[CANCER RESEARCH 26 Part 1, 1189-1200, June 1966]

Epidemiology of Hodgkin's Disease

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Summary

The epidemiologic features of Hodgkin's disease vary with age at clinical onset. Three age periods can be distinguished: 0–14, 15–34, and 50 and over. The epidemiologic features of the disease in these 3 periods are summarized in Table 9. Bimodality of the age incidence curve augments the idea that the entity as now described is heterogeneous.

Two hypotheses are proposed on the basis of the epidemiologic evidence and a brief consideration of pathology and prognosis. First, patients now categorized as having Hodgkin's disease include at least 3 subgroups, the etiology of which may be quite distinct. Second, Hodgkin's disease in young adults is a chronic granulomatous inflammation, whereas that occurring in persons over 50 is a neoplasm.

Introduction

In this paper, information available on the descriptive epidemiology of Hodgkin's disease—the who, when, and where of its distribution—will be reviewed. Analytic epidemiologic studies of this disease, so far as I am aware, do not exist, since etiologic hypotheses of sufficient specificity to be tested epidemiologically have not yet been developed. However, some valuable descriptive data have been published in the past decade. A review of these may help to suggest or select hypotheses worthy of testing in the future.

Descriptive Epidemiology

Frequency

About 3200 deaths are now attributed to Hodgkin's disease annually in the United States. The annual death rate in the period 1958–62 was 23/million for white males and 13/million for white females. The lifetime probability of dying from Hodgkin's disease before age 75, assuming freedom from competing causes of death, is about 2.1/thousand for white males and 1.2/thousand for white females. Incidence rates are somewhat higher than mortality rates. The U. S. 10 cities survey of 1947 gave annual incidence rates of 35/million for white males and 26/million for white females, with lifetime probabilities to age 74 of 3.2 and 2.0/thousand, respectively (12). Some of the difference between these incidence and mortality rates may be attributable to differences in time and area of observation. However, a substantial proportion of persons with Hodgkin's disease live long enough to have their deaths attributed to other causes, so that it is not unexpected that incidence rates are higher than mortality rates.

Age

Hodgkin's disease has a characteristically bimodal age curve, illustrated in Chart 1 from a survey of the incidence of lymphomas in Brooklyn, New York, 1943–52 (29). On a semilogarithmic scale, age curves for reticulum cell sarcoma and lymphosarcoma increase approximately linearly throughout life to age 75. (Little attention should be paid to the fluctuations in the curve for lymphosarcoma under age 30—each point in this section of the curve is based on less than 10 cases.) The curve for Hodgkin's disease fits quite well with those of the other lymphomas at ages over 45, but in the age range 15–40 it manifests a distinct bump, almost as though a separate group of cases with a symmetrical age distribution around age 25–29 has been superimposed on the basic lymphoma pattern.

In 1957, I pointed out that this bimodality is evident in the 4 incidence surveys published up to that time and, to a lesser degree, in U. S. mortality data. Dörken noted the characteristic in mortality data from the German Federal Republic (11). It is also clearly seen in recent U. S. mortality data (Chart 2) and in the extensive data from the Danish Cancer Registry published by Clemmesen (4) (Chart 3). A point of considerable interest, to which we shall return, is that in the Danish data the 2 modes are of approximately equal prominence, whereas in the United States the 1st mode is much less marked than the 2nd. Bimodality by age is also evident in recent incidence surveys of New York State, 1941–60 (14), Saskatchewan, 1946–59 (33), and the U. S. Army, 1941–46 (7) and in data for 1958–62 from the Cancer Registry of Norway (E. Pedersen, personal communication). The bimodality appears, therefore, to be a constant feature of this disease.

This observation makes it desirable to examine the descriptive features of Hodgkin's disease separately in different age groups. This we shall do, wherever possible, in the ensuing data. Appropriate age groups, judged by inspection of Charts 1, 2, and 3, would seem to be: 0–14, prior to the 1st mode: 15–34, the 1st mode; 35–49, intermediate between the 1st and 2nd modes; 50+, the 2nd mode.

Sex

In U. S. mortality data, 63%[1] of white Hodgkin's patients are males (Table 1). Large incidence surveys give comparable results —58% in the U. S. 10 cities (12), 61% in Brooklyn (29), 59% in Denmark (3). In the United Kingdom, mortality data indicate

[1] All the percentages in this section are derived after correction for unequal sex distribution in the population at risk. The rate for males multiplied by 100 is the numerator; the sum of the rate for males and females is the denominator.

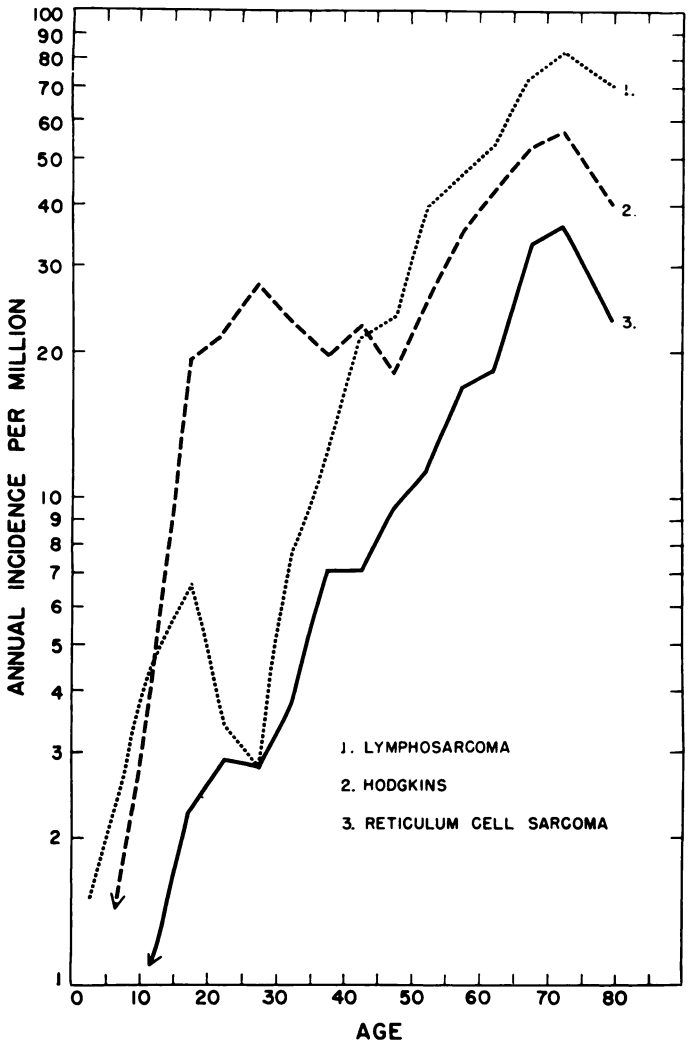

CHART 1. Age-specific incidence rates of Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma, Brooklyn, 1943–52.

a somewhat higher sex ratio—66%. Some authors presenting series of cases coming to particular hospitals have reported the impression that there has been an increasing representation of females during the past few decades. This impression is not confirmed in mortality data. Table 1 indicates that the sex ratio for whites has remained virtually unchanged since 1923. The same is true in England and Wales over a somewhat longer period (Table 2). In Denmark, the sex ratio of incident cases was 59% in 1943–47 and 60% in 1953–57.

