Is Hodgkin’s Disease Infectious?¹

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Summary

All available epidemiological evidence suggests that Hodgkin’s disease is an environmental disease. Recently, several groupings of Hodgkin’s disease have been described in which cases were linked to other cases, either directly or through a single healthy intermediary. The characteristics of these groupings and those of the epidemic curve in Albany County, N. Y., suggest that Hodgkin’s disease may be infectious under certain circumstances. This possibility is further supported by the observation that prior tonsillectomy might be a predisposing factor to the development of this disease. Although all of the features of Hodgkin’s disease are consistent with an infectious etiology, objective epidemiological studies with new methodological approaches will be required to evaluate this hypothesis further.

It is not easy to discuss the question of infectivity in a disease for which there is no known cause. In this circumstance, one must rely on the epidemiological observations which suggest that a disease may be infectious. While epidemiological studies alone can never determine the specific etiology of a disease, they can often indicate whether its characteristics are consistent with those of an environmental agent (22). Through analysis of international comparisons, clustering in time and space, migration studies, familial aggregation, and such variables as age, sex, race, and socioeconomic status, the epidemiologist can frequently make deductions concerning various aspects of a disease. Thus, by careful consideration of time, place, and person factors, Medin noted the epidemic character of poliomyelitis in 1887 and, in 1905, before the infective nature of this disease had been demonstrated by transmission to monkeys, epidemiological evidence was presented to incriminate schools in its dissemination (52). It was also deduced that a carrier state must exist to explain satisfactorily the mode of spread of this apparent infectious process (65).

Before discussing the question, “Is Hodgkin’s disease infectious?” it would perhaps be best to review the evidence suggesting that it is an environmental disease.

Is Hodgkin’s Disease an Environmental Disease?

Marked differences in the frequency of Hodgkin’s disease have been observed in different populations. Thus MacMahon (42) showed that the heights of the 1st mode (early adult peak) of Hodgkin’s disease vary greatly in different countries, being particularly pronounced in The Netherlands and Denmark. In Japan, however, this early age peak is absent (42) whereas, in such diverse countries as Peru (57) and Lebanon (4), it predominates. While geographical differences can be observed in environmental or genetic diseases and combinations of the two, analysis of these differences over time can provide information on possible interactions between man and his environment. MacMahon (42) showed that between 1943 and 1957, the incidence of Hodgkin’s disease among Danish males under the age of 49 years was higher in the rural counties than in the capital and suburban areas. Fasal et al. (27) found that mortality and incidence rates for this disease were higher at younger ages among California male farm and Norwegian male rural residents. Similar observations have been made by Dörken et al. (23) in Northern Germany. Other studies suggest that socioeconomic factors play an important role in Hodgkin’s disease. In the United States, the disease is associated with a high socioeconomic status for patients 15 years of age or more. However, little is known about the importance of this variable in younger age groups in this country (42). Cohen et al. (17) also found that among white male American soldiers during World War II, patients with Hodgkin’s disease were better educated and of higher economic class than matched controls. Other reports suggest that there is a high frequency of this disease among male children in poor areas (4, 18, 57). Using incidence data from various countries, Correa and O’Conor (19) carry these observations a step further, for they have identified 3 epidemiological patterns for Hodgkin’s disease and related each pattern to the economic stratification of the communities studied. One pattern, characterized by high incidence and mortality rates in male children, low incidence in the 3rd decade of life, and a 2nd peak of high incidence in the older age groups, seems to occur in developing countries. Another pattern characterized by very low rates in children and a high young adult peak is prevalent in urbanized countries. The 3rd pattern is intermediate in type and is found in rural areas of developed countries. The obvious implication of this study is that the marked international differences in the frequency of Hodgkin’s disease, as well as urban-rural and socioeconomic factors, might be explained by different interactions between environment and host.

