EPIDEMIOLOGICAL EVIDENCE ON THE NATURE OF HODGKIN'S DISEASE

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THE question of whether the disease processes of Hodgkin's disease are fundamentally neoplastic or inflammatory in nature remains unresolved. The opinions of pathologists range from the belief that Hodgkin's disease, reticulum-cell sarcoma, and lymphosarcoma are neoplasms originating in a common stem cell and differing only in dominant cell type,[4, 10, 20, 32] to the concept that the tissue changes cannot be differentiated from the granulomatous changes found in tuberculosis, brucellosis, syphilis, and a number of other known infections.[21, 31] Many comprehensive reviews of the topic have been assembled.[4, 10, 11, 28, 31]

Recently the interpretation favoring the neoplastic concept of the disease has prevailed. In the *Sixth Revision of the International Lists of Diseases and Causes of Death,* published in 1948, Hodgkin's disease was included for the first time in the chapter on neoplasms.[34] Two facts in particular have favored the development of the neoplastic theory—considerable experimental study has failed to demonstrate the presence of an infective agent with any degree of regularity, and there has been increasing realization of the frequency with which both Hodgkin's granuloma and the frankly neoplastic Hodgkin's sarcoma may be found in the same patient at the same or different times.[4, 10] Neither of these features is conclusive however, and the question cannot be considered settled with any finality.

TABLE 1

MEAN ANNUAL INCIDENCE OF HODGKIN'S DISEASE IN THE WHITE POPULATION OF BROOKLYN, 1943 TO 1952, ACCORDING TO SEX AND AGE OF PATIENTS

Age at diagnosis	Number patients			Incidence per million		
	M	F	Total	M	F	Total
0-4	0	0	0	0.0	0.0	0.0
5-9	2	1	3	2.2	1.1	1.7
10-14	3	5	8	3.5	6.2	4.8
15-19	16	18	34	18.3	20.0	19.2
20-24	29	16	45	29.4	15.1	22.0
25-29	27	33	60	26.1	29.3	27.8
30-34	24	24	48	24.3	21.9	23.0
35-39	23	19	42	22.9	17.1	19.9
40-44	26	19	45	26.8	18.7	22.7
45-49	20	12	32	22.7	13.4	18.0
50-54	25	17	42	30.2	20.5	25.3
55-59	37	10	47	54.1	15.0	34.8
60-64	30	17	47	54.7	31.2	43.0
65-69	28	16	44	69.7	36.8	52.6
70-74	20	10	30	82.3	36.1	57.7
75 and more	11	8	19	53.6	30.1	40.3
ALL AGES	321	225	546	25.7	17.4	21.5

It is the purpose of the present communication to present data on some features of the descriptive epidemiology of Hodgkin's disease and to discuss their relevance to the question of the nature of this disease.

MATERIAL

Original data are derived from a study in which an attempt was made to assemble clinical and pathological records of all residents of Brooklyn, New York, diagnosed as having leukemia or any lymphoma in the period 1943 to 1952. Sources of data were: (1) a complete survey of the records of thirty-four Brooklyn hospitals; (2) a selective survey of records of certain hospitals in other boroughs of New York City; and (3) death certificates of Brooklyn residents dying in any of the five boroughs of New York City. The methodology has been more fully described elsewhere.[17] With respect to Hodgkin's disease, records of 573 Brooklyn residents diagnosed for the first time in the period 1943 to 1952 were obtained. When clinical records were found, only pa-

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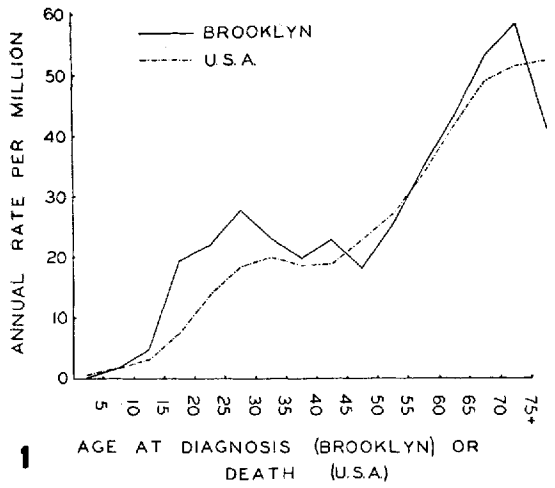
Read before the Epidemiology Section of the American Public Health Association, Atlantic City, New Jersey, November 14, 1956.

