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Summary of Informal Discussion on Biostatistical and Epidemiological Factors in Hodgkin's Disease[1]

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Following the presentation of the paper by Dr. MacMahon, Dr. Hutchison opened the discussion by saying that the more we study Hodgkin's disease, the more its heterogeneity seems to fall into patterns. Dr. MacMahon approached this problem by asking whether there was something about the epidemiological evidence that might guide the Committee in proposing a staging system. He reminded the Committee that whatever it did propose might require revision, especially if some of the clues that he described meant what they seemed to mean. Dr. Hutchison, however, suggested that the opposite question might be fruitfully approached, namely, what contribution could staging make to the elucidation of the epidemiological puzzle. This might be useful if a stage were not a purely transitional characteristic but rather a more fundamental property of the disease.

Dr. Hutchison suggested that if different etiological groups do exist, they might differ importantly with respect to the stage distribution of the cases in these groups. To put it another way, a patient in a given stage might have a high probability of belonging to one etiological group. This would, of course, relate to stage at the time of diagnosis, since the extent of disease in a given individual changes with time. The point made was that the extent to which the disease had progressed before diagnosis might reflect some basic characteristic of the process. For example, if one type of the disease tended to disseminate after a relatively small number of cell divisions, a tumor mass might not gain attention before multiple, dispersed tumor deposits had occurred. Such a disease would rarely be staged in a localized category. Again, if one type commonly arose in deep tissue such as the mediastinal nodes or spleen, while it might be diagnosed by a chance routine X-ray or physical examination, it was more likely to be found only after attention had been drawn to it through spread to a peripheral site. Alternatively, a tumor might remain silent until it reached a sufficient volume to cause symptoms at its site of origin. A rapidly progressive tumor might be found while still localized because of the suddenness of its manifestation, which could have been overlooked if it had come on more slowly.

When patients were categorized by initial extent of upper torso disease, the most frequent presentation was that of a single region involved: about 34% of Dr. Hutchison's recorded cases had only 1 region involved at the time of diagnosis; in 28%, 2 regions were involved; and in 21%, 3 regions were involved. When histology was taken into account, 43% of the mixed cell cases had a single region involved when first diagnosed. On the contrary, for nodular sclerosing disease, only 22% had 1 site involved at diagnosis. This, Dr. Hutchison thought, was due to the fact that mixed cell disease commonly arose in a peripheral site, whereas nodular sclerosis was commonly found in the mediastinum but was detected there only when it had already spread to a peripheral region. Nodular sclerosis almost invariably fell into contiguous patterns of regions involved at the time of diagnosis. Ninety-two % of his nodular sclerosing disease fell into a contiguous pattern. In sharp contrast, mixed cell disease had been found in contiguous groups only 46% of the time. Indeed, this is the proportion which would be expected to have contiguous patterns if lymph node spread within the upper torso were completely random.

If staging were to help in making comparisons between groups of patients from a wide variety of reporting sources, the procedure must be simple. Careful clinical examination and good reporting on mediastinal X-rays must be assumed. Lymphography and laparotomy might not, however, be done in all centers. The most useful staging for comparison between diverse centers would be a prelaparotomy or prelymphographical stage or both. For special institutions where detailed diagnostic studies were required, the information would be valuable in assessing the prognosis and in making treatment decisions.

The chairman congratulated Dr. MacMahon on his work and, particularly, on continuing to point out and refusing to be shaken in his demand that the bimodal age distribution curve had to be explained. The chairman said, however, that he was not completely happy about the explanation offered. He thought that to divide Hodgkin's disease into separate nonmalignant and malignant disorders did not account for the fact that his cases, when plotted by age and histology, gave a bimodal age curve both for lymphocytic predominance and for mixed cellularity and lymphocytic depletion. The "odd man out" was nodular sclerosis. The chairman had for some time been suggesting that Hodgkin's disease was a progressive disorder, proceeding from lymphocytic predominance to lymphocytic depletion and making this transition quite rapidly at times. Nodular sclerosis seemed to him to represent a hold-up of this progress in patients who had some resistance to the disease. Such resistance was commoner in the young and particularly well seen in women. He was interested in Dr. Rappaport's data that some patients may live for years following treatment for Hodgkin's disease, remain well, and yet at postmortem examination be found to have Hodgkin's disease still present in the lymph nodes, but always in the

[1] This chairman's summary includes a section on the discussion which followed the presentation of the three Committee reports.

nodular sclerosis form. He had thought that Hodgkin's disease was one progressive disorder with a variable host resistance which disturbed the age distribution curves.