As mentioned previously, place variations in the rates of Hodgkin’s disease do not prove that the disease is environmental. However, when found in an area with a relatively homogeneous population, such variations strongly suggest an environmental etiology. Thus, a crucial question concerning the above observations is whether the epidemio-

¹ Presented at the International Symposium on Human Tumors Associated with Herpesviruses, March 26 to 28, 1973, Bethesda, Md. Supported in part by Grant CA 13893 from the National Cancer Institute, NIH.
logical patterns observed are fixed or dynamic; that is, can a shift in type occur temporally with increased urbanization of a given area? A partial answer may be provided by previous studies which show variations in mortality rates for different regions of the United States. Cole et al. (16) reported that mortality rates from Hodgkin's disease in young adults from 11 contiguous southern states were significantly lower than those recorded in the north. This observation was true for both the 1949 to 1954 and 1959 to 1961 periods. What is more intriguing is the suggestion that, during these 2 periods, a shift in mortality pattern occurred in the Mountain States from one of uniformly low rates for both the 15 to 34 and the 45 years-and-greater age groups, to the Southern pattern characterized by rates in the older age group approximate to the national average and rates in the young adult age group below the national average. Unfortunately, this important study was not designed to consider other factors pertinent to the above question, such as childhood mortality rates and urbanization. With respect to childhood Hodgkin's disease, Fraumeni and Li (28) reported higher mortality rates in the southern United States than in the North during the period 1960 to 1964, especially for males. Although entirely speculative, considering the partial overlap in the time period studied by Fraumeni and Li (28) and Cole and McMahon (16), it is possible that during the early 1960's the southern United States had a pattern characterized by high mortality rates in children, especially males, low rates in the 3rd decade of life, and a 2nd peak in the older age group. This pattern would correspond to the pattern described by Correa and O'Connor (29) for developing areas and would be consistent with the economic growth trend in this part of the United States. Shimkin's study (55) also suggests the possibility of a shift in pattern for Hodgkin's disease related to increasing urbanization. Between 1921 and 1951, mortality rates rose in the United States from 6.9 to 17.0/million population. Furthermore, the mean age at death from Hodgkin's disease increased by 3.5 years between 1925 and 1950. This increase in mean age was associated with a decline in mortality rates in the 0 to 4 and 5 to 14 age groups and a progressive increase in rates for all older age groups, the rise being close to 2-fold for each of these age groups. Clearly, there is a need for studies that attempt to relate age-specific incidence rates of Hodgkin's disease in a well-defined area to changes in urbanization and economic growth, sex ratio, urban-rural differences, and histological subtype over long periods of time.

Other epidemiological studies provide additional indirect evidence suggesting that Hodgkin's disease is an environmental disease. Modan et al. (46) studied the mean annual incidence of the various lymphomas for different Israeli migrant populations, and no ethnic differences were found in the incidence of Hodgkin's disease. The Japanese migrant studies of Haenszel et al. (32) showed that the standard mortality rates for Issei males and females were more closely aligned to United States white than to Japanese. Furthermore, no differences in mortality rates were found in Japanese and Caucasians living in Hawaii (7). Macklin (40) analyzed cases of various tumors in twins and found that tumors affect both members of a monozygous twin pair more frequently than do dizygous twin pairs, the age of onset of the tumors being more nearly identical in monozygous than in dizygous twins. However, his study and review of the literature revealed no instance in which both members of a monozygous twin pair had Hodgkin's disease, and only 1 example of the disease affecting 1 monozygous twin. Peyron and Kobozieff (49) collected 98 pairs of twins with various tumors. In 23 pairs of monozygous twins, only 1 member of a twin pair had a tumor, and there were no cases of Hodgkin's disease. Charache (12) presented 2 additional monozygous twin pairs with only 1 affected member. Finally, in the only 2 systematic studies of familial Hodgkin's disease (21, 51), there was a greater similarity in the time of onset than in age at onset. This suggests that environmental similarities between familial cases are more important than genetic factors. It would seem, therefore, that the evidence derived from a variety of different epidemiological studies indicates that Hodgkin's disease is an environmental disease.

Is Hodgkin's Disease an Infectious Disease?