This study was aided by a field investigation grant (CS9435) from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

The author is indebted to the medical, administrative, and record-room staffs of many hospitals in Brooklyn and other boroughs of New York City. A list of these hospitals was published in a previous communication.[17]

The author is also indebted to the Board of Health of New York City, New York, for permission to review death certificates and to the Bureau of Records and Statistics of the Department of Health, New York City, for providing tabulated information.

Received for publication December 26, 1956.



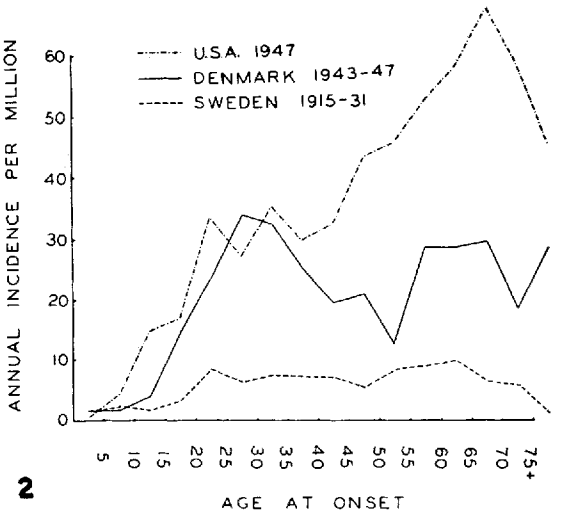


FIG. 1. Hodgkin's disease: incidence in Brooklyn, 1943 to 1952, and death rate in the United States, 1949 to 1953.

FIG. 2. Age-specific–incidence curves for Hodgkin's disease: data from three previous morbidity surveys. Sources of data are Dorn and Cutler (U.S.A.),[6] Clemmesen, Busk, and Nielsen (Denmark)[3] and Uddströmer (Sweden).[30]

tients for whom the diagnosis was supported by biopsy or autopsy were included in the series. A number of patients for whom clinical records were not found, but for whom the item "duration of illness" as completed on the death certificate indicated onset within the study period, were included. The major criteria of diagnosis for these patients were as follows: autopsy report, 119; biopsy report, 382; and death certificate, 72.

Most of the following tabulations are based on the 546 white patients included in this series. The total white population of Brooklyn averaged 2,540,828.

INCIDENCE IN BROOKLYN

Mean annual incidence of Hodgkin's disease in the white population of Brooklyn during 1943 to 1952 was 21.5 per million population.

Table 1 gives the mean annual-incidence rates according to sex and age at diagnosis. The age trend is illustrated in Fig. 1. The striking feature is the bimodality of the curve. There is one peak of incidence in the 25 to 29-year age group, and a second at 70 to 74 years.

Annual age-specific–incidence rates taken from, or calculated from, data given in three previous reports in which cases from clinical sources can be related to specific populations are illustrated in Fig. 2. The studies are those of Uddströmer,[30] Clemmesen et al.,[3] and Dorn and Cutler,[6] which presented all ascertained cases of Hodgkin's disease in Sweden, 1915 to 1931; Denmark, 1943 to 1947; and ten metropolitan areas of the United States, 1947, respectively. While the individual curves are quite different from each other, each is consistent with the suggestion of one peak of incidence in young adults and a second peak at older ages. Although still present, the bimodal pattern is not so distinct in the material from the state of Washington presented by Thorson and Brown.[29] The number of cases is smaller, however, and the use of ten-year, instead of five-year, age groups tends to obscure the bimodality.

DEATH RATE IN THE UNITED STATES

In addition to the Brooklyn age curve, mean annual age-specific–death rates from Hodgkin's disease in white persons in the United States are illustrated in Fig. 1. Data are from *Vital Statistics of the United States* for 1949 to 1953.[23] Once again, the curve is definitely bimodal, although the first mode is less distinct than in the curve for the Brooklyn data. The same phenomenon, of a sharper peak of incidence in the 20- to 34-year age group in rates calculated from age at onset or diagnosis, than in rates plotted against age at death, is seen when the Danish data recorded by Clemmesen et al.[3] (Fig. 2) are compared to age-specific–death rates in the same country (Fig. 4). It may be attributable in part to the longer sur-

vival of the group of patients age 0 to 39 than of the group age 40 years or more.

