pancreas between diabetics and nondiabetics at the time of death. Cancer of the pancreas, however, does constitute a greater proportion of all cancers among diabetics than among nondiabetics (columns 4 and 5 of Table 7). Furthermore, it is more frequently reported among diabetics than might be expected on the assumption that diabetes and cancer of the pancreas are independently distributed among the dead (columns 6 and 7 of Table 7).

Second, it would be desirable to ascertain this relationship on the assumption that deaths from these two causes fall independently on the total population. Data for this purpose are not available but there may be some value in evaluating the 1940 United States mortality data regarding diabetes and cancer of the digestive organs and peritoneum, which includes cancer of the pancreas. From Table 2 it can be seen that for 753 persons, death was charged to both diabetes and cancer of the digestive organs and peritoneum. This is 35 times the expected frequency, namely, $(39{,}006) \times (72{,}775) \div 131{,}669{,}275$, or 21.6, and appears to indicate a positive association between diabetes and cancer of the digestive organs and peritoneum.

Thus there are indications from mortality data that diabetes and cancer of the pancreas are positively associated among the dead and that diabetes and cancer of the digestive organs and peritoneum are positively associated in the total population. What is the relationship revealed by morbidity data? Unfortunately, a separate code classification was not assigned to cancer of the pancreas in the National Health Survey. The data for cancer of the digestive organs and peritoneum, therefore, have been analyzed. These data for diabetics and for nondiabetics with sinusitis are given in Table 8.

Judged by the reported prevalence rates for all persons included in the survey, cancer of the digestive organs and peritoneum was reported somewhat more frequently than expected among female diabetics, but not among males. In contrast, both male and female nondiabetics with sinusitis were reported to have fewer cases than expected. None of these findings, however, are statistically significant.

If the greater prevalence of cancer among diabetics is ascribed to the fact that cancer of the pancreas occurs more frequently than expected among diabetics, how may we account for the fact that, according to the National Health Survey data, cancer other than of the digestive organs and peritoneum also is reported somewhat more frequently than expected among diabetics especially the females (columns 8 and 9, Table 8). The latter findings, expectation measured by prevalence among the total survey population, may be significant for females and for both sexes combined but not for males. Similarly, from the United States mortality data for 1940 (Table 2) there are indications that diabetes and cancer other than of the digestive organs and peritoneum are reported as joint causes of death more frequently than would be expected.[12] Finally, analysis of the detailed data for the experience of the George F. Baker Clinic in Boston indicates that for the ten-year period from 1929 to 1938 the reported mortality from cancer other than of the pancreas was greater than expected.[13]

Thus, while available mortality and morbidity data are not inconsistent with the possibility that cancer of the pancreas occurs more frequently than expected among diabetics, they do not support this hypothesis as the complete explanation for the excess prevalence of cancer among diabetics. And if, as may be reasonable to assume, existing cancers of the pancreas are more

[12] The reported number of deaths from both diabetes and other cancers was 595, which is 24 times the expected number – 25.3 or (39.006) × (85.608) ÷ 131.669 275.

[13] This statement is based on Marble's findings (3) that 13 per cent of all cancers were due to cancer of the pancreas. On this basis, of the 83 deaths reported from all forms of cancer, 11 would be due to cancer of the pancreas and 72 to cancer of other organs. The latter, as is evident from Table 1, exceeds the expected number even if it is assumed that none of the cancers primarily affected the pancreas.

frequently diagnosed among diabetics than among nondiabetics, it would be more probable that some other factor or factors accounted for the excess prevalence of cancer among diabetics.

For practical purposes, therefore, it may be assumed that cancer is more prevalent among diabetics than among nondiabetics. However, though no conclusion is tenable from the evidence presented to explain this phenomenon, the findings appear to indicate that the incidence of cancer is higher among diabetics than among nondiabetic individuals.

Summary

1. The consensus as expressed in the literature supports the hypothesis that cancer occurs more frequently than expected among diabetics.

2. In the two most comprehensive clinical reports in the literature, the data were not controlled for age, sex, color, and period of observation and the significance of the findings was evaluated on the basis of noncomparable control groups.

3. However, even with the elimination of most of the statistical objections to the data as previously published for the experience of the George F. Baker Clinic in Boston, the diabetics are found to have at least one-third more cancer deaths than expected during the ten-year period from 1929 to 1938.

4. Mortality data are relatively easy to obtain but they are subject to misuse and misinterpretation. Those obtained from death certificates alone are not complete, especially for contributory and associated causes.

5. From data on death certificates for deaths which occurred in the United States in 1940, it is shown that in the universe of dead persons cancer was less frequently reported among diabetics than among nondiabetics. This finding is confirmed by data from death certificates and matched hospital case histories for a selected sample of New York City white deaths classified by age and sex.

6. That these data appear to indicate that cancer and diabetes are positively associated is shown by the facts that among

the dead cancer is as frequently associated with diabetes as it is with other conditions (syphilis and tuberculosis) that are generally recognized to be associated with cancer, and that cancer is more frequently associated with diabetes than it is with other conditions (cardiovascular-renal diseases) that are not thought to be associated with cancer.

7. Applying the principle advanced by Wilson that one should use a universe of living persons in order to reason regarding the functioning state of individuals, it is shown that cancer and diabetes were reported as joint causes of death in the United States in 1940 and in New York City in 1930 more frequently than would be expected if these two causes fell independently upon the total population.

8. Morbidity data are difficult to obtain and those collected by canvasses are subject to diagnostic inaccuracy and other possible biases, but they do afford the best source for statistical evidence regarding the functioning state of individuals.