From an epidemiological viewpoint, the only evidence that would suggest that a disease that is environmental is also infectious is the demonstration of apparent person-to-person transmission. Recent epidemiological studies in various communities of upstate New York have suggested that horizontal transmission may occur with Hodgkin's disease (62, 64). To date, 4 distinct groupings of Hodgkin's disease have been reported (39, 62). It is important to realize that none of these studies represents statistical attempts to establish space-time clustering. The peculiar feature about all of the groupings is that each case was linked to at least 1 other case, either directly or indirectly, through a single contact. In all instances the contacts remained in good health but their associates (friends, classmates, or relatives) subsequently developed Hodgkin's disease. Considering only the 49 Hodgkin's disease cases in the reported groupings, there were 27 males and 22 females, all Caucasian and ranging in age from 14 to 74 years. Thirty-eight of the 49 cases were under the age of 40 years. With the singular exception of the group reported by Klinger and Minton (39), all others had linked patients over the age of 40 years. Furthermore, in the Albany grouping, all histological subtypes of Hodgkin's disease were present, and no statistically significant difference was observed when the age of patients was tabulated according to the 4 Rye Conference subtypes. There were 18 instances of case-to-case links. While these undoubtedly represent the strongest associations, all cases were linked through well-established relationships. This is perhaps best illustrated by the fact that in the Albany grouping, of the 15 cases outside the school system, 9 lived in the same house with a school-aged contact. Furthermore, in the Albany grouping, all histological subtypes of Hodgkin's disease were present, and no statistically significant difference was observed when the age of patients was tabulated according to the 4 Rye Conference subtypes. There were 18 instances of case-to-case links. While these undoubtedly represent the strongest associations, all cases were linked through well-established relationships. This is perhaps best illustrated by the fact that in the Albany grouping, of the 15 cases outside the school system, 9 lived in the same house with a school-aged contact who had a specific relationship to one or more school-based cases. These observations suggested that Hodgkin's disease is transmissible directly or indirectly through some carrier.

In addition to the linkage characteristics mentioned, all of the Hodgkin's disease groupings have other similarities. Thus they were all school based, 3 in high schools and one in a medical college. A feature peculiar to all of the groups is
that, initially, they centered around a core or clique of students, all of whom knew each other before any member developed Hodgkin’s disease. During a certain period of time they were either directly or indirectly exposed to patients with this disease, and in the years that followed the disease was diagnosed in some of these students, their friends and relatives, as well as the friends and relatives of clique students without Hodgkin’s disease. Thus in the Albany grouping, Hodgkin’s disease was introduced into a well-defined clique of students repetitively from 1948 through 1953. From 1952 through 1968 the disease was diagnosed in various members of this clique, and between 1955 and 1971 some of their relatives and friends became ill. In the downstate New York grouping (62), there were no cases of Hodgkin’s disease in persons under 30 years of age, among the residents of a small town, from 1960 through 1962. However, in 1963 the disease was apparently introduced into a high school by an English teacher, and during the years that followed, several students developed the disease. All of the student-aged cases from that high school, in fact from the whole community, that were diagnosed between 1963 and 1971, had several things in common. They were all close friends before and during the time the teacher entered the school; they all attended the same high school but were not in the same classes; and they all had tutorial contact with this teacher. Other characteristics which all the reported groupings had in common were apparent transmission from young to young and old, but rarely from old to young, and a time interval of years between diagnoses of most linked cases. This latter observation suggests that if Hodgkin’s disease is an infectious disease, it may have an incubation period of several years.

The fact that all of the Hodgkin’s disease groupings have so many similar characteristics strongly suggests that what has been observed is not a fluke but a phenomenon. However, it remains to be determined whether the linkage patterns observed are indicative of the manner in which Hodgkin’s disease is transmitted at the community level, or of a sociological phenomenon unrelated to the disease. Unfortunately, there are at present no sociological studies that are directly applicable to this specific question. Nevertheless, the difficulty in establishing linkage patterns similar to those described for Hodgkin’s disease has been well-established by sociological studies referred to as “small world” studies (61). These investigations suggest that an average of 5 intermediary people are required to interlink 2 randomly selected individuals from a given population.

In the Albany study (62), 2 control groups (hospitalized burn patients and a student control group) were selected for an examination of the question of interpersonal linkages. Although neither control group was ideal, since the clique of students was itself formed on the basis of interpersonal contact (35), some valuable information was obtained from both. The inability to link burn patients, even through an intermediary, despite the fact that burn injuries requiring hospitalization are at least 10 times as common as new cases of Hodgkin’s disease, indicates the great difficulty in linking patients, especially with a disease that is not infectious. Furthermore, the complete inability to link student controls, who attended the same high school during the same period as the clique, to any Hodgkin’s disease case suggests that what occurred was specifically related to this clique.