Bimodal age-incidence curves are unusual and suggest either that different etiological mechanisms are operating at different periods of the age span, or that different disease entities have been incorporated in the original classification. Further analyses were therefore conducted to determine whether the disease occurring in young adults and in older age groups has similar demographic characteristics.

SEX INCIDENCE

Three hundred twenty-one (58.8 per cent) of the 546 white patients in the Brooklyn material were males. Age-specific–incidence rates for the sexes separately are given in Table 1 and illustrated in Fig. 3. The higher incidence in males is more evident in the later part of the age-incidence curve (40 and more) than in the earlier part (0 to 39). The same situation is evident in the data of Uddströmer, who noted that after the fourth decade, the incidence tended to increase in males but not in females. In Table 2 sex ratios are compared according to a threefold grouping by age at onset in the five series in which the data were available on a community basis. The age group 0 to 9 years is separated because of the observation of Wallhauser,[31] confirmed by Smith,[27] that males predominate to an unusual degree among patients in this age group. This feature is evident from Table 2. In addition, the sex ratio is lower in the 10 to 39- than in the 40 and more age group in each series. The difference is significant in three of the individual series and highly so in the combined total for the five series.

FIG. 3. Sex- and age-specific–incidence rates of Hodgkin's disease in Brooklyn, 1943 to 1952.

Shimkin,[24] examining United States death statistics for 1925 to 1950, noted a characteristic change in the sex ratio of deaths from Hodgkin's disease with age. There was a marked male predominance in the age group 5 to 14 and a lesser peak at 45 to 54. Interpretation of changes in sex ratio according to age at death is difficult, since, in addition to changes that are associated with age at onset or diagnosis, the picture will be affected by sex differences in duration of disease after diagnosis. There is general agreement that such differences exist in Hodgkin's disease in the form of a longer expectation of life for females than for males.[22, 25] However, to assess the

TABLE 2

SEX RATIOS, PERCENTAGE MALE, RELATED TO AGE AT ONSET, IN FIVE SERIES OF PATIENTS WITH HODGKIN'S DISEASE

	Age groups								
	0-9		10-39 (1)		40 and more (2)		All ages*		Difference between (1) & (2)
Series	No.	%	No.	%	No.	%	No.	%	
Uddströmer[30]	34	91.2	278	53.2	224	65.6	536	60.8	12.4 ± 4.4†
Clemmesen et al.[3]	6	...	211	54.5	167	58.7	392	56.6	4.2 ± 5.1
Dorn and Cutler[6] (white patients)	5	...	157	48.4	223	62.8	385	56.9	14.4 ± 5.2†
Thorson and Brown[29]	5	...	56	69.6	72	80.6	133	75.9	11.0 ± 7.7
Present data (white patients)	3	...	237	51.5	306	64.4	546	58.8	12.9 ± 4.3†
FIVE SERIES	53	84.9	939	53.2	992	64.5	1,992	59.7	11.3 ± 2.0†

*Figures for "all ages" include 8 patients of unstated age in the series of Clemmesen et al.[3]
†Difference exceeds twice its standard error.

TABLE 3

MEAN ANNUAL DEATH RATE FROM HODGKIN'S DISEASE IN WHITES AND NONWHITES, UNITED STATES, 1949 TO 1953

Age	Death rate per million		Percentage excess in whites
	White	Nonwhite*	
0-39	9.9	7.0	41.4
40 and more	32.6	20.6	58.3
ALL AGES	18.0	11.9	51.3

*The data for nonwhites are standardized to the age distribution of the white population within each broad age group.

effect this will have on sex ratios related to age at death would require much more detailed information on survival related to sex and age than is presently available. The high sex ratio in the 5- to 14-year age group noted by Shimkin[24] is, of course, a reflection of the male predominance in cases with onset in childhood. In the same data, the two age groups 15 to 24 and 25 to 34 appear to have generally lower sex ratios than any other age groups, except possibly the last two. This again is compatible with the change in sex ratio with age at onset noted previously, although, probably for the reasons just outlined, the difference between age periods is not so well marked as in the material in which age at onset was recorded. The reason for the increasing contribution of females to the total death rate seen in the final age groups is not clear. It is not evident in age-incidence curves showing age at onset or diagnosis.