Charts 2 and 3 show that the bimodality by age is exhibited by both sexes. Chart 3 also suggests that the sex ratio may be lower in the 1st mode than in the 2nd. Data on this point, from 5 incidence surveys, are given in Table 3. In 4 of the 5 surveys, the sex ratio is significantly lower for the 15–34 age group than for the 50 and over group. Comparable rates in these exact age groups cannot be derived from the data published by Thorson and Brown (42), but I have shown earlier (29) that in this survey the crude sex ratio is appreciably lower in the 10–39 age group than at ages over 40; the effect of correction would be to increase the difference between the crude sex ratios, since females tend to exceed males in the general population in the older age groups. Data for sex and age simultaneously were not published by Meighan (33), and no data for females were given by Cohen *et al.* (7), reporters of the only other incidence surveys. Thus it is possible to test the hypothesis of a difference in sex ratio in the 2 modal age periods in 6 incidence surveys. The data of 5 support the hypothesis. In fact, except in the case of the data from Norway, a sex ratio barely above 1:1 seems to be characteristic of the 15–34 age group, in contrast to almost 2:1 in the 50 and over group.

At first sight it is puzzling that this difference in sex ratio between age groups is not evident in mortality data, either in the United States (Table 1) or in England and Wales (Table 2). However, it is a consistent feature of survival studies in this disease that females have much better survival rates than males (1, 22, 41). Few authors have considered the influences of age and sex simultaneously, but it seems likely that the sex difference in survival is greatest in the young adult ages (22, 34)—the ages that show the longest over-all survivals (1). A sex difference in survival affecting persons first diagnosed between 15 and 34 years of age provides a ready explanation of the fact that the

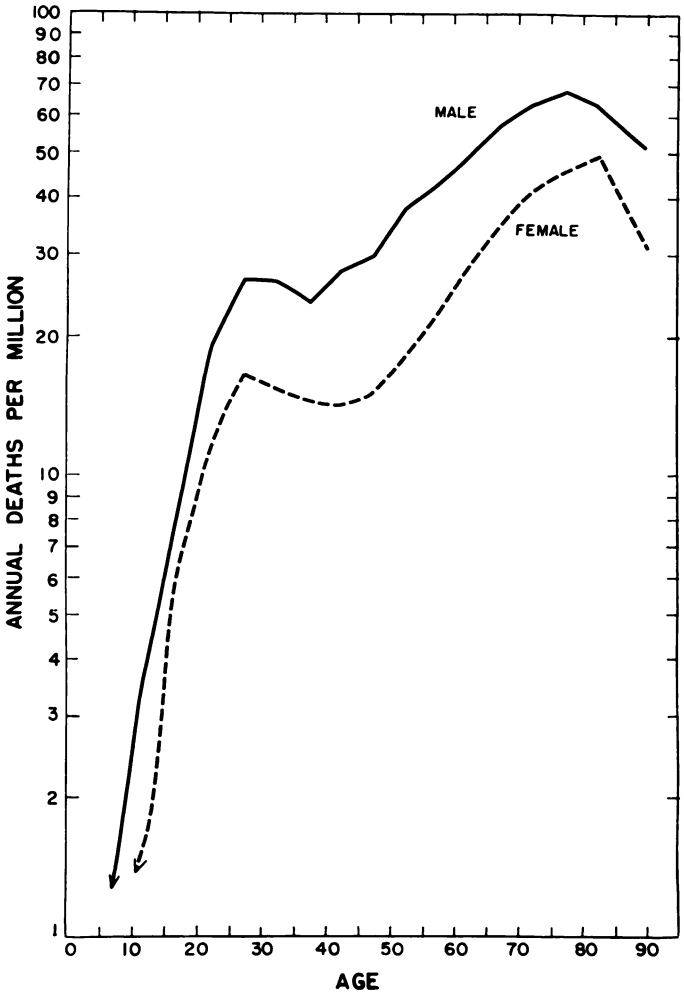

CHART 2. Age-specific mortality rates from Hodgkin's disease by sex, United States, 1958–62. (Data from National Center for Health Statistics (44).)

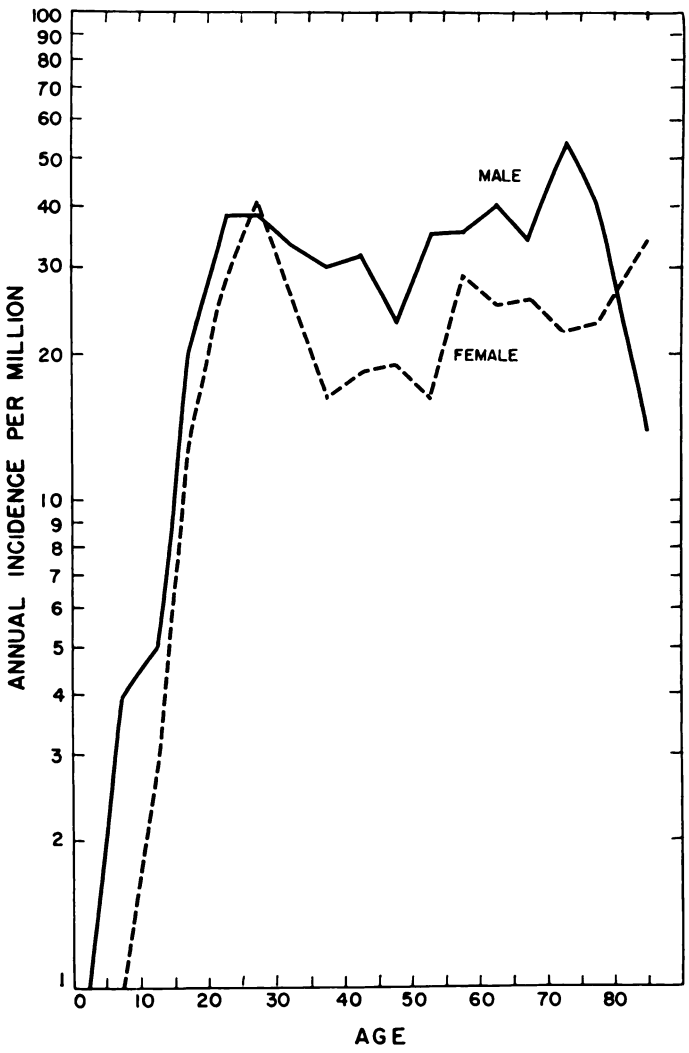

CHART 3. Age-specific incidence rates of Hodgkin's disease by sex, Denmark, 1943–57. (Data from Clemmesen (4).)

sex ratio in this age group is higher in mortality than in incidence data.

