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Epidemiological Considerations in Staging of Hodgkin's Disease

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It has not been easy to decide what would be appropriate items for discussion under the title, "Epidemiological Considerations in the Staging of Hodgkin's Disease." Cancer staging has traditionally been based only on clinical assessment of the extent of spread of the disease, presumably because this was the first major determinant of prognosis to be recognized. Although many other kinds of variable have been found to influence the survival of patients with particular cancers and must therefore be taken into consideration when comparing groups of patients undergoing different treatments, such variables have not been incorporated into staging schemes–in my view correctly so. Thus, while the following epidemiological considerations should be of interest to anybody concerned with Hodgkin's disease, there may be some question as to their relevance to the concern of this particular meeting.

Hodgkin's Disease: How Many Diseases Does It Include?

Among epidemiological considerations in the staging of Hodgkin's disease, one of the first would seem to be the question of whether Hodgkin's disease as we now define it is indeed a single disease entity, for if the rubric were found to encompass more than one disease it would become necessary to ask whether a single staging system is appropriate for all its forms.

A considerable amount of evidence has accumulated on this question since it was reviewed for the American Cancer Society-National Cancer Institute Conference in 1965 (12). At that time, as previously (11), it was necessary to accept the truism that categories of diseased individuals created by classification in one dimension (whether etiology, pathology, clinical manifestations, or prognosis) will not necessarily be congruent with categories created by classification in any of the other dimensions. It was therefore conceivable that, even if patients with Hodgkin's disease did encompass persons with diseases of different etiologies, they might still constitute a group that could usefully be considered as a single disease category for diagnostic and therapeutic purposes. Today, however, evidence is accumulating of correspondence between subgroups of histological, clinical, and etiological classifications. It seems now, therefore, that the etiological heterogeneity, if it exists, may well have relevance to matters of therapeutics and prognosis.

Epidemiological Features. The shape of the age-specific incidence curve for Hodgkin's disease is bimodal, with peaks in the decade from 20 to 30 and in old age, and a distinct trough between these 2 peaks. Recent publications (1, 5, 17, 20) have confirmed that this bimodality is a consistent and widespread finding. If Hodgkin's disease were to be subdivided on the basis of the shape of the age curve alone, one would suspect that patients with onset between 15 and 34 years of age comprise one homogeneous group and those with onset at over age 50 make up another, with patients aged 35 to 49 being a mixture of the 2 groups. The disease in childhood has its own distinct characteristics and probably constitutes yet a 3rd etiological entity (2, 8, 11). However, in this country Hodgkin's disease is relatively rare in childhood, and only the differentiation of the disease in persons over 15 years of age will be considered in this paper.

The group of patients diagnosed between 15 and 34 years of age differs from those diagnosed in old age in a number of epidemiological features. Early population series suggested that the young adult disease occurred with approximately equal frequency in men and women, while elderly men experienced about twice the risk of elderly women (11, 12). The much more extensive incidence data now available in the International Union Against Cancer compilation of information from cancer registries (5) suggest that this distinction is not as clear-cut as it appeared in the earlier data. In fact, in most areas for which data are reported, rates for men exceed those for women at all ages. Nevertheless, there is a fairly consistent tendency for the sex differential to be greater in the elderly than in young adults, with ratios of male to female rates generally lying between 1.0 and 1.5 in the 15- to 34-year age group and being 1.5 or higher in the elderly.

In the eastern United States, Jews show about twice the risk of Hodgkin's disease after 50 years of age as do white non-Jews, a differential also seen for leukemia and other lymphomas (13, 15), but no excess risk of disease in the 15- to 34-year age group (11). In the southeastern United States, mortality among young adults is only about one-half that in the rest of the country, although Hodgkin's disease mortality among the elderly there is comparable to that in the rest of the United States (3).