Another important question is whether the linking of the 34 lymphoma cases was possible only because they occurred during periods of high incidence in Albany. This seems unlikely for several reasons: (a) the inability to link burn cases, which in any given year are much more common than Hodgkin’s disease cases; (b) in the upstate and downstate groups (62), linkages were established similar to those in Albany, but there was no increased incidence of Hodgkin’s disease in the counties in which these events occurred. This observation suggests that Hodgkin’s disease cases can be linked in settings other than epidemic ones; and (c) in Albany County, only 12 of the 34 linked cases were diagnosed from 1953 through 1959, the period when the average incidence in Albany County was significantly higher than in the rest of upstate New York. Most of the additional cases were diagnosed in later years. Furthermore, during the period 1963 to 1969, when the average incidence in Albany County was lower than in the rest of upstate New York, 6 interlinked cases were diagnosed, and in 1970, when the county rate for Hodgkin’s disease was around 2.5/100,000/annum (well below the average annual incidence rate of 3.7/100,000/annum for Albany County from 1950 through 1970), 6 additional interlinked cases were diagnosed.

What additional evidence is there to suggest that Hodgkin’s disease might be infectious? The evidence for transmissibility would clearly be strengthened if one could follow the subsequent time-place associations of individuals (case or contact) involved in 1 of the groups studied and find that they were associated with other Hodgkin’s disease groups, all possessing similar characteristics to those described. While such intensive investigation has not been conducted for all the cases and contacts in the 3 upstate New York Hodgkin’s disease groups as yet, other groups, smaller in size but with similar features, have been discovered. Thus, in Albany, there are at least 4 well-defined situations in which a member of the clique (case or contact), upon graduating from high school, left the county and attended college or worked in another area of New York State. In all 4 instances, prolonged interpersonal contact could be established between these individuals and others who subsequently developed Hodgkin’s disease.

Examination of the incidence curve of Hodgkin’s disease in Albany County, N. Y., provides additional evidence suggesting infectivity. Two approaches were taken: analysis of the annual incidence rate on the basis of year of diagnosis within the county from 1950 through 1970; and comparison of the annual incidence rates on the basis of year of diagnosis Cancer Bureau, with the rest of upstate New York. Both approaches suggested that there was an apparent epidemic curve for Hodgkin’s disease in Albany County from 1953 through 1959. If the events that occurred in Albany County during the period 1948 to 1953 paralleled those for the Albany Hodgkin’s disease clique, a possible explanation for this curve is available. During this 6-year period, various members of the clique had repetitive contact with at least 4 patients with the disease. It could therefore be hypothesized that an apparent epidemic occurred in Albany County over the subsequent years because of many sources of infection.
Nicholas J. Vianna

and obviously large numbers of susceptible individuals. This interpretation must be considered as conjectural, since the cases in the Albany group represent only a small portion of the 208 cases diagnosed in the county during the study period. However, if true, it does provide a plausible explanation for the event that followed, namely a significantly lower case rate in the county during the period 1963 to 1969, when compared with the rates for either the county or the rest of upstate New York during the period 1953 through 1959. The observation that the epidemic period was followed by one in which there was a marked reduction in the number of susceptibles (community immunity) and the fact that an age shift occurred from a younger to an older age group, are suggestive of characteristics frequently encountered in community outbreaks due to certain viral agents.

Finally, the proposition that the risk of developing Hodgkin’s disease is 2.9 times higher among individuals up to the age of 40 years who had tonsillectomies than among those who did not, is certainly compatible with an infectious etiology (64). The major criticism of this study was that no information was provided on the socioeconomic comparability of cases and controls in the preliminary report (53). This is an unlikely explanation for the differences observed between cases and controls, since the 2 groups did not differ significantly with respect to educational level and occupation. A recent report by Johnson and Johnson (38) presents data that the authors interpret as not supporting the tonsillectomy hypothesis. However, reevaluation of the data presented, either by analyzing all subjects (Hodgkin’s disease cases and all their siblings), or through matched-pair analysis, indicates that there is a relative risk of 2.1 (P. Cole, personal communication; Ref. 50) that is consistent with the previously reported relative risk (64).