One further explanation must be considered. Females, because they are more conscious of lumps, because they see doctors more frequently, or for other sex-related reasons, may have their disease diagnosed earlier than males. This possibility is suggested by the observation that the proportion of cases diagnosed in more localized stages of Hodgkin's disease is higher among females than among males (22, 41). To explain the observations, this earlier diagnosis would have to affect cases incident in the 15–34 age group substantially more than those at later ages. One can readily conceive of reasons why such factors might be particularly effective during the reproductive years. The effect, if it were substantial, could give the appearance of both (*a*) longer survival for females than for males, and (*b*) earlier age at onset among females, even if there were no difference in prognosis for males and females with comparable stages of illness and the sex ratio of risk of onset were similar at all ages.

However, so far as the relatively crude clinical staging now available can provide a basis of comparison, females have better survival than males in comparable stages. Moreover, although stage of disease at diagnosis is highly related to survival, there is little relationship between duration of symptoms and stage at diagnosis (22), and long duration of symptoms before diagnosis is associated with good rather than poor prognosis (20, 22, 36). It seems unlikely, therefore, that a prolongation in survival of a subgroup of patients with Hodgkin's disease could be explained by earlier chronologic diagnosis. More likely, females have an innately slower developing disease in which longer duration allows greater opportunity for diagnosis in a localized stage. This interpretation would favor the conclusion derived from incidence data that the sex ratio of cases with onset in the 15–34 age group is substantially lower than that of cases with onset in later ages.

Regarding the age group 0–14, the sex ratios shown in Table 3 are quite variable. However, high sex ratio seems to characterize the younger members of the 0–14 group. I have found in the literature 122 cases of Hodgkin's disease in children under 10 years of age, reported either as case reports or in incidence surveys since 1930. The sex ratio of this group is 85% male. The sex ratio also seems to be particularly high in this age group in areas and times when the disease is relatively frequent at these ages.

Ethnic Group

U. S. nonwhites have lower Hodgkin's disease mortality rates than whites (15), as shown in Table 1. The same relationship, with approximately the same order of magnitude of difference, is seen in incidence rates (12, 29). An examination of Table 1 reveals no consistent pattern in the ratio of white to nonwhite rates, except that (*a*) rates for nonwhites approach those for whites most closely in the age range 35–49, and (*b*) rates for nonwhite males are closer to those of white males than those for nonwhite females are to those of white females, particularly in the more recent years. I am unable to offer any palatable interpretation of these patterns. There is no consistent difference between the age groups 15–34 and 50 and over in the ratio of white to nonwhite rates.

In the Brooklyn lymphoma survey already referred to, leukemia and the solid lymphomas shared the characteristic of being 1.5–2 times as common in the Jewish population, both native and foreign-born, as in the Catholic or Protestant groups (30, 31, 35). In the case of Hodgkin's disease, only cases incident over 40 years of age showed this relationship; among cases incident under 40 years of age, the 3 religious groups were represented in proportion to their prevalence in the population (29).

Marital Status

Cohen *et al.* (7) noted that, among men developing Hodgkin's disease in the U. S. Army between 1941 and 1946, the proportion who were married at the time of induction (20.6%) was lower than in a sample of all inductees (34.0%). This proportion would be influenced by social class, and it has not been determined whether there is an association of Hodgkin's disease with marital status that is independent of the associations with social class and occupation discussed below.

TABLE 1

AVERAGE ANNUAL DEATH RATES FROM HODGKIN'S DISEASE PER MILLION POPULATION, UNITED STATES, 1933–62[a]

COLOR AND TIME PERIOD	0–14 YEARS			15–34 YEARS			35–49 YEARS			50+ YEARS			ALL AGES		
	Rates		% Male	Rates		% Male	Rates		% Male	Rates		% Male	Rates		% Male
	M[b]	F		M	F		M	F		M	F		M	F	
Whites															
1923–27	4.8	2.4	66.7	8.7	4.9	64.0	13.1	7.6	63.3	24.3	14.4	62.8	12.0	6.9	63.5
1933–37	5.1	2.2	69.9	12.1	7.6	61.4	20.5	11.5	64.1	38.7	24.0	61.7	17.7	10.5	62.8
1949–52	2.4	1.0	70.6	17.6	10.7	62.2	26.1	13.7	65.6	49.6	30.2	62.2	22.0	12.8	63.2
1953–57	2.2	0.9	71.0	18.0	11.6	60.8	27.2	14.1	65.9	52.6	30.7	63.1	22.9	13.2	63.4
1958–62	1.9	0.7	73.1	19.9	12.4	61.6	27.0	14.6	64.9	50.4	29.6	63.0	22.8	13.2	63.3
Nonwhites															
1923–27	2.6	1.9	57.8	5.0	2.4	67.6	9.3	4.4	67.9	9.4	3.9	70.7	6.1	3.0	67.0
1933–37	3.4	1.5	69.4	7.2	4.9	59.5	12.1	8.7	58.2	21.4	10.4	67.3	10.3	5.9	63.6
1949–52	2.2	1.8	55.0	12.4	7.5	62.3	21.3	11.9	64.2	28.6	16.2	63.8	14.7	8.6	63.1
1953–57	1.5	1.0	60.0	13.5	6.3	68.2	22.0	10.1	68.5	32.5	14.5	69.1	15.8	7.3	68.4
1958–62	1.9	0.8	70.4	11.8	7.0	62.8	24.4	9.6	71.8	36.6	15.4	70.4	17.0	7.5	69.4

[a] Da a are from the United States vital statistics (44).

[b] M, male; F, female.

Within each of the broad age groups shown, rates are standardized in 5-year age groups to the distribution of the total U.S. population in 1960. Sex ratios are calculated as described in the text footnote. Data for 1923–27 are for the registration states only.

TABLE 2

AVERAGE ANNUAL DEATH RATES FROM HODGKIN'S DISEASE BY AGE AND SEX, ENGLAND AND WALES, 1911–60[a]

TIME PERIOD	0–14 YEARS			15–34 YEARS			35–49 YEARS			50+ YEARS			ALL AGES		
	Rates		% Male	Rates		% Male	Rates		% Male	Rates		% Male	Rates		% Male
	M[b]	F		M	F		M	F		M	F		M	F	
1911–15	7.2	3.0	70.6	8.5	4.8	63.9	10.3	5.3	66.0	20.8	11.2	65.0	11.3	5.8	66.1
1916–20	5.9	2.3	72.0	8.7	4.2	67.4	11.0	5.6	66.3	21.3	13.0	62.1	11.2	5.9	65.5
1921–25	6.9	3.0	69.7	11.2	5.6	66.7	13.9	6.3	68.8	26.7	14.6	64.6	14.0	7.0	66.7
1926–30	6.9	1.9	78.4	12.6	7.0	64.3	17.3	7.7	69.2	29.0	17.4	62.5	15.6	8.0	66.1
1931–35	7.8	2.3	77.2	15.1	7.9	65.7	20.3	10.7	65.5	32.9	16.6	66.5	18.0	8.7	67.4
1936–40	6.5	2.3	73.9	14.1	7.9	64.1	18.9	10.1	65.2	31.5	17.0	64.9	16.7	8.7	65.7
1941–45	5.1	1.6	76.1	14.8	8.6	63.2	20.8	9.7	68.2	32.5	17.9	64.5	17.1	8.8	66.0
1946–50	4.5	1.3	77.6	16.3	9.2	63.9	25.9	11.0	70.2	35.6	18.0	66.4	19.0	9.1	67.6
1951–55	3.2	1.2	72.7	19.7	10.5	65.2	26.6	12.0	68.9	41.0	21.4	65.7	20.9	10.5	66.6
1956–60	2.5	0.9	73.5	21.0	10.8	66.0	28.3	12.7	69.0	43.0	24.0	64.2	21.8	11.2	66.1

[a] Data on 5-year age-specific rates are from Case and Pearson (2).