COLOR

There were twenty-seven Negroes among the 573 Brooklyn patients. On the basis of the age-specific rates observed in the white population, thirty-four Negro patients would have been expected. The incidence in white persons was apparently higher therefore than in Negroes, but not so much so as has been evident in previous studies of death statistics.[9, 24] For example, in the years 1949 to 1953 age-standardized death rates in white and nonwhite persons in the United States were 18.0 and 11.9 per million per annum respectively—a white excess of 51.3 per cent.

In these same United States statistics, the excess of the death rate in whites compared to that in nonwhites is somewhat lower in the age group 0 to 39 than after that period (Table 3). However, less complete diagnosis in the older age groups acting differentially on the white and nonwhite populations is a ready explanation of this difference.

RELIGION

Distribution according to religion, and by implication according to some ethnic tendencies, is examined in view of the previous demonstration of association of leukemia death rate with this variable.[18] In Table 4 the distribution by religion of a series consisting of all deaths from Hodgkin's disease in Brooklyn of white Brooklyn residents during 1943 to 1952 is compared with that of a systematic 1-in-200 sample of deaths in Brooklyn of white Brooklyn residents from all causes during the same period. The religious affiliation of the cemetery of burial as indicated on the death certificate is used as the index of religion, and has been previously shown to be satisfactory for this purpose.[18] From series of 367 deaths from Hodgkin's disease and 1,119 comparison deaths, patients buried outside the city (six and twenty-three cases), and deaths under 1 year of age (zero and fifty cases) have been excluded. The method of examination is more completely described in the study of leukemia referred to previously.

Comparing the distributions of the two series in Table 4 an excess of deaths of Jewish patients in the Hodgkin's disease series is seen. The ratio of the proportions of deaths of Jewish patients in the Hodgkin's disease and comparison series suggests that after standardization for age differences, Hodgkin's disease appears as cause of death about one and a half times more frequently among Jewish than among non-Jewish patients.

TABLE 4

PERCENTAGE DISTRIBUTION, BY RELIGION, OF DEATHS FROM HODGKIN'S DISEASE AND A COMPARISON SAMPLE OF ALL DEATHS, BROOKLYN, 1943 TO 1952

Age at death*	Pt. group	No. pt.	Religion, %			
			Catholic	Jewish	Protestant	Total
0-39	Hodgkin's disease	115	43.5	35.7	20.8	100
	Comparison sample	68	49.4	31.9	18.7	100
40 and more	Hodgkin's disease	246	34.2	45.9	19.9	100
	Comparison sample	978	42.9	32.2	24.9	100
ALL AGES	Hodgkin's disease	361	37.1	42.7	20.2	100
	Comparison sample	1,046	45.0	32.1	22.9	100

*In each age group, figures for the comparison sample are standardized to the age distribution of the Hodgkin's disease patients within the same group.

TABLE 5

DEATH RATES FROM HODGKIN'S DISEASE IN SELECTED COUNTRIES, 1950 TO 1952

Country	Death rate per million*			Percentage U.S. rate		
	Age 0-39	Age 40 & more	All ages	Age 0-39	Age 40 & more	All ages
United States (white)	9.9	32.6	18.1	100	100	100
Canada	8.7	29.1	16.0	88	89	88
Denmark	15.0	25.7	18.8	152	79	104
Finland	9.5	21.5	13.8	96	66	76
Norway	11.4	22.8	15.5	115	70	86
Sweden	7.9	22.6	13.2	80	69	73
England & Wales	10.1	25.0	15.4	102	77	85
Ireland	9.5	27.8	16.1	96	85	89
Scotland	10.7	30.2	17.7	108	93	98
France	10.1	20.6	13.9	102	63	77
Germany	9.0	21.7	13.6	91	67	75
Italy	10.7	31.1	18.0	108	95	99
Netherlands	17.6	23.7	19.8	178	73	109
Switzerland	12.9	25 7	17.5	130	79	97
Australia	5.9	21.5	11.5	60	66	64
Japan	1.8	13.3	5.9	18	41	33

*Within each broad age group all rates have been standardized to the age distribution of the United States white population in five-year groups.

In Table 4 this association is also examined separately for the two age groups 0 to 39 and 40 and more. The excess proportion of deaths among Jews in the Hodgkin's disease series is seen to be almost entirely restricted to the later age period. The difference between the two age groups in the proportion of deaths among Jews in the Hodgkin's disease series approaches significance (10.2±5.6). By contrast, the proportion of deaths among Jews in the comparison sample is about the same in the two age periods. That this is not merely a circumstance of the small number of comparison deaths under 40 years of age is suggested by the data of Deardorff,[5] in which only minor changes with age are seen in the proportion of Jewish residents of New York City as a whole.