If the tonsillar hypothesis is substantiated further, it will provide strong supportive evidence for the viral hypothesis in Hodgkin’s disease. However, the question of the compatibility of this hypothesis with certain well-established characteristics of the disease can be partially answered now. The most common site of early detection of Hodgkin’s disease, the lower cervical nodes (56), is the region of lymph nodes that drain the pharyngeal tonsils. Furthermore, the average survival figure for Hodgkin’s disease is around 3 years (26), and there occurs a sharp increase in the mortality rate around the 11th year of age (45). These observations suggest that there is an upturn in the incidence of the disease around the 8th or 9th years of age, the time at which the lymphatic system begins to undergo physiological regression (45).

Another fact consistent with a possible association between prior tonsillectomy and Hodgkin’s disease is that, in the United States, both the operative procedure (66) and the disease (42) are more prevalent among higher socioeconomic groups. Two additional points worthy of note are the rarity with which Hodgkin’s disease involves the pharyngeal tonsils (2, 8, 36) and the fact that, prior to involuting, the tonsils are immunologically competent (31), acting as a barrier to the entry of various viruses (48). It seems reasonable, therefore, that a similar defense mechanism may be involved with Hodgkin’s disease. Finally, it is important to realize that the tonsillectomy hypothesis represents an attempt to evaluate the possible role of lymphatic tissue involvation in the pathogenesis of Hodgkin’s disease. Clearly, not everyone who develops the disease has had a tonsillectomy, nor is the opposite true. However, physiological lymphatic regression is a process that begins around the 8th year of life and levels off around the age of 45 years. The fact that these periods correspond well with the onsets of each mode of the characteristic age-specific incidence curve of Hodgkin’s disease (42) is potentially a matter of great importance.

Hodgkin’s Disease as an Infectious Disease

There has been a great deal of controversy concerning the nature of Hodgkin’s disease. Is it infective in origin, neoplastic, or more than 2 distinct entities, as has been suggested (42)? Unfortunately, there are no answers to these questions. However, a pertinent question at our present level of knowledge is whether the descriptive epidemiological characteristics of Hodgkin’s disease are compatible with an infective origin. While an exercise of this type invites much speculation, it can also serve to sharpen our views on certain critical features of this disease. Furthermore, it might provide the epidemiologist and laboratory investigator with new approaches to the question of etiology.

Perhaps the first thing to consider is that the incidence (all ages) within most countries varies only slightly from one time period to another (22). There also appears to be a relatively even geographical distribution of Hodgkin’s disease cases (all ages) in most countries (6, 13, 23, 42, 61). Thus, if Hodgkin’s disease is an infectious disease, its most prevalent pattern must be an endemic one. In attempting to establish whether an endemic disease can, under certain conditions become epidemic, one must first consider the background frequency of that disease. Clearly, if the disease is capable of reaching pandemic levels, as do certain strains of influenza, it may be sufficient to examine national rates. However, when dealing with a very rare disease, such as Hodgkin’s disease, one is obliged to study smaller areas (although sufficiently populated so that one might expect a certain number of cases to occur per year) over a prolonged period of time. This is especially true if there is evidence to suggest a long incubation period for that disease. Unfortunately, this has been attempted rarely, and the only evidence to suggest that Hodgkin’s disease may assume epidemic proportions at the community level comes from the Albany study (62).

Although there are many references in the literature to apparent case-to-case spread (21, 29, 44, 54, 61), neighborhood cases (24), and time-space clusters (6, 15, 30), it is apparent that even at the community level, case-to-case contact cannot be established for all cases diagnosed over a prescribed period (62). No relationship to any disease in household pets or domesticated animals has been found (33), and it seems uncertain whether any closely comparable disease in such animals has been identified (20). Furthermore, since Hodgkin’s disease is essentially worldwide in distribution, it seems unlikely that ecological factors, known to affect mosquito and wildlife populations, play an important role. If then Hodgkin’s disease has a reservoir that is...
Is Hodgkin’s Disease Infectious?

entirely human, as the available evidence suggests, one must hypothesize a carrier state to explain both the preponderantly endemic pattern for the disease and the inability to establish case-to-case linkages in most instances. If a carrier state does not exist, for a disease in which man is the only reservoir, one would reasonably expect that the disease would cease to occur in a community and would remain absent until a fresh case is imported from the outside. This is extremely unlikely, considering the rarity of Hodgkin’s disease. Thus, if Hodgkin’s disease is an infectious disease, it is probably an endemic disease with a carrier state, that can become epidemic at the community level under certain circumstances.

