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Formal Discussion of Brian MacMahon's Paper, "Epidemiological Considerations of Staging in Hodgkin's Disease"

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I would like to thank Dr. MacMahon for pulling together this extensive group of studies for us and for bringing the material up to date. The recent tonsillectomy association is particularly intriguing and requires confirmation in other series. Clearly, the more this disease is studied, the more its heterogeneity seems to fall into patterns. I have nothing to add to the interpretation of the patterns, and I will leave it to the chairman to consider the evidence distinguishing an infectious and a host resistance theory.

I shared Dr. MacMahon's bewilderment when the inclusion at this meeting of a title relating epidemiology to staging was proposed. Dr. MacMahon has approached the assignment from the point of view of the contribution that epidemiology might hopefully make to staging; that is, is there something about the epidemiological evidence that might guide the subcommittee that will propose the staging system to be used for the coming years? He finds that he is not able to make any suggestions other than to remind them that whatever they propose may require revision if some of the clues he has described mean what they seem to mean.

It occurs to me that the opposite question might be fruitful, *i.e.*, what contribution can staging make to the epidemiological puzzle? If the stage were a purely transitory characteristic of Hodgkin's disease, any such contribution would be unlikely. I would like to suggest, however, that the stage may be a more fundamental characteristic of the disease. If different etiological groups exist within Hodgkin's disease, these groups may differ importantly with respect to the distribution of stage of cases in the several groups. Conversely, cases of a given stage may have a high probability of belonging to a particular one of the etiological groups.

Before pursuing this thought briefly, I should perhaps call to mind that I am assuming stage to refer to the extent of disease at time of diagnosis. While it is clear that the extent of disease in a given individual commonly changes over time, nevertheless the extent to which disease has progressed before it comes to diagnosis may well reflect some basic characteristics of disease. Some theoretical ways in which this could come about may be mentioned. First, if a disease tends to disseminate after a relatively small number of cell divisions, it may be impossible for a given tumor mass to gain attention before multiple, dispersed tumor masses are detectable. Such a disease will rarely be staged in a localized category. As another instance, if a disease commonly or invariably arises in a deep tissue, for example, mediastinal nodes or spleen, its detection depends on several circumstances. It may be diagnosed by routine chest X-ray or routine physical examination, it may be diagnosed as a result of secondary extension to a peripheral site, or it may be diagnosed when the tumor reaches sufficient volume to cause symptoms in its site of origin. As a final example, a very rapidly progressing tumor may be diagnosed in a localized stage because of the suddenness of its manifestations, while similar symptoms coming on gradually might be overlooked.

A few data from a collaborative Hodgkin's clinical trial are relevant. When we categorize initial extent of upper-torso disease in terms of the number of upper-torso regions involved, we find the most frequent presentation to be a single involved region (34%), while about 28% have 2 regions and 21% have 3 regions involved. Involvement of 4 or 5 regions is uncommon. When individual histologies are considered, mixed cell type is more concentrated in the cases with 1 region (47%) involved and has smaller proportions with 2, 3, 4, or 5 involved. Nodular sclerosing disease is relatively unlikely to present with 1 site involved (22%) and is substantially more likely to have 2 or 3 regions involved. I think that the principal feature of the nature of disease reflected here is the anatomic site of origin. Mixed cell disease commonly arises in a peripheral site and comes to attention as a result of this palpable and visible disease. It is therefore diagnosed in the Rye Stage I_1. Nodular sclerosing disease commonly arises in the mediastinum but comes to diagnosis at the time it spreads to peripheral areas. It is therefore uncommonly diagnosed in Stage I_1. This tendency to higher staging for nodular sclerosing disease does not carry in it an implication of poor prognosis.

In this same material, we have investigated the characteristic of contiguity of involved sites. For the upper-torso disease, it seems useful for the present purposes to consider the mediastinum to be contiguous with the 2 sides of the neck. Each side of the neck is contiguous with the mediastinum and the ipsilateral axilla. The 2 sides of the neck are not contiguous with one another. Under these considerations, nodular sclerosing disease almost invariably falls into contiguous patterns of regional involvement at time of diagnosis (45/49 = 92%). Mixed cell disease, in sharp contrast, is found in contiguous groupings only 45% (12/26) of the time. This is just about the proportion of cases that would have contiguous patterns if spread within the upper torso were completely random for mixed cell disease. It is suggested here that, if contiguity of initial involvement is accepted as a

characteristic of staging, this characteristic may be correlated with etiologically different subgroups.

I would like to emphasize Dr. MacMahon's suggestion that the subcommittee concerned with staging confine the staging rules to characteristics that describe the extent of disease at diagnosis and that they not include histological classification, constitutional signs, or demographic variables as part of staging. The staging system should facilitate investigation of the association between the extent of disease and these other characteristics. It should not assume that we already know the combinations most relevant to etiology, prognosis, or treatment decisions. The staging rules might also take up the issue of the diagnostic studies to be used in staging. If one of the purposes of staging is to make comparisons of groups of patients from a wide variety of reporting sources, as with the End Results group, the procedure of staging must be simple. It must be assumed that peripheral lymph node areas have been carefully examined by all groups reporting and that the mediastinum has been observed by X-ray. It cannot be assumed that lymphography or laparotomy or both have been done at all centers, and at this date it can be assumed that mediastinoscopy has rarely been done. The most useful staging for comparisons among many diverse centers would, I believe, be the prelaparotomy, prelymphography stage. For special investigations where the investigator is in a position to require certain diagnostic studies, the information from laparotomy and lymphography may be generally available and should, of course, be used. In assessment of prognosis and making treatment decisions for individual patients, all available information should be used, but even when this is available it would be useful to record the prelaparotomy, prelymphography stage of the patient for broad intergroup comparative studies.