[b] M, male; F, female.

Within each broad age group, rates are standardized to the same population as in Table 1.

Social Class

Table 4 shows standard mortality ratios for Hodgkin's disease and the other lymphomas in the 5 social classes used by the Registrar General for England and Wales (see Table 6 for definitions). The basis of classification is, of course, the occupation of the decedent or, in the case of a married female, of her husband. Data for Hodgkin's disease can only be derived from the 1949–53 report. High mortality ratios in the upper social classes are characteristic of the lymphomas as a group.

Although not directly pertinent to the present discussion, I cannot resist pointing out the epidemiologic puzzle posed by the fact that multiple myeloma, which is the only lymphoma that is more common in nonwhites than in whites in this country, is the member of the group showing the most marked relationship to social class—in the opposite direction than would be predicted from the white-nonwhite relationship.

Table 5 shows the social class relationship for Hodgkin's disease in 3 age groups. The relationship is present, and of approximately the same order of magnitude, in all 3 groups.

These findings are consistent with the observation of Cohen *et al.* (7) that the proportion of men whose preservice occupation was classified as "low" was smaller for patients with Hodgkin's disease (56.3%) than for a representative sample of enlistees (67.1%). The Hodgkin's disease patients also differed from the

TABLE 3

AVERAGE ANNUAL INCIDENCE RATES OF HODGKIN'S DISEASE PER MILLION POPULATION, BY AGE AND SEX, AND CORRECTED SEX RATIOS; 5 INCIDENCE SURVEYS

SEX	SURVEY	AGE (years)				ALL AGES
		<15	15–34	35–49	50+	
Male	1	2.9	6.1	9.2	9.4	6.5
	2	1.7	24.9	24.2	52.2	27.1
	3	7.0	27.3	42.0	68.4	35.4
	4	3.3	32.5	28.5	37.1	25.2
	5	3.2	29.1	27.9	48.2	25.3
Female	1	0.8	6.2	3.9	4.5	3.7
	2	2.0	21.8	16.5	25.7	17.5
	3	5.0	30.1	27.5	38.8	26.1
	4	1.2	27.0	17.6	23.8	17.6
	5	2.8	20.1	16.9	33.3	17.2
% Male	1	78.4	49.6	70.2	67.6	63.7
	2	45.9	53.3	59.5	67.0	60.8
	3	58.3	47.6	60.4	63.8	57.6
	4	73.3	54.6	61.8	60.9	58.9
	5	53.3	59.1	62.3	59.1	59.5

All rates are standardized in 5-year age groups to the total U. S. population, 1960. The surveys are:

1. Sweden, 1915–31 (43).
2. Brooklyn, New York, 1943–52, whites (29).
3. U. S. 10 cities, 1947, whites (12).
4. Denmark, 1943–57 (3).
5. Norway, 1958–62 (E. Pedersen, data from the Cancer Registry of Norway, personal communication).

sample in preservice years of schooling, the proportions having less than 9 years of schooling being 22.5% and 29.7%, respectively.

The problem is confounded by the observations of LeShan *et al.* (27) that a group of men who subsequently developed Hodgkin's disease in the army (presumably some of the same patients as in the Cohen series) had higher Army General Classification Test ("intelligence") scores than average for the army and that the Hodgkin's disease patients tended to come from occupations whose members scored highly on the AGCT. It remains to be seen which of the several closely related variables involved—socioeconomic status, duration of education, intelligence, and occupational class—is most closely related to Hodgkin's disease risk.

Occupation

Hodgkin's disease is not among the causes of death for which the Registrar General has published mortality ratios in detailed occupational groups. The 12 "socioeconomic groups" provide a somewhat finer breakdown than the "social classes," and data for these are shown in Table 6. The only group showing a mortality ratio disconsonant with that of its social class is the group of clerical workers, whose ratio of 134 is significantly higher than the ratio of 100 exhibited by social class III (semi-skilled workers) as a whole.

Uddströmer (43) reported no association with occupation among Swedish cases during 1915–31, but the available census data seem to have been not entirely satisfactory. I have been unable to locate any more detailed information on occupation and Hodgkin's disease. A case history study might be useful.

Familial Incidence

There have been numerous case reports of Hodgkin's disease in more than 1 member of a family and 2 systematic studies of familial incidence in series of cases (10, 37). Data are still inadequate, but it seems likely that the close relatives of patients with Hodgkin's disease do experience a risk of the disease that is

TABLE 4

STANDARD MORTALITY RATIOS (SMR's) BY SOCIAL CLASS; LYMPHOMAS AND LEUKEMIA; MALES AND MARRIED FEMALES, AGED 20–64, ENGLAND AND WALES, 1949–53[a]

POPULATION	SOCIAL CLASS[b]	HODGKIN'S DISEASE	LYMPHOSARCOMA AND RETICULOSARCOMA	MULTIPLE MYELOMA	LEUKEMIA
Males	I	*142*	*138*	*188*	123
	II	110	104	101	98
	III	100	103	104	104
	IV	93	*86*	92	93
	V	*87*	91	*76*	*89*
Married females	I	*174*	*182*	*190*	*145*
	II	95	111	90	92
	III	104	100	101	102
	IV	95	95	107	104
	V	*74*	*74*	75	*87*

[a] From the Registrar General's Decennial Supplement (38).
[b] Class I is high; Class V low.
Italicized SMR's differ significantly from 100 ($P < 0.05$).

TABLE 5

AVERAGE ANNUAL DEATH RATES FROM HODGKIN'S DISEASE PER MILLION POPULATION BY AGE AND SOCIAL CLASS, MALES AND MARRIED FEMALES, ENGLAND AND WALES, 1949–53[a]

SOCIAL CLASS[b]	MALES			MARRIED FEMALES		
	20–34 years	35–54 years	55+ years	20–34 years	35–54 years	55+ years
I	40.1	33.9	58.4	16.2	20.2	32.4
II	25.7	29.7	44.3	9.3	13.0	21.3
III	20.9	28.3	44.5	12.5	11.2	26.1
IV	17.2	26.4	37.7	12.7	11.1	18.5
V	19.5	26.0	36.1	7.6	8.8	15.3
Total	21.4	28.1	40.4	11.8	11.7	21.6
Ratio I/V	2.1	1.3	1.6	2.1	2.3	2.1

[a] Data from the Registrar General's Decennial Supplement (38).
[b] Class I is high; Class V low.