It is suggested therefore that Hodgkin's disease in patients more than 40 years of age shares with leukemia[18] and lymphosarcoma[16] the feature of more frequent diagnosis among Jewish than among non-Jewish people in this community. The disease as affecting the younger ages does not share this characteristic, or, if it does, the association is much less marked.

DEATH RATES IN OTHER COUNTRIES

Death rates from Hodgkin's disease according to age have been calculated for fifteen countries besides the United States for which data are published by the World Health Organization.[35] With the exception of that for Japan, all the age trends were found to be distinctly bimodal, as noted in the United States data.

Death rates standardized to the age distribution of the United States' white population are shown in Table 5. When the total death rate for all ages is considered, two countries—the Netherlands and Denmark—are seen to have rates slightly higher than that of the United States. The total range, however, is small, particularly if the data for Japan are excluded. A wider range of variation is evident if rates in the age groups 0 to 39 and 40 and more are considered separately. There is little correlation between rates for the same countries in the two age groups. For example, the rate for the United States, which is the highest in the 40 and more group, is exceeded by that of eight of the fifteen other countries in the 0- to 39-year group. The Netherlands, with the highest rate in the 0 to 39 period, is ninth in the older age group.

Two interesting patterns are illustrated in Fig. 4. The first, typified by the curves for the Netherlands and Denmark, and evident also in the data for Switzerland, is characterized by high rates in the younger age group and relatively low rates in old age. In the case of Denmark, this pattern can also be demon-

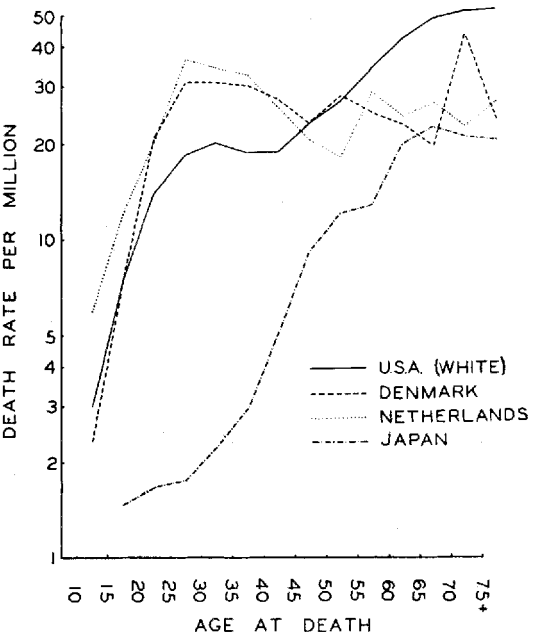


FIG. 4. Age-specific-death rates from Hodgkin's disease in four selected countries, 1950 to 1953.

strated by comparing incidence rates in that country (Fig. 2) with the Brooklyn incidence data (Fig. 1).

The second interesting pattern is seen in the age trend for Japan. Of course, the completeness of the data from this country may be questioned. Nevertheless, the disease is diagnosed in Japan with some frequency, as evidenced by the fact that the death rate in the older age groups approximates that of the Netherlands and Denmark (Fig. 4) and a number of other European countries. The virtual absence of the disease in the age groups less than 40 is therefore particularly interesting, even when reservations related to diagnostic difficulties are considered. The age trend for deaths from Hodgkin's disease in Australia shows a pattern somewhat similar to that for Japan, although the disease is appreciably more common in individuals less than 40 years of age in Australia than it is in Japan.

SECULAR CHANGES IN INCIDENCE

The recorded death rate from Hodgkin's disease has increased progressively in the United States since 1921.[24] There was no significant increase in Australia between 1908 and 1950.[14] In the United States death rates from Hodgkin's disease in childhood have decreased, in contrast to the regular increases observed in all other age groups. However, adult age groups more than and less than 40 years of age have been equally affected by the increase.[24]

That the same generalizations apply to the situation in Sweden is suggested by comparison of the incidence data for this country in 1915 to 1931 reported by Uddströmer[30] with present-day death rates. Uddströmer pointed out the increased incidence evident between the early and late years of his study.