Dr. MacMahon said that there are 2 hypotheses, one about which he felt reasonably confident, namely, that etiologically speaking there are 2 disorders. He thought this to be compatible with the chairman's idea that nodular sclerosis represents a host resistance. He also thought that the question of what factors are responsible for different host resistances is bound up with the idea that there are 2 different etiologies. The hypothesis about which he was less confident is that 1 of the 2 groups is nonneoplastic. He does not believe that this Hodgkin's disease is a viral-induced cancer because it does not look correct to him from the point of view of age distribution or histology.

Dr. Ultmann thought that it was possible that a single etiological agent might express itself in a variety of ways. Host resistance might have different histological expressions. He thought that the malignant lymphomas developing following organ transplants showed that certain types of cancers can be brought out by manipulation of the immunological apparatus. He felt that we might be clouding the issue of a single etiological factor by confusion with a variety of host responses.

Dr. Lukes said that he had suggested that Hodgkin's disease had a long induction phase leading to different types of tumors with different rates of development. He objected to calling all of them cancers, since they have different degrees of activity. He thought that the inflammatory-like phase which demonstrates the host struggle is the factor that makes Hodgkin's disease so distinctive.

Dr. Rappaport pointed out that if you searched field by field, you could find a great histological identity between nodular sclerosis and other forms which were not nodular sclerosis. He thought that we were not dealing with 2 neoplastic processes from the histological standpoint, only a peculiar desmoplastic reaction which was not unique to Hodgkin's disease.

Dr. Lukes discussed Hodgkin's disease as a process with lymphocytic predominance as a good response which was gradually lost, and of lymphocytic depletion as an immunological failure much like that seen in immunosuppressant states. He wondered whether nodular sclerosis might not involve the thymic portion of the immunological system and the remainder, the nonthymic-dependent system.

Dr. Dorfman pointed out that nodular sclerosis might involve inguinal nodes more often than was realized. He found that, of 293 biopsies coded as nodular sclerosis during a 2-year period, 18 had been derived from inguinal lymph nodes. Interestingly enough, 10 of these patients were male.

Dr. Kaplan thought that these were usually older patients, that they more commonly developed lower spinal involvement, and that they did not usually have mediastinal disease. He also felt that they did not have a particularly good prognosis. He thought that the notion of nodular sclerosis as a disease of the young female, involving the mediastinum and with a good prognosis, was generally true; but that nodular sclerosis in older age groups generally not involving the mediastinum and with a poor prognosis, also occurred. He also said that in some centers in South and Central America there seemed to be almost an absence of the early nodular sclerosis age peak. He liked to think of Hodgkin's disease as a single entity with different contributive etiologies and different host response factors modulating the expression of the disease process. He thought that Hodgkin's disease was clearly a cancer even in the early stages on the basis of the evidence of aneuploidy and clonal derivation. The long evolution might be related to ideas which he and the chairman had put forward 12 years ago about the possible relationship between this disease and a graft-*versus*-host type of reaction.

Dr. Tubiana pointed out that the sex ratio varied very much with age, from 2.5 for young people to 1 in the middle-aged groups and over 2 again for the more aged people; he stated that the sex ratio went up just before puberty to 5 or 6. He thought that this might be related to some hormonal factor and that the age incidence curves might just reflect defects in hormonal balance. He received some support from Dr. Rappaport who thought that special attention should be given to children under the age of 10 with Hodgkin's disease, where there was a male predominance of 90 to 95% and where the lymphocytic predominance type of disease was common. Even the nodular sclerosis cases in this age group seem to have a great deal of lymphocytic infiltration.