TABLE 6

STANDARD MORTALITY RATIOS (SMR's) BY SOCIOECONOMIC GROUP; LYMPHOMAS AND LEUKEMIA; MALES AGED 20–64, ENGLAND AND WALES, 1949–53[a]

Socioeconomic group	Corresponding social class[b]	Hodgkin's disease	Lymphosarcoma and reticulosarcoma	Multiple myeloma	Leukemia
Higher administrative, professional, etc.	I	*142*	*138*	*188*	123
Farmers	II	119	93	91	102
Other administrative, professional, etc.	II	109	100	100	101
Shopkeepers (owners)	II	112	117	114	92
Clerical workers	III	*134*	128	126	110
Shop assistants	III	96	94	83	83
Personal service	III	105	100	129	91
Foremen	III	81	84	95	110
Skilled workers	III	98	105	101	105
Agricultural workers	IV	88	*75*	115	100
Semi-skilled workers	IV	94	86	81	92
Unskilled workers	V	*87*	92	*76*	*88*

[a] Data from the Registrar General's Decennial Supplement (38).

[b] The correspondence is not complete.

Italicized SMR's differ significantly from 100 ($P < 0.05$).

significantly higher than that of the general population, though still small. On the basis of comparison with patients with other diseases (mostly neoplasms) seen at the same institution, Razis *et al.* suggest that the risk to close relatives is about 3 times that of the general population (37).

Two patterns are prominent in the reports—Hodgkin's disease in 2 siblings, and Hodgkin's disease in parent and child. Regarding the first pattern, some observations may be made—very cautiously in view of the number of cases involved. In the 2 systematic series referred to (10, 37), there are 7 sibships with 2 affected members, and 1 sibship with 3 affected, in which the authors regard all the cases as confirmed and in which the diagnosis is definite Hodgkin's disease and not some other lymphoma. First it is noteworthy that among these 17 affected individuals, 11 were between 20 and 35 years of age, and only 2 (aged 44 and 50) were over 40 years of age. In the total series of Razis *et al.*, 35% of cases were 40 or older. No particular pattern of concordance or discordance for sex is evident. Second, as noted by Razis, a number of the cases had onsets at similar times to their affected siblings. One can sometimes discern whether familial concentration results from genetic or environmental similarities by comparing cases within families according to (*a*) their age and (*b*) the chronologic time at onset. In a genetic disease with a definite age association, one expects affected siblings to develop the disease at similar ages (after allowing for chance fluctuations and assuming other factors determining age at onset to be the same), and one would not expect the chronologic time of onset to be similar except insofar as siblings tend to reach similar ages within a few years of each other. On the other hand, an environmental factor, particularly an infectious agent, producing familial concentration might produce onsets in similar periods regardless of the ages of the siblings. Thus, greater similarity in time of onset than in age at onset suggests an environmental interpretation; the reverse does not rule out environmental interpretation but implies that the responsible environment is a continuing one that is not limited to short time periods. DeVore and Doan (10) do not give date of onset in their cases. The 5 Razis sibships provide 7 comparisons of pairs (the sibship with 3 affected providing 3 "pairs"). In 6 of the comparisons, the interval between onsets is shorter than the difference between the ages at onset; in 1 the reverse is the case. The mean interval between onsets is 2.6 years, and the mean difference between ages, 7.9 years. The longest interval between onsets—7 years—occurred in the sibship with 3 affected and occurred between the 1st and last sibling to be affected. There are at least 2 jokers in this pack: (*a*) the small number of cases, and (*b*) the fact that cases with similar dates of onset may have been more completely ascertained in these surveys, in both of which ascertainment was probably quite incomplete.

The 2 series provide 12 pairs of parent-child combinations satisfying the same criteria as the sibling pairs. In 6 pairs the mother was affected, and in 6, the father. No relationship between sex of affected child and of parent is evident. The same method can be applied here as to the sibling pairs. In 5 of the 8 pairs reported by Razis, onset in parent and child was within 2 years and in 1 pair it was within 5 years, there being obviously a generation's difference in age within each of these pairs. Interestingly, or perhaps coincidentally, the parent was the 1st affected in all 6 pairs. In the 2 remaining pairs, the age at onset in the parent and child was similar and the dates of onset were a generation apart. In the 4 DeVore and Doan pairs, the ages at onset suggested that dates of onset were similar in 1 pair, a generation apart in 2 pairs, and in-between in 1. Thus out of 12 pairs, 7 had the similar date of onset that is incompatible with a genetic interpretation. It should be noted that the parent-child data are even more susceptible to artifacts resulting from incomplete ascertainment than were the sibling data, since ascertainment of parents recently affected is presumably much better than for parents who died a matter of 20 or 30 years ago. If this is the case, the risk to children of affected individuals must be considerably higher than we now suspect.

Perhaps too much is being made here of data that are inade-

quate in both quantity and quality. However, I believe that studies of familial incidence should have a high priority in further investigations into the etiology of this disease.

Razis *et al.* state that there are 2 pairs of twins concordant for Hodgkin's disease reported in the literature up to 1959, 1 of which is said to be "unconvincing." They add a 3rd pair—males, with onsets at 18 and 29 years of age—which are said to be dizygous. The basis for the diagnosis of zygosity is not given (37).

There are 3 published reports of husband and wife being affected. In 1 instance the 2 illnesses began within a few months of each other (10). In another, the illness in the wife began the year after the husband's death (32). In the 3rd instance, there was an interval of 9 years between death of the husband and onset in the wife, but this interval was broken by a 4.5-year course of Hodgkin's disease in their 18-year-old daughter (18).

Time

Shimkin showed that between 1923–27 and 1948–51 there was a substantial increase in mortality rates attributed to Hodgkin's disease in this country (40). Table 1 indicates that, at least in whites, the increase did not persist after 1950. Over-all, rates for whites of both sexes remained constant between 1949–52 and 1958–62. Two relatively minor changes may be noted in this later period: (*a*) continuation of the decline in the 0–14 age group, and (*b*) a 15% increase in the rates in the 15–34 age group. Regarding the fact that the 15–34 age group is the only group to show a continuing increase in rates, we may also note that between 1933–37 and 1949–52 this group experienced a relatively greater rate of increase than any of the other age groups. This is not true between 1923–27 and 1933–37, when the rate of increase was approximately the same in all age groups over 15 years of age.

For nonwhites, a different pattern is evident. Females show much the same trends as whites, except that rates for the 15–34 age group have not increased since 1949–52. However, rates for nonwhite males continued to increase after 1949–52, the increase affecting the age groups over 35, rather than the 15–34 group as in whites.