Irregularities in age curves that are based on data derived from cross sections of the population may sometimes be explained by the fact that changes over a period of time have affected particular cohorts of the population.[15] However, in the circumstance of a regular increase in incidence, as noted for Hodgkin's disease, it is not possible to explain the bimodal age curve in this way. Such an explanation would require several changes in the direction of the trend with time.

SURVIVAL

In comparing the behavior of this disease in young and older adult age groups, it is of interest to examine for trends in length of survival related to age. Jackson and Parker[13] and Shimkin et al.[25] examined this question on series of 171 and 254 patients respectively. Each reported no change in prognosis with age. The latter authors grouped cases in patients less and more than 40 years of age without revealing significant differences in survival. However, in the data of Jackson and Parker[13] a definitely shorter median survival is seen in the older age groups, beginning with the group 40 to 49. Some irregularity is evident, but in general the patients in the age groups more than 40 have median survivals half or less than those in the younger age groups. The authors' conclusion that age has no effect on prognosis is unexplained. Uddströmer, examining data on 494 patients, reported definitely shorter survival among those in the age groups more than 55. Although the trend is most marked at more than age 55, examination of the data reveals definite worsening of prognosis for those as young as 40 to 44. Gall and Mallory[8] also noted much shorter survival for patients who were more than 50 years of age at onset.

In the present series, follow-up to the end of 1952 was available for 77 per cent of the 474 white patients ascertained from hospital records. (Patients ascertained from death certificates are excluded since no information on time of diagnosis was available for this group and they are of course selected in respect to survival.) Using the life-table method, and including untraced patients as "at risk" during the total period of observation, the percentage of survivors at various periods up to three years after diagnosis are shown in Fig. 5. Separate trends are shown for males and females and for age groups less than and more than age 40. The data indicate a definite difference in prognosis between the two age groups. Correction of the figures for the group 40 and more, by eliminating the number of deaths that would have been expected in the group on the basis of current age-specific death rates, raises the three-year–survival percentage from 15.8 (both sexes) to only 17.6, compared to 38.1 per cent for patients less than 40. The difference between the two age groups is therefore not explained by the higher death rates from other causes in the older age groups.

The reliability of these findings is qualified by the high percentage of failures in follow-up. However, these failures will affect the absolute values rather than the comparison of the two

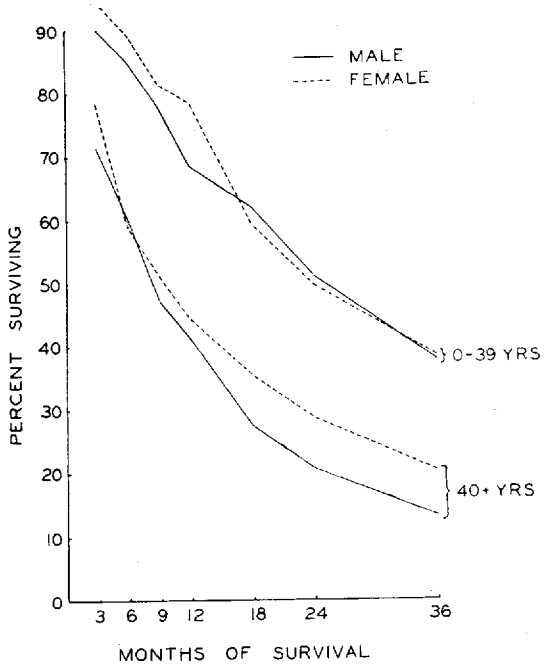


FIG. 5. Percentage survival of 474 white patients after diagnosis of Hodgkin's disease, related to age and sex.

age groups, unless the probability of follow-up is related to age. The percentage of losses is higher in the less than 40 age group (28 per cent of 218 patients) than in those 40 and more (18 per cent of 256 patients). Three-year–percentage survivals have therefore been recalculated on two hypotheses: (1) that patients lost to follow-up died at the time of loss; and (2) that such patients survived the whole three-year period. Under these two hypotheses, three-year survivals for the group 0 to 39 years of age were 24 and 53 per cent respectively; for the group 40 years and more corresponding figures were 10 and 28 per cent. Although the absolute-survival rates vary considerably under these two hypotheses, it is not likely that the difference between the two age groups is related to this circumstance, since, in order to explain the difference in this way, it would be necessary to assume that all of the patients less than 40 years of age who were lost to follow-up died at the time of loss, but that all of the patients more than 40 who were lost survived the three-year period. It seems more likely that the higher percentage of patients traced in the older age group is related to the poorer survival of this group, since the method of the study was such as to give somewhat greater likelihood of follow-up for dead than for surviving patients.