9. Data for white persons, 25 or more years of age, included in the National Health Survey, indicate that cancer is more prevalent than expected among diabetics. Among the 2,912 males and 5,278 females reported as diabetic, cancer was recorded for 18, or 0.6 per cent, of the males and for 37, or 0.7 per cent, of the females. The ratio of observed to expected number of cases of cancer (expectation measured by the prevalence among all persons of specific age groups above age 25 in the survey) was 1.26 for males and 1.43 for females; the findings for males may be due to chance sampling but those for females and for both sexes combined are statistically significant.

10. That these findings do not arise from any known bias in the data is shown by the fact that cancer was not reported more frequently than expected among nondiabetics with sinusitis. Other facts and analyses are cited in substantiation of the quality of the data and the validity of the findings.

11. No conclusion is tenable from the evidence presented to explain the excess prevalence of cancer among diabetics; the findings, however, appear to indicate that the incidence of can-

cer is higher among diabetics than among nondiabetic individuals.

References

1. Hoffman, Frederick L.: The Mortality from Cancer Throughout the World. Newark, N. J., The Prudential Press, 1915, pp. 192–194.

2. Wilson, Edwin B. and Maher, Helen C.: Cancer and Tuberculosis with Some Comments on Cancer and Other Diseases. *American Journal of Cancer,* 1932, 16, pp. 227–250.

3. Marble, Alexander: Diabetes and Cancer. *New England Journal of Medicine,* 1934, 211, pp. 339–349.

4. Joslin, Elliott P., *et al.*: The Treatment of Diabetes Mellitus. Philadelphia, Pa., Lea & Febiger, 1940, 7th Ed., pp. 580–586; 1946, 8th Ed., pp. 653–659.

5. Ellinger, Friedrich and Landsman, Harold: Frequency and Course of Cancer in Diabetics. *New York State Journal of Medicine,* 1944, 44, pp. 259–265.

6. Maynard, G. D.: A Statistical Study in Cancer Death Rates. *Biometrika,* 1910, 7, pp. 276–304.

7. Hanssen, Per: Diabetes Mellitus in Bergen, 1925–1941; a study of morbidity, mortality, causes of death and complications. Oslo, Norway, Johan Grundt Tanum, 1946.

8. Berkson, Joseph: Limitations of The Application of Fourfold Table Analysis to Hospital Data. *Biometrics Bulletin,* 1946, 2, pp. 47–53.

9. George F. Baker Clinic, Boston, and Metropolitan Life Insurance Company, New York: Diabetes in The 1940's. New York, Metropolitan Life Insurance Company, September, 1940, Chart 10, p. 14.

10. Bureau of the Census, United States Dept. of Commerce: Vital Statistics Rates in the United States, 1900–1940. Government Printing Office, 1943, Table 23, p. 434.

11. Bureau of the Census, United States Dept. of Commerce: Vital Statistics of the United States, 1940, Part I. Government Printing Office, 1943, Table 21, pp. 570–623.

12. *Ibid,* p. 569.

13. From a study, jointly sponsored by the New York City Departments of Health and Hospitals, which was directed by the Department of Health with the assistance of a grant from the New York Foundation. The data are based on information recorded on death certificates and matched hospital case histories for all deaths which were reported in proprietary hospitals in 1937–1939 and 1941 and for some of the deaths which were reported in selected municipal hospitals in January and February of those years. Excluded are deaths due to accidental causes and others certified by the medical examiner's office, and those for which hospital case histories could not be obtained. Data from that study for nonwhite deaths have not been used in this paper.

14. Pearl, Raymond: Cancer and Tuberculosis. *American Journal of Hygiene,* 1929, 9, pp. 97–159.

15. Carlson, H. A. and Bell, E. T.: A Statistical Study of the Occurrence of Cancer and Tuberculosis in 11,195 Post-mortem Examinations. *Journal of Cancer Research,* 1929, 13, pp. 126–135.

16. Levin, Morton L., *et al.*: Syphilis and Cancer. *New York State Journal of Medicine,* 1942, 42, pp. 1737–1744.

17. Wilson, Edwin B.: Morbidity and The Association of Morbid Conditions. *Journal of Preventive Medicine,* 1940, 4, pp. 27–38.

18. Department of Health, City of New York: Joint Causes of Death. *The Weekly Bulletin,* 1931, 20, pp. 333–340.

19. *See* reference 11, Table 11, p. 224.

20. Perrott, George St. J.; Tibbits, Clark; and Britten, Rollo H.: The National Health Survey—Scope and Method. *Public Health Reports,* 1939, 54, pp. 1663–1687. Reprint No. 2098.

21. Britten, Rollo H.; Collins, Selwyn D.; and Fitzgerald, James S.: The National Health Survey—Some General Findings. *Public Health Reports,* 1940, 55, pp. 444–470. Reprint No. 2143.

22. Spiegelman, Mortimer and Marks, Herbert H.: Age and Sex Variations in the Prevalence and Onset of Diabetes Mellitus. *American Journal of Public Health,* 1946, 36, pp. 26–33.

23. McKittrick, L. S. and Root, H. F.: DIABETIC SURGERY. Philadelphia, Pa., Lea & Febiger, 1928.

24. Hoffman, Frederick L.: Cancer of the Pancreas. *New England Journal of Medicine,* 1934, 211, pp. 65–169.

25. Ingelfinger, Franz J.: The Diagnosis of Cancer of the Pancreas. *New England Journal of Medicine,* 1946, 235, pp. 653–661.