Mortality data for England and Wales (Table 2) are available more consistently and over a somewhat longer time period. They show the same decline in the 0–14 age group beginning in the 1930's that was seen in the United States. Otherwise, rates in all age groups have increased consistently through 1956–60. In Australia, on the other hand, mortality attributed to Hodgkin's disease increased only very slightly between 1920 and 1950 (24).

With the exception of the decline in rates for the 0–14 age group and the over-all increases in rates in all other age groups that have occurred over several decades in the United States and England and Wales, none of the trends observed in mortality data seem noteworthy, particularly when one considers possible changes in case fatality rates, diagnostic procedures, and other factors leading to misinterpretation of changes in mortality rates. Perhaps all that can be said with confidence is that Hodgkin's disease appears not to be decreasing in frequency. The increasing number of long survivals being reported for cases with onset in young adult life perhaps adds confidence to the suggestion that in the United States the disease may still be increasing slowly in the 15–34 age group.

Data from the Danish Cancer Registry allow an examination of recent trends in incidence rates. They are shown in Table 7. Increases are seen in the 15–34 and the 50 and over age groups. Since rates in the 35–49 age group have declined, the bimodality of the age curve has become more striking in Denmark, particularly among females.

Turning to another variety of time association, Cridland has reported a seasonal trend in onset of clinical Hodgkin's disease, with a peak in December and January (8). The data came from a very highly selected group of cases—106 of the 269 total cases seen at the institution in the study period—with lymphadenopathy limited to 1 peripheral site at onset and no deep involvement within 6 months of onset. Cridland considered the possibility that upper respiratory infections might draw attention to swollen cervical glands. However, only 10% of patients presented with upper respiratory infections, and these were not most prevalent in December and January. Seasonal variation in onset of symptoms has also been noted for leukemia (25) and a number of other cancers (26). In the latter conditions, the latent period between exposure to causal factors and onset of clinical disease is known to be several years in mean duration, and it seems likely that the seasonal variation relates to perception and diagnosis rather than to etiologic factors. The duration of the latent period in Hodgkin's disease is unknown, but this type of consideration, together with the highly selected nature of Cridland's series, makes the observation somewhat less challenging than it might first appear.

Place

The most striking geographic variations in frequency of Hodgkin's disease are seen in international comparisons. The patterns are striking not so much for the differences between countries in over-all mortality rates—a phenomenon that in this disease in particular is open to interpretation in terms of differ-

TABLE 7

AVERAGE ANNUAL INCIDENCE OF HODGKIN'S DISEASE PER MILLION POPULATION, DENMARK, 1943–57[a]

SEX	PERIOD	AGE (years)				ALL AGES
		<15	15–34	35–49	50+	
Male	1943–47	3.2	27.3	32.2	30.1	22.8
	1948–52	3.2	35.2	28.9	35.6	25.7
	1953–57	3.6	35.0	27.8	44.4	27.6
	1943–57	3.3	32.5	28.5	37.1	25.2
Female	1943–47	1.6	26.3	18.6	17.5	16.2
	1948–52	1.9	25.5	20.3	25.7	18.4
	1953–57	0.9	30.0	13.9	27.0	18.4
	1943–57	1.2	27.0	17.6	23.8	17.6

[a] Data from Clemmesen (3). Within each of the broad age groups shown, rates are standardized to the average distribution of the total Danish population, 1943–57.

ences in diagnostic practices and customs—but rather for the fact that the international picture varies according to the age group considered.

We have already noted that in Denmark the 2 modes in the age distribution have approximately equal prominence, whereas in the United States the 2nd mode is considerably larger than the 1st. A pattern very similar to that of Denmark is seen in the Netherlands, where the Hodgkin's disease rate under 40 years of age is 80% higher, but the rate over 40 is 30% lower, than in U. S. whites (29). Other countries having higher rates than the U. S. under 40 years of age and lower rates after that age include Great Britain, Norway, France, Italy, and Switzerland. The latter group resembles the United States, however, in having the 2nd mode substantially larger than the 1st.

On the other hand, in Japan, in those ages corresponding to the 1st mode in the United States and Europe the disease is very rare. The death rate does not rise above 3/million/annum until age 40 and yet, in the older age groups, death rates of 20/million are comparable to those in the Netherlands, Denmark, and other European countries (Chart 4).

It is possible to explain these patterns in terms of diagnostic customs, but the explanation would be complex and involve different types of diagnostic prejudices at different ages, as well as in different countries. The more parsimonious hypothesis would seem to be that international variation in the frequency of Hodgkin's disease in young adults does not parallel the variation in frequency in the middle aged and elderly. Certainly it would appear a sufficiently likely and important hypothesis to warrant further investigation.

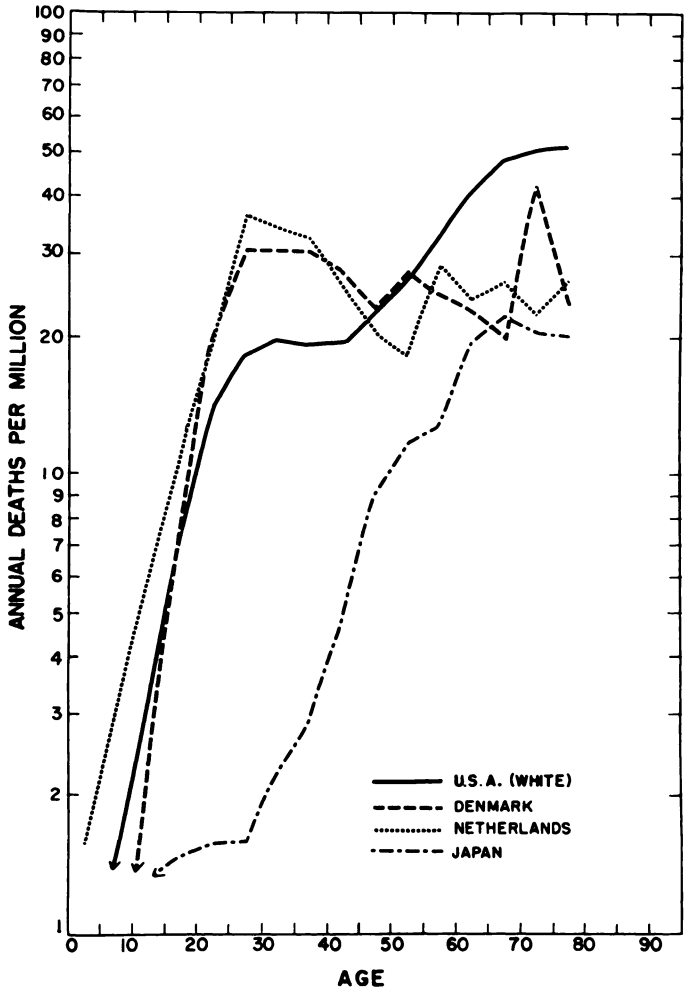

CHART 4. Age-specific death rates from Hodgkin's disease in 4 countries, 1950–53. (From MacMahon (29).)