DISCUSSION

The term "Hodgkin's disease" is descriptive of certain characteristic though variable pathological and clinical findings. It is without etiological implications. The pathological and clinical features of the condition include aspects suggestive of both infective and neoplastic forms of disease. The problem posed by this situation has been resolved by some writers with the hypothesis that the condition occupies an intermediate position between these two disease groups—either that a neoplastic virus, such as that of the Rous sarcoma, is the causative agent,[12, 19] or that neoplastic changes may be superimposed upon a primarily infective lesion.[2, 7, 33] The evidence reviewed here suggests an alternative hypothesis—that Hodgkin's disease is a syndrome that includes the common clinical and pathological end results of distinct etiological processes.

Specifically, the trend in age incidence suggests the possibility of at least two etiological entities—the first with maximum incidence in the 20- to 34-year age groups and the second showing increasing incidence with age after 35 or 40. The epidemiological features of the disease in these two age periods differ in many particulars. In the present study, differences have been noted in sex ratio, geographic incidence, survival, and possibly racial and religious incidence. Only in secular change in incidence has the behavior of the disease in the two age groups been comparable. To these features of difference may be added the fact that patients in whom sarcomatous changes are found are predominantly in the older age groups. In the present material, specific histological diagnoses were not recorded with sufficient frequency for adequate analysis. However, in the material of Jackson and Parker,[13] 6 per cent of the 169 patients less than 40 years of age were diagnosed as having the sarcomatous form of the disease, compared to 26 per cent of the 160 patients of 40 or more years of age.

It is clear that no one of the above listed features is in itself conclusive evidence of fundamental difference in the nature of the disease at different ages. Each can be interpreted as due to relatively minor factors modifying incidence of the same disease process at different ages. However, the number of the differences between the two age groups and the markedly bimodal nature of the age-incidence curve itself suggest that the difference between

the disease as it occurs in the two age groups may be in such fundamental areas that it would not seem appropriate to consider the condition as a single disease.

The question may then be raised—to what extent is the suggested etiological differentiation by age group interchangeable with the common pathological one into sarcoma, granuloma and paragranuloma? In the Brooklyn material, 44 per cent of the patients were less than 40 years of age. (Of course, sharp delineation between the two groups at age 40 is not intended. This age is merely suggested as a point above or below which the majority of the cases of any one type seem likely to fall. Age curves for different countries might suggest points of delineation other than the one selected for use here on the basis of the Brooklyn data.) From this fact alone—that there are approximately equal numbers of patients older and younger than age 40—it is obvious that the pathological and epidemiological classifications are not interchangeable, since in the pathological classification the granuloma is by far the most common form of the disease. Thus, although the sarcoma occurs almost solely among those in the age groups more than 40, 75 per cent of the patients in this group do not have the sarcoma (according to the data of Jackson and Parker[13]). (It should be noted that an accurate estimate of the incidence of sarcomatous changes in Hodgkin's disease in patients more than 40 years of age is not available. The granuloma and the sarcoma may be found in the same patient at different times or at different biopsy sites,[4, 10] and complete ascertainment would require complete autopsy examination of a series of patients of this age group.)

In the data of Jackson and Parker,[13] paragranuloma occurs relative to the granuloma with almost equal frequency in patients older or younger than age 40 (14 and 15 per cent respectively), and there is therefore no reason to suspect that the granuloma-paragranuloma distinction coincides with any part of the epidemiological differentiation.

In short, the pathological classification, as presently understood, does not coincide with the epidemiological differentiation by age group, except insofar as the sarcomatous form is restricted to those who are more than 40 years of age. However, we are unaware of any specific search for pathological differences between the disease occurring in patients younger and older than 40 years.