There are also interesting international differences. The International Union Against Cancer cancer registry data (5) confirm the earlier impression from mortality data (11) that the disease of young adults is more common in Denmark than in the United States, while the reverse is true in the elderly. Mortality data suggested a similar pattern in the Netherlands and Switzerland, but registry data are not available for these countries. The reverse pattern is seen in data reported from 2 Japanese registries (5), the disease being uncommon in Japan

Table 1

Cases of Hodgkin's disease reported from Miyagi and Okayama Prefectures, Japan, and expected number based on rates in Denmark

Data for Miyagi, 1962–1964. Data for Okayama, 1966. Expected values based on rates for Denmark, 1958–1962, specific for sex and 5-year age group. Source of data: Doll *et al.* (5).

Age	No. of cases	
	Observed	Expected
0–14	3	5.6
15–34	1	76.8
35–49	5	39.3
50+	22	51.2
All ages	31	172.7

at all ages but virtually nonexistent in young adults (Table 1). Applying age-specific rates from Denmark to the populations covered by the 2 Japanese registries, we derive an expected value of approximately 51 cases of Hodgkin's disease in persons age 50 and over; only 22 were reported. However, on the same basis the expected value at ages 15 to 34 is approximately 77, and only 1 case was reported.

Histology. There is evidence that the disease in young adults and the one in the elderly are also distinguishable on histological grounds. In a study by Newell *et al.* (18) of material from 284 cases of Hodgkin's disease, 23 histological features were scored, without knowledge of the age, sex, or clinical characteristics of the patients from whom the material came. Five of the scored histological features showed significant values in a discriminant function analysis aimed to categorize patients into the age classes 15 to 34 or 50 and over. Features characteristic of the disease in young adults were high scores for eosinophils, Reed-Sternberg cells, fibrosis, and areas of preserved architecture and low scores for atypical mitoses. Characteristics of patients in the 35- to 49-year age group (material from whom did not enter into the analysis designed to identify the discriminating factors) fell between those of the 2 other age groups, as would be predicted if the 35- to 49-year-old patients comprised a mixture of the disease seen in the young and that seen in the elderly.

There is also evidence of correspondence between the histological classification of Lukes *et al.* (10) and age of the patients, at least for certain of the histological categories. This evidence comes from the series recently published from the Royal Marsden Hospital by Smithers (20). This series is particularly useful because it is the first series classified by Luke's criteria and containing substantial numbers of older patients. Smithers and we have disagreed on the interpretation of some of the observations deriving from this series (14, 20), but we are in agreement that patients with nodular sclerosis fall predominantly into the young adult age groups, as Keller *et al.* (9) had noted earlier. Our own interpretation of the Marsden data is that the patients in the lymphocyte depletion and mixed cellularity groups fall predominantly into the elderly group, although Smithers believes that these groups themselves show bimodality. The situation with respect to Lukes' lymphocyte predominance group is not clear. In the Marsden series, this group appears equally represented in both age groups, but Davidson and Clarke—on the clinical grounds discussed below—place this group in the category of disease seen in the elderly (4).

An important link in this chain of evidence has recently been provided by Strum and Rappaport (21), who have demonstrated the constancy of histological type of disease in the same patient at different points in the course of the disease, a feature that seems particularly characteristic of nodular sclerosis. Without such constancy, it would of course be difficult to sustain the concept that histological types of disease were etiologically distinct.

Clinical Features. It has been recognized for some time that Hodgkin's disease in young adults has a much more favorable prognosis than that in the elderly (11). Recent series show a 5-year survival about twice as high for young adults as for the elderly (1, 6, 16).

Bjelke (1) has pointed to a difference between age groups in the distribution of clinically evident disease. Among patients with disease apparently limited to 1 site at the time of diagnosis, this site was the neck in 63% of patients under 45 years of age but in only 38% in patients 65 years of age and older. The single site was retroperitoneal in only 5% of patients under 45 years of age but 33% in patients 65 years and older.