Dr. MacMahon continued this point by saying that he thought that the high sex ratio in childhood and the fact that the disease at this age was common in certain parts of the world was an indication that Hodgkin's disease might well have a 3rd category. He thought that we should beware of interpretation of the sex ratio in the elderly where there was a great excess of females at risk.

The discussion lead by Dr. Carbone then turned to the reports of the Committees.

There was a long discussion about dividing the staging procedures into a clinical stage and a pathological or surgical stage, and over the question of what should be called localized disease and how far contiguous spread could proceed until it was regarded as disseminated.

Differences about pathological staging were resolved by an agreement that all removal of tumor for section performed to determine spread (after the initial biopsy had been done to establish the nature of the disease) should be included in the pathological staging. The question of what should be called localized disease was resolved to the satisfaction of most, but not all, by saying that disease was localized if the whole extent was thought to be due to direct extension rather than to blood-borne metastasis. It was agreed, for example, that spread from a hilar lymph node through the lobe of one lung would be regarded as localized as would spread from abdominal nodes directly into vertebral bodies. It is clear that such direct extensions from primary foci, although serious, do not carry the same grave prognosis as that due to disseminated tumor spread. It was therefore agreed that to put such local extensions into Stage IV was unjustified. It was clear that the Committee would have to resign itself to a certain amount of uncertainty in this regard, but they intended it to be clearly understood that local disease was different from widespread extension and that such cases should be taken out of Stage IV.

The discussion about pathological staging was prolonged but was clarified largely by the insistence of Dr. Tubiana that

clinical staging must be clear-cut, comparable, and something that could be done by everyone, it should not include extra investigations not universally done, although these clearly make a difference to treatment selection.

The spleen caused particular trouble. It was admitted that there is no satisfactory method of determining splenic involvement other than by splenectomy and serial section. It was also clear that splenectomy provided information of unusual importance when negative which was not comparable to that provided by the removal of a single negative node or a small piece without evidence of tumor taken from the liver or other regions.

Bone marrow biopsy caused further discussion, led by Dr. Rosenberg who thought that it might be positive in at least 5% of all Stage III cases and that it should be recommended in all Stage IIB and Stage III patients. It was agreed that it would be included in the pathological staging but should not change the clinical stage even when positive. Dr. Kaplan pointed out that he did not regard a negative liver or bone marrow biopsy as a definite result since they are sampling procedures but that a positive result was of a very different order of significance. He thought that bone marrow biopsy might be mandatory in clinical Stage II and Stage III and that the patient would be scored as a pathological Stage IV if it was positive but that this would not affect the clinical stage. The only finding which could be negative and yet influence the pathological stage so that it is different from the clinical stage would be a negative spleen. It would be possible to have a clinical Stage III spleen, which on section became a pathological Stage II.

The discussion then turned to the difficulties involved in being certain that lymph nodes removed at laparotomy were those which had been reported as positive or negative on lymphography. It was clear that some careful review work on the lymph nodes removed and their site relative to the lymphogram report was needed. It was seen that, while histological examination of a lymph node carried a far greater certainty than a lymphogram report, it was a sampling procedure involving a very small proportion of the total node region surveyed.

There was a discussion about recording the negative evidence from multiple pieces removed for biopsy, particularly at laparotomy. It was agreed that multiple negative biopsies could not be ignored as though a full investigation had not been done and that such patients had been more fully investigated but that this did not affect the stage category allocated.

The general opinion at the end of the discussion seemed to be that, despite its complexities, the system provided an opportunity for useful comparison at the clinical stage level without wasting the staging implications of the data collected by more detailed investigation.

The last part of the discussion was concerned with how such recommendations might be presented. Dr. Kaplan suggested a trial period before advocating general adoption. This would give the opportunity for revision after a wider audience had seen the proposals, perhaps at a meeting in 1 year's time.

Dr. DeVita feared that publication would mean adoption and that this might lead to too many changes, but in general a 1-year trial within the group was thought to be wise.

The rest of the discussion dealt with the method of getting textual agreements and timing. Dr. Anderson talked of the other committees (national and international) and how arrangements for agreement could best be reached.