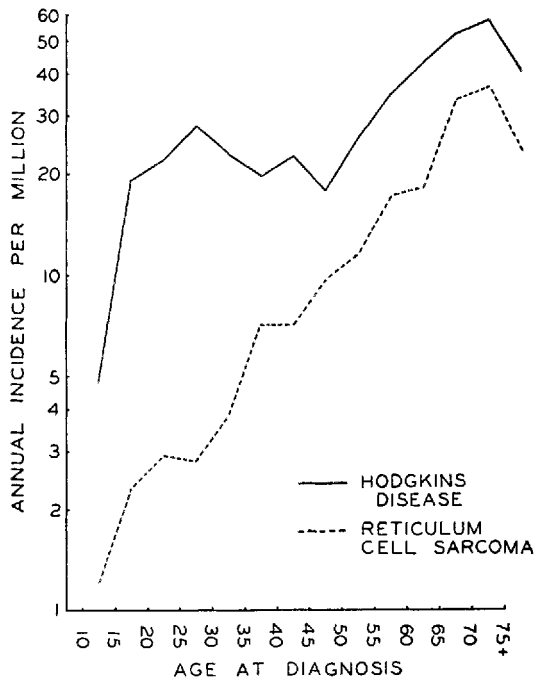


FIG. 6. Age-specific-incidence rates for Hodgkin's disease and reticulum-cell sarcoma, Brooklyn, 1943 to 1952.

The further question of the neoplastic or infective nature of Hodgkin's disease can then be posed separately for each of the two broad age groups for which separate etiologies are hypothesized. At the outset it should be made clear that the terms "infective" and "neoplastic" are not used to describe a dichotomy. The fact that neoplastic conditions may be associated with "infective" agents of a specialized type does not detract from the utility of an attempt to categorize the disease into a broad group of diseases from which we expect particular types of behavior and particular types of response to preventive measures.

With respect to those cases falling into the later part of the age-incidence curve, two features are suggestive of neoplasm: (1) the frequency with which changes recognized by pathologists as frankly neoplastic (sarcoma) are found; and (2) the age-incidence curve, which, showing regular increase with age after early middle age, is typical of a neoplasm. Neither of these features is conclusive, but they are each more suggestive of neoplasm than of infection.

The similarity[26] or even the identity[1, 4] of the histological pictures of Hodgkin's sarcoma and reticulum-cell sarcoma has been attested to frequently. In Fig. 6 the age-incidence curve for Hodgkin's disease (all forms) in

Brooklyn is compared with that for reticulum-cell sarcoma in the same population. The similarity of the two curves in the second half of life is remarkable, since, even between known neoplastic disorders, differences in shape and slope of the age-incidence curve are usual. The sex ratio of patients with reticulum-cell sarcoma in Brooklyn (193 patients, 60.1 per cent male) is also similar to that of Hodgkin's disease in patients more than 40 years of age (306 patients, 64.4 per cent male) (difference 4.3± 4.4).

As just noted the frequency with which sarcomatous changes may be found with complete examination in patients with Hodgkin's disease more than 40 years of age is unknown but is not less than 25 per cent. These features suggest that the relationship between Hodgkin's granuloma occurring after 40 years of age, Hodgkin's sarcoma, and reticulum-cell sarcoma is a close one.

On the other hand, none of the forementioned features suggestive of neoplastic disease are found in the group of patients less than 40 years of age among whom the maximum incidence is in the 25 to 29-year age group. The sarcomatous form is unusual, and the age-incidence curve is quite unlike that of a neoplastic disorder. For example, the trend in the first half of life stands out strikingly compared to that of reticulum-cell sarcoma (Fig. 5).

The high rates for the disease in this age group in the three traditional dairy-producing countries (Netherlands, Denmark, and Switzerland) are provocative and warrant further investigation.

SUMMARY

By survey of hospital records and death certificates, a series of 573 residents of Brooklyn, New York, diagnosed as having Hodgkin's disease during the period 1943 to 1952 was assembled. For all but seventy-two of these, diagnosis was supported by biopsy or autopsy.

The age-incidence curve was distinctly bimodal, with one peak in the age group 25- to 29- and a second in the 70- to 74-year group. Similar bimodality is evident in mortality statistics for the United States and in data from previous morbidity surveys.

Further examinations were conducted separately for patients more than and less than 40 years of age. The disease as it affects these two groups appears to differ in sex ratio, geographic incidence, survival, frequency of sarcomatous change, and possibly racial and religious incidence.

It is suggested that Hodgkin's disease as presently understood may be a syndrome including the common clinical and pathological end results of at least two distinct etiological processes. There is no evidence as to the nature of Hodgkin's disease as it occurs in persons less than 40, and this portion of the age-incidence curve for the disease is quite unlike that of any known neoplastic disorder. On the other hand, the disease as it affects the older age groups (40 and more) has features characteristic of known neoplasms. It is suggested that there is a close relationship between Hodgkin's granuloma in persons more than 40, Hodgkin's sarcoma, and reticulum-cell sarcoma.

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