Davidson and Clarke have distinguished 2 clinical categories of Hodgkin's disease on the basis of distribution of disease assessed by radiography and lymphography (4). Their Type I ("superficial") disease is characterized by involvement of superficial lymph nodes in the groins, axillae, and neck (although abnormalities of pelvic or retroperitoneal glands are said to coexist frequently). In their Type II ("central") disease, the abnormality is primarily in the mediastinum and adjacent areas of the lower neck and abdomen. The intriguing thing about this classification is that it seems to overlap both with the epidemiological categories and, to some extent at least, with the histological categories of the Lukes classification. Type I disease has a peak age at onset over 50 years, has a 2:1 male over female risk differential, and is said to be manifested by most cases of lymphocyte predominance and about two-thirds of the cases of mixed cellularity. Type II disease has a peak age at onset between 15 and 25 years of age, has an approximately equal sex ratio in Davidson and Clarke's series, and comprises most cases of nodular sclerosis and about one-third of the cases of mixed cellularity.

In conclusion, there is evidence that Hodgkin's disease in young adults differs from that in the elderly not only with respect to epidemiological features but also in histological and clinical characteristics. The total picture is still by no means clear, largely because investigations to date have been concerned predominantly with one or another aspect of the disease (its epidemiology, its clinical features, its anatomic distribution, its histology, or its prognosis). A large and representative series of cases analyzed from all of these standpoints simultaneously would make a great contribution to our understanding of this disease.

Whether or not these differences between age groups indicate that we are dealing with 2 entirely different diseases (or 3 diseases if we include that in young children),

distinguishable on the basis of age, is still an open question. To the suggestion that Hodgkin's disease is one progressive neoplastic disorder the manifestations of which are influenced by host-tumor interactions that vary with age and sex (20), I can only respond that it is surprising to me that geographic and ethnic factors such as are known to affect the occurrence and manifestation of nearly all neoplastic disorders should, in this disease, show such striking predilection for different age groups in different parts of the world and even in different parts of the same country.

At the very least, the evidence is sufficient to warrant careful attention to and reporting of the ages of patients included in studies of potential etiological factors. At the present time, one can search in vain for the ages of patients that were the source of material for many reported studies of microbiological, immunological, and other potential causal factors in Hodgkin's disease.

What does all this mean with respect to the problem of staging? If indeed the 2-disease hypothesis were to gain credence, one might well wish to consider the formulation of 2 different staging systems, particularly since both the independent variables (site and extent of disease) and the dependent variable (prognosis) differ markedly between the 2 categories as distinguished on the basis of age. At this time, however, it would seem that the most useful objective would be to ensure that, either within a staging system or complementary to it, sufficient information on site and extent of disease is recorded for fuller investigation of clinical patterns in relation to histological and epidemiological features. Since much greater detail than is commonly included in a staging system will be required, it seems likely that the recording of such information would indeed be complementary to, rather than an integral part of, the staging process, although a staging scheme that would be a collapsed version of a detailed descriptive scheme would be very useful.

The Nature of Hodgkin's Disease

A 2nd epidemiological matter that may be considered relevant to the staging of Hodgkin's disease is the question of whether we are dealing with a neoplastic or an inflammatory process, since clinicians have thus far displayed little interest in developing staging systems for inflammatory diseases. The question of inflammation or cancer has of course recurred constantly in the history of investigation of Hodgkin's disease. An attractive feature of the 2-disease hypothesis has been the possibility of resolving this issue in terms of one disease being a cancer and the other an inflammation.

There is little doubt that at least one of Hodgkin's diseases, that seen in the elderly, is neoplastic. This disease shares many of the epidemiological featues of the other solid lymphomas and, in addition, frequently shows histological features that are unequivocally neoplastic–those of the late-lamented "Hodgkin's sarcoma."

The situation regarding the disease of young adults is less certain. Histological features typical of neoplasm are infrequent, and the age incidence curve, peaking in the 3rd decade, is not typical of a cancer. Bjelke (1) has pointed out that sarcoidosis and tuberculosis, which have certain clinical or pathological resemblances to Hodgkin's disease, also show a predilection for the 15- to 34-year age group and that the same is true of infectious mononucleosis–a disease that has been reported in conjunction with Hodgkin's disease in a number of cases.