TABLE 8

AVERAGE ANNUAL INCIDENCE OF HODGKIN'S DISEASE PER MILLION POPULATION BY PLACE OF RESIDENCE, DENMARK, 1943–57[a]

SEX	RESIDENCE	AGE (years)				ALL AGES
		<15	15–34	35–49	50+	
Male	Capital and suburbs	2.1	29.2	29.8	39.0	27.1
	Provincial towns	1.6	35.3	22.5	36.7	24.3
	Rural areas	4.9	32.8	31.0	37.3	26.3
Female	Capital and suburbs	0.5	28.8	17.8	29.4	19.3
	Provincial towns	2.1	25.1	17.2	20.9	16.5
	Rural areas	1.6	27.5	18.0	21.0	17.3

[a] Data from Clemmesen (3). Rates are standardized as in Table 7.

Geographic variation within the United States is less striking. Mortality data do show high rates in the Northeast and low rates in the South and the Mountain States (17). The range, in terms of standard mortality ratios, is from 82 in the West South Central States to 132 in New England (data from special tabulations prepared by the National Center for Health Statistics, unpublished). However, under the conditions of standard diagnosis pertaining among army personnel during the Second World War, the distribution by U. S. Census Divisions, either at birth or at time of induction, was similar for Hodgkin's disease patients and a sample of all inductees (7). The geographic variation in mortality rates in the U. S. may well, therefore, be a function of diagnostic and reporting practices.

A comparison of urban and rural residents, based on the Danish Cancer Registry data, is shown in Table 8. No remarkable differences are evident. Under age 15, the disease is more common in rural areas than in the capital; over 50 rates are higher in the capital for females but not for males. No difference between urban and rural rates was observed in Sweden by Uddströmer (43).

In Danish data for 1942–46, Clemmesen *et al.* noted that both Hodgkin's disease and myeloid leukemia showed a significant tendency to cluster by year in some districts (5). Although there has been considerable interest recently in the question of clustering in leukemia, the observation with respect to Hodgkin's disease appears not to have been followed up.

Hypotheses

The observations described prompt some hypotheses regarding the etiology of Hodgkin's disease. I acknowledge the speculative nature of the following discussion and justify it only with the hope that the hypotheses proposed may suggest potentially profitable avenues of investigation.

Heterogeneity of Hodgkin's Disease

The major hypothesis to be proposed is that what is now called Hodgkin's disease is a grouping of at least 3 entities which probably have quite distinct etiologies. Studies of the pathology of Hodgkin's disease and of the survival of affected persons also leave a clear impression of heterogeneity in the entity as now understood. The emphasis in this paper is on the epidemiologic evidence, but it is necessary to point out that the evidence for heterogeneity is not restricted to this field.

EPIDEMIOLOGIC EVIDENCE. The epidemiologic evidence distinguishes 3 subgroups of Hodgkin's disease on the basis of age at clinical onset. The 1st subgroup comprises cases with onset in childhood. The 2nd subgroup has a peak risk about 25–30 years of age; probably most patients between 15 and 34 belong to this subgroup. The 3rd subgroup has a peak risk in old age; probably most patients over 50 years of age belong to it. The group of patients with onset between 35 and 50 probably comprises a mixture of the 2nd and 3rd subgroups. The epidemiologic features of these 3 subgroups are summarized in Table 9. They differ sufficiently to make one suspect that they have different etiologies. Apart from the bimodality of the age curve itself, the differences in sex ratio and in international distribution are probably the most suggestive features.

PATHOLOGY. Hodgkin himself was hardly silent before others began explaining what he really meant. The process has continued, and with successive redefinitions the pathologic entity has become more homogeneous. However, it does not yet seem to have achieved such a degree of homogeneity as to warrant the belief that no further subdivisions or refinements are likely.

Pathologic accounts attest to the variation in nature and proportion of the cells observed in affected glands. The giant cells of Sternberg and Reed have for many years been accepted as the crucial diagnostic finding. When making a histologic classification of diseases of lymph glands, one obviously uses criteria that make sense to histologists, as apparently this particular criterion does. It is worth bearing in mind, however, that the usefulness of a histologic criterion will ultimately depend on its relevance to nonhistologic features—in particular, etiology and/or prognosis. To my knowledge, this relevance has not been demonstrated for the Reed-Sternberg cell or any of the other histologic features used to define Hodgkin's disease. One need not be overprotective, therefore, in defending the current pathologic boundaries of the disease.

Within its existing boundaries, the disease is also quite susceptible to pathologic redefinition and subdivision. In 1934, Gordon wrote, "When the three characteristic changes of fibrosis, giant cells, and eosinophils are all present, the evidence for lymphadenoma is complete. In practice, however, a considerable number of cases occur in which one or more of these three changes are lacking .... I suspect that there are a number of distinct conditions hitherto undifferentiated in this group of atypical cases" (16). Jackson and Parker's subdivision into paragranuloma, granuloma, and sarcoma is widely accepted and used (21). The subdivision appears to be meaningful in that the 2 small groups separated from the main body of cases—paragranuloma and sarcoma—do have nonhistologic characteristics, i.e., survival and age distribution, that make their differentiation useful. However, in any representative series, the great majority of cases (commonly 80 to 90%) fall into the granuloma category, which limits the usefulness of the classification for survival and etiologic studies. Recently, Lukes has offered a 6-stage classification that shows association with clinical characteristics and with prognosis (28). My purpose is not to evaluate or compare histologic classifications, but only to point out that the concept

TABLE 9

EPIDEMIOLOGIC FEATURES OF 3 SUBGROUPS OF HODGKIN'S DISEASE PATIENTS

VARIABLE	SUBGROUPS, DISTINGUISHED BY AGE AT CLINICAL ONSET		
	0–14 years	15–34 years	50 years and over
Peak age of onset	?	25–29	65–74
Sex ratio (% male)	85%	54%	63%
Race (U. S. A.)	?	Negro rates approximately 75% of white rates	Negro rates approximately 75% of white rates
Religion (New York City)	?	No association	Jews higher than Catholics or Protestants (approximately × 2)
Socioeconomic status (U.K., U.S.A.)	?	Associated with high socioeconomic status (approximately × 2)	Associated with high socioeconomic status (approximately × 2)
Secular trend (U.S.A.)			
Last 40 years	Decline (65%)	Increase (140%)	Increase (110%)
Last 15 years	Decline (20%)	Slight increase (15%)	Constant
Urban:Rural (Denmark)	Rural higher than urban rates	No difference	No difference for males; urban higher for females (?)
International comparison	Reported very high in some areas (e.g., Peru)	More common in Netherlands (× 1.8) Denmark (× 1.5) and 7 other reporting countries than in U.S.; almost absent in Japan	More common in U.S. than any other country reporting mortality; as common in Japan as in some European countries
Familial concentration	?	Small but definite	?

of heterogeneity of Hodgkin's disease is prevalent among pathologists.