One of the most distinctive features of Hodgkin’s disease is the bimodality of its age-specific incidence curve in most countries (6, 23, 41, 43). Changes in the incidence of a disease with age are frequently encountered in many infectious diseases. However, an observation that provides a possible clue to the interpretation of at least 2 age groups (0 to 14 years and 15 to 34 years) in the Hodgkin’s disease age-specific incidence curve is that, with increasing urbanization and economic growth, rates decline for children but increase for young adults (19). This concept may be crucial to our understanding of how age relates to the development of Hodgkin’s disease, for when an infectious disease is endemic in a community, its age incidence will be largely determined by the degree of immunity conferred by an attack. Furthermore, endemic diseases often show a high preponderance of infections in childhood (10). Thus, a possible explanation for the high incidence of childhood Hodgkin’s disease in developing countries is that overcrowding, associated with poorer areas, increases the proportion of children who contract the infection. Conversely, with subsequent economic development, crowding ceases to be a factor, children are less likely to be exposed, and the disease occurs primarily in young adults. Crowding exerts other effects on many infectious diseases (59). In addition to its effect on incidence, crowding introduces a factor of closeness which can increase the frequency, duration, and dosage of infection, all of which result in a greater severity and mortality due to the disease. It would seem reasonable then to expect children in developing countries to have more unfavorable histological subtypes of Hodgkin’s disease, compared with children from urbanized areas who have this disease. This appears to be true, as exemplified by a comparison of the histological subtypes usually found in children (15 years of age or less) in the United States (5, 58) with those from underdeveloped countries (9, 19, 57). It should be mentioned, however, that crowded living conditions are particularly common in lower social classes, and therefore the role of other factors, such as poor nutrition in childhood, cannot be excluded.

In considering the adult peak of Hodgkin’s disease, it is important to realize that none of the patterns presented by Correa and O’Conor (19) shows a dissociation between the occurrence of childhood, young adult, and adult Hodgkin’s disease. That is, where the incidence of either childhood or young adult disease is high or intermediate, so follows the adult peak. These authors further suggest that a pattern exists that is characterized by uniformly low rates for all ages. Perhaps the only country in which an age dissociation has been observed is Japan, where only an adult peak is present (42). However, there appear to be many as yet unexplained peculiarities about the whole lymphoma pattern in this country (3). Thus, Hodgkin’s disease is about 3 times as prevalent as reticulum cell sarcoma in the United States and Great Britain. In Japan, the latter is the most common lymphoma. Furthermore, certain histological characteristics of Hodgkin’s disease are unusual in Japan, as is the marked eosinophilia associated with the other lymphomas in this country. Finally, contrary to the experience in the United States and other Western countries, in Japan Hodgkin’s disease is associated with an estimated clinical course of approximately 1 year, and reticulum cell sarcoma is not associated with the shortest survival. All of these discrepancies make it difficult to interpret the lymphoma pattern in Japan and to relate it to patterns in other countries. It is possible that there are genetically or environmentally governed variations in host reactivity and that in Japan this becomes manifest by a merging of the histology of Hodgkin’s disease with that of reticulum cell sarcoma (3). It is equally possible that Hodgkin’s disease in this country represents a separate entity, different in etiology from the disease in younger age groups.