The strongest evidence for the neoplastic nature of Hodgkin's disease is the observation by Seif and Spriggs (19) and earlier workers of apparent clonal origin of cells from lymphatic tissue from affected individuals. The individuals from whom this tissue was derived–including at least one in whom the clonal origin was confirmed by the presence of marker chromosomes–include patients in the 15- to 30-year age range.

On the other hand, recent observations have suggested that infectious agents may play an important etiological role. Vianna *et al.* (22) have estimated, on the basis of a case-control study, that the risk of Hodgkin's disease under 40 years of age is almost 3 times as great for tonsillectomized persons as for those who have not been tonsillectomized. The implication of a role for an environmental, possibly microbiological agent, to which the oropharyngeal lymphoid tissue normally acts as a barrier is strong (32). It is to be hoped that this important observation will soon be reexamined in other series. If it is confirmed, it will be of considerable interest to know whether the same relationship holds for Hodgkin's disease in the elderly.

The same workers have also recently reported a remarkable cluster of 12 cases of Hodgkin's disease, 4 among the alumni of 3 consecutive classes of a single high school and the remainder among their relatives or associates (24). Needless to say, evidence of infectivity of a Hodgkin's disease agent would not preclude the neoplastic nature of the disease it produced.

Although this problem is one of considerable immediate interest to students of Hodgkin's disease, one must again confess doubt as to its relevance to the matter of staging at the present time. Certainly, if the young adult disease did prove to be nonneoplastic, there would be considerably less enthusiasm for staging it, but as long as the disease is being treated as if it were neoplastic there seems to be no reason not to attempt to stage it as if it were.

Demographic Variables and Prognosis

Of interest to epidemiologists and biometricians, as well as to clinicians, are the demographic variables that are associated with survival in cancer. In Hodgkin's disease there are several variables of etiological significance (geographic, ethnic, socioeconomic) for which relevance to prognosis has, as far as I am aware, never been investigated. There are, however, 2 such variables, age and sex, that have a very considerable influence on prognosis. There is no doubt that a model incorporating age, sex, and histological characteristics as well as extent of clinical disease would predict survival very much better than one based on extent of disease alone. Should, then, a staging scheme take cognizance of such variables?

In my view, it would be as much of a mistake to include epidemiological variables in a staging scheme as it would be to incorporate histological characteristics. This is not to say that such factors may not usefully be considered when

evaluating the prognosis for an individual patient or even in considering the most appropriate therapeutic regimen, but rather that the development of classifications based on several different axes, such as have in fact been proposed (7, 25), is undesirable because it limits the kinds of combinations that can be evaluated. While standard terminology and agreement on classification of individual variables is desirable, our knowledge is too limited to be frozen by classifications that appear to take cognizance of all known variables.

A case in point is the classification of Davidson and Clarke (4) already referred to, which describes 2 types of Hodgkin's disease. This classification is based on a mixture of histological criteria and distribution of disease. It appears that, in the author's minds, the classification is basically one of distribution of disease, with Type I disease being "superficial" and Type II "central." However, because of the authors' impressions of correspondence between certain histological categories and disease distribution, cases of lymphocyte predominance are classified as Type I and cases of nodular sclerosis as Type II. It would seem preferable to base the classification solely on distribution of disease, while still recording histological type. If in fact all cases of lymphocyte predominance do have the "superficial" distribution then they will in any case be classified as Type I, and, similarly if all cases of nodular sclerosis exhibit the "central" distribution they will fall into Type II. However, the automatic classification of patients showing these histological features into the corresponding clinical type inhibits analyses designed to evaluate precisely how much correspondence between histological and clinical types there is.

I have already referred to the need for the evaluation of prognosis in a large and representative series in which clinical, histological and epidemiological predictors are considered. It is my strong feeling, however, that at this stage of knowledge each of these kinds of variable should be categorized separately, and that classificatory schemes that combine more than a single axis of classification whether called staging or some other form of classification, are undesirable.

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