SURVIVAL. A decade or so ago, people began to write about "benign Hodgkin's disease" (19) and, more recently, about its cure (13). Certainly there is a definite though small number of cases with survivals of 15 and 20 years after diagnosis. Easson and Russell (13) present a large series of cases of Hodgkin's disease in which, among the clinically localized cases receiving "full radical treatment," the mortality 10 years and more after diagnosis was no larger than that of the general population and in which none of the 10-year survivors showed evidence of disease. Easson and Russell estimate that 40% of clinically localized cases may be curable in this sense, and since the clinically localized cases constituted a third of their total series, we may suppose that this represents about 10–15% of the cases seen at a large institution such as the Christie Hospital. These cases are in striking contrast to the rapidly fatal form in which the disease can present.

However, the wide variation between individual cases in survival in Hodgkin's disease is not the most pertinent feature in the present context—it is seen in many, if not most, diseases that are regarded as etiologic and pathologic entities. What is remarkable in Hodgkin's disease is the extent to which mean duration of survival varies according to age and sex. This variation has already been referred to. Its extent varies from study to study, but generally speaking, persons over 50 years of age have 5-year survival percentages less than half those of younger patients, and the influence of sex is almost as striking (1). At least 2 authors (22, 34) have reported that the sex difference is more striking in young adults; I have been unable to determine from published material whether the sex difference is restricted to young adults or whether it is also evident in cases with onset over 50 years of age. Data presented by Dr. Easson at this meeting suggest that it may indeed be restricted to cases in the young adult age groups. Associations of survival with other demographic variables that are related to incidence have not been examined, so far as I have been able to determine.

It seems fairly clear that the epidemiologic subdivision of Hodgkin's disease, based on age, is meaningful in terms of survival. It has already been noted that age-corrected survival rates are much better for young adults than for persons over 50 and that the sex difference in survival is particularly marked in the young adult group. The hypothesis of the existence of 3 diseases of different etiologies would be greatly strengthened if it were possible to show pathologic differences in the disease in the different age groups. There is certainly one such observation—that the sarcoma in the Jackson and Parker classification occurs almost exclusively in patients over the age of 40 (21). However, as noted, this classification distinguishes only a small proportion of the total cases of Hodgkin's disease. There seems to have been no attempt to associate finer characteristics of the pathologic picture with age. From the point of view of further examination and development of this hypothesis, this seems to be one of the most urgent needs.

Malignant Neoplasm or Malignant Inflammation?

In spite of the increasing proportion of Hodgkin's disease patients that have long periods of survival after diagnosis, there is no doubt that the disease is still, by and large, a malignant one. Whether this malignancy is of a neoplastic or an inflammatory nature is still an open question. The arguments in favor of inflammation have included: (*a*) The pathologic picture in cases of granuloma and paragranuloma is that of an inflammation, not a neoplasm; (*b*) The clinical features, particularly the frequency of pyrexia, are suggestive of inflammation; (*c*) The similarity in time of onset of familial cases suggests infection. The possible artifact in the data on this point has been noted.

The arguments in favor of neoplasm have included: (*a*) Pathologic findings that are frankly neoplastic (sarcoma) may occur simultaneously with or subsequently to granuloma and paragranuloma in the same gland, or in other glands in the same patient; (b) The disease has been thought to be inevitably fatal. (As noted, the disease is not now considered inevitably fatal, and even if it were, this is neither a necessary nor sufficient criterion of malignant neoplasia when treated.); (*c*) The disease progresses from site to site within the body. (This characteristic, while suggestive, is also not limited to neoplastic diseases.); (*d*) In spite of considerable effort, no causal infectious agent has been identified (23).

We note that the most crucial criterion of neoplasia—the 1st—applies only to cases corresponding to the 2nd mode of the age risk curve, and also that it is only in this group that the criterion of inevitable fatality, if it is applicable at all, can be applied. Cases in the 15–34 age group have none of the characteristics that are suggestive of neoplasm, and yet they do have the characteristics suggestive of inflammation.

A 2nd hypothesis is therefore generated—the Hodgkin's disease that occurs in young adults is an inflammatory granuloma; that which occurs in older persons is a neoplasm. The hypothesis states that the 2 diseases are quite distinct—a patient has 1 or the other from the beginning and runs the course appropriate to his particular disease—and not that the inflammatory granuloma becomes neoplastic with the passage of time, as has been suggested as an alternative hypothesis to reconcile infectious and neoplastic characteristics. This hypothesis has implications for treatment, of course, as well as to the search for a more specific etiology.

Specific Etiology

I have carried my speculations far enough without offering hypotheses about specific etiology. I would like, however, to summarize the features of the 3 hypothesized diseases that seem most pertinent to the search for specific etiology.

1. THE CHILDHOOD DISEASE. There is no mode in the age risk curve of Hodgkin's disease in childhood such as is seen for leukemia. I am not sufficiently familiar with the pathology and pathologic history of this disease to know whether its declining frequency results from increasing rigidity of criteria for diagnosis as Hodgkin's disease, and whether the reported very high relative frequency of the disease in this age group in South America and other areas results from similar factors. Pathologic definition of the disease would seem to be an important first step. The very high sex ratio (85% male) is noteworthy.

2. THE DISEASE IN YOUNG ADULTS. Here we are looking for causative agents of a disease that is probably infectious in nature, though of very low infectivity (as judged from the familial data),

has a peak incidence between 25 and 30 years of age, has almost equal incidence in the 2 sexes although much more favorable survival for females than for males, is associated with high socioeconomic status, and is substantially more common in the Netherlands and Denmark than in other European countries and the United States, though virtually nonexistent in Japan.

3. THE DISEASE IN THE ELDERLY. This disease shows many of the epidemiologic features of lymphosarcoma and chronic lymphatic leukemia—increasing incidence with age after about age 40, male-to-female ratio of approximately 2:1, high rates in the United States, association with high socioeconomic status, and high rates in the Jewish population of the United States. It is probably a neoplasm, and its etiology is probably similar to that of other members of the lymphoma group.

Testing the Hypotheses

Short of actual identification of specific infectious or carcinogenic agents, I am unable to propose any single test that would allow acceptance or rejection of the hypotheses discussed above. However, the sum of information from the following studies might provide the basis for convincing arguments either as to the homogeneity or heterogeneity of Hodgkin's disease, or as to the infectious nature of some or all of the present entity:

1. A comparison of the detailed histologic features of Hodgkin's disease in young adults and in the elderly.
2. A comparison of the immunologic characteristics of young and elderly patients with Hodgkin's disease.
3. A survey of Hodgkin's disease in selected countries (e.g., Netherlands, Denmark, U.S.A., Japan) to determine whether the patterns observed in mortality data are evident in pathologically verified material. Pathologic examination of other lymphomas and other conditions with which Hodgkin's disease may be confused would be necessary.
4. Studies of the familial concentration of Hodgkin's disease and of the time relationships within families showing multiple cases.
5. Studies of clustering of Hodgkin's disease in time or place.
6. Continued search for an infectious agent, particularly in material from young adult patients.

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