Another important epidemiological feature of Hodgkin’s disease is that the sex ratio in younger patients (15 to 34 age group) is about 1:1, in contrast to almost 2:1 for the 50 and over age group (42). This appears to be a fairly constant characteristic in most countries although, in Norway, a male preponderance is observed throughout the bimodal age curve (6). The greatest difference in sex ratio however, is found when the 0 to 9 age group (3:1) is compared with the 15 to 34 age group (42). We have, therefore, a situation in which at least 2 and probably 3 changes in sex ratio occur. Interpretation of sex differences in the incidence of infectious diseases is always fraught with uncertainty, but if a disease shows a marked excess of incidence in 1 sex during the early years of life, this may well result in a higher level of immunity in that sex at older ages, which in turn will affect the sex distribution of infection in the older ages. This concept appears to provide a plausible explanation for the change in sex ratio observed between those aged 0 to 9 and the young adult age groups of Hodgkin’s disease. It is exceedingly more difficult to explain the difference in sex ratio between the young adult and older age groups. One may be tempted to explain this difference on the basis of either different etiologies or some process that occurs in the older age group. One must realize however that, considering the overall incidence of Hodgkin’s disease (all ages) and the male excess in both the very young and the old, this is primarily a disease of males. It seems more reasonable then to ask not why is there a male excess in the 50 years and older age group, but why isn’t this excess manifest in the 15 to 34 age group? One possible reason is an extension of the explanation given for the change in sex ratio observed between the childhood and young adult age groups. Thus, it is conceivable that the relatively greater young adult male immunity is not permanent. Another possibility is that the rate of physiological lymphoid involution in the female lags behind that of the male, and is therefore capable of a greater
degree of response to the initial Hodgkin's stimulus. Lymphoid stimulation of some type appears to be a prerequisite for the development of Hodgkin's disease and other lymphomas (25). In normal persons there are marked variations in lymphocyte reactivity which are not specifically age related (11). In general, however, lymphocyte and lymphoid reactivity is high around adolescence and levels off between the ages of 15 and 45 years. It seems possible that there are stages, during this period of decline in reactivity, when lymphoid tissue is refractory, to varying degrees, to the specific type of stimulation that ultimately results in Hodgkin's disease. It is also possible that, during such periods, the tumor cannot become fully established or progress with its normal velocity, due to an inability to induce an immune response with antibody production which would provide a mode of self-protection. What is being proposed is that there exists a different gradient of host responsiveness to the Hodgkin's disease stimulus for males and females which closely parallels the level of lymphoid tissue reactivity. Thus, after the age of 15 years, the incidence of Hodgkin's disease increases in females to a point where it approaches that of males, and this relative increase persists until the decline in lymphocyte reactivity in females approximates that of males, around the age of 45 years. These propositions, although entirely speculative, provide a plausible explanation for the relative rarity of this disease in the trough between the 2 modes of the Hodgkin's disease curve. They may also explain the fact that excess, observed in the 50 years-and-greater age group, is a fairly constant characteristic of the bimodal Hodgkin's disease curve (6, 14).

In "looking at Hodgkin's disease as though it is an infectious disease," it appears to be highly unlikely that 3 distinct entities are involved. Although most of the epidemiological characteristics of the diseases are compatible with a single disease process, infectious in etiology, there are sufficient unknown factors to leave this question open at present. Understanding the lymphoma pattern in Japan is of great importance in this matter. However, the issue as to whether Hodgkin's disease is 1 or 2 distinct entities will not be resolved by histological surveys, mortality studies in different countries, or time-space cluster analysis based on inappropriate time and space coordinates. This may account for the variable results such analyses have produced in the past (1, 6, 24). To establish proper coordinates, one must rely on the information derived from the Albany and other groupings. These studies will be expanded, not to prove or disprove that Hodgkin's disease is 1 or 2 entities, but to establish whether the epidemiological characteristics described to date (62) hold true as more patients are linked. Clearly, if the likely "incubation period" is years, it does no good to use 1 to 365 days as one's time coordinate. Similarly, it is useless to select residence at diagnosis or place of death, if schools and other places are the important coordinates. For example, it is unlikely that significant time-space clustering would be established for infectious mononucleosis, if place of residence were selected as the space coordinate (47). Considering the age incidence of this disease and what we know of its behavior, schools would seem to be more appropriate places. The point here is that we cannot expect a disease to conform to preset coordinates, unless they reflect how that disease behaves in both time and space.

References

Is Hodgkin's Disease Infectious?

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Nicholas J. Vianna

Cancer Res 1974;34:1149-1155.

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