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Summary of Informal Discussion on the Prognostic and Therapeutic Implications of Staging in Hodgkin's Disease

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Dr. Kaplan's presentation on the contiguity and progression of Hodgkin's disease promoted an intense discussion. Dr. Rosenberg cautioned that, although spread by direct contiguity would explain most of the distributions observed in the Stanford experience, their cases were heavily weighted by nodular sclerosing disease, and different distribution patterns might emerge in other histological types of Hodgkin's disease.

Professor Smithers challenged both the interpretation of direct contiguity of spread by lymphatic channels in all situations and the probability of reverse flow in the thoracic duct to explain spread from cervical lymph nodes to the abdomen. He agreed that the disease does spread along the lymphatics, but this is only part of the story. He stressed the improbability of reverse flow in the thoracic duct and showed pictures of lymphography studies in which hilar nodes and even axillary nodes can be filled after contrast is injected in the foot. He pointed out that it was highly improbable that involvement of the spleen can be explained by direct lymphatic spread. In his opinion, blood stream dissemination may be common because 75% of the lymph of the body enters the blood stream directly by way of the thoracic duct; this appears to be the only explanation of spread to spleen.

In answer to the challenge, Dr. Kaplan related the published works by Tabahashi and Abrams, and by Benninghoff and his colleagues, in which reverse flow in the thoracic duct was demonstrated. He also pointed out that he is in agreement that the spread is in the antegrade direction in most cases but that reverse flow is the most likely explanation in exceptional cases, such as the patient who had disease in the left neck treated in 1962 and had a negative lymphogram in 1962, 1965, and 1968 but a positive one in 1969. Dr. Kaplan doubted the possibility that the disease in the abdomen might remain microscopic for 7 years when it had been macroscopic in the neck previously.

Pertinent to this problem, Dr. Viamonte stated that, in the thousand or more lymphographic studies he had reviewed, he had observed reverse flow in the thoracic duct only when it was completely obstructed or in traumatic amputation of the duct.

The chairman (Dr. Peters) offered the opinion that disease in the abdomen can remain silent for many years in patients who have had radiation therapy administered to the neck during the long period before lymphography. To illustrate this point, she described the case of a 9-year-old boy who had right and left neck irradiation in 1946 and who remained well until 1968 when a laparotomy was performed to explain gastric symptoms. At laparotomy, he had a mass in the epigastric region with diffuse infiltration into all the adjoining structures, including the stomach. The paraaortic nodes were still discrete but involved. The pathology was still lymphocytic and histiocytic (diffuse) Hodgkin's disease. This patient probably had slowly progressive subdiaphragmatic disease for 22 years. The lymphogram was preoperatively positive, but the paraaortic involvement appeared to represent a late extension in the abdomen. Thus lymphography alone may not always point up the abdominal disease. The chairman made a plea that the mode of spread, which is unproven, is not nearly as important as one's ability to recognize the most probable pattern of disease distribution in each patient, and this can now be predicted fairly accurately by histology, chest X-ray, and physical examination. In fact, the high risk sites of involvement can often be identified after palpating the neck and axillae without further information.

In nodular sclerosing disease, the pattern of the contiguity of disease is readily apparent in most cases, but in the other histological types there is some need for speculation. This opinion was supported by Dr. Johnson and had been introduced earlier by Dr. Rosenberg. Dr. Johnson was reminded of the fairly rapid spread sometimes in the other histological types, suggesting a succession of regional responses to an inciting agent rather than direct spread from a single focus.

The chairman suggested that one can predict fairly rapid spread of the disease in patients who, by physical examination alone, are found to have noncontiguous involvement, according to her experience. Dr. Kaplan agreed in situations which were obvious, such as massive disease in both axillae, etc., but cautioned that noncontiguity might be disproven in some cases if nonpalpable nodes were excised and proven to be involved.

The problem of the "exceptional" cases was introduced by Dr. Johnson. He related the history of a patient who had had a laparotomy and splenectomy with negative findings when first evaluated but who later developed inguinal involvement in spite of the fact that no change was observed in the 2nd lymphogram when the inguinal disease was discovered. In this case, contiguous spread could not be demonstrated.

Dr. Dorfman added the caution that recurrent lymph nodes are not always evidence of disease.

In the discussion to this point, it became clear that much more evidence is required to prove direct lymphatic spread or blood stream dissemination but that several patterns of disease emerge which have a histological relationship. The distributions of disease which topographically appear to be contiguous cannot always be explained on the basis of direct lymphatic spread. Nevertheless, a clinical classification can be

based on the apparent distributions, as there are a few patterns of disease which are very prevalent and which can be successfully treated when all the apparent and predicted sites of disease are encompassed.

A discussion on the identity of the neoplastic cell in Hodgkin's disease followed but is omitted here because it is not directly relevant to the topic of this conference. Dr. Kaplan presented evidence from the recent literature which, he believes, leaves no doubt about the malignant nature of this disease.

The paper given by Dr. Musshoff also promoted much discussion. Dr. Kaplan was quick to point out that Dr. Musshoff's material was further evidence of direct lymphatic extension even to extralymphatic sites immediately adjacent to groups of lymph nodes in presentations which were predominantly lymphatic. Both Professor Smithers and Dr. Kaplan agreed that a true Stage IV should be limited to those cases in which disseminated disease is evident and that those patients with limited extralymphatic disease adjacent to the involved lymph nodes should be allotted to the appropriate earlier stage (*i.e.*, Stages II or III) in spite of the contiguous spread to other structures. This concept applies chiefly to spread (*a*) to adjoining lung in nodular sclerosing disease, as previously demonstrated by Dr. Rosenberg earlier in the conference, and (*b*) to adjacent bone regions, as was beautifully demonstrated by Professor Musshoff, but the histological relationship in his cases was not clear.

In contrast, the possible relationship between vascular invasion observed in the original biopsy material and the probability of hematogenous spread was stressed by Dr. Kaplan. He pointed out that the overall percentages of vascular invasion in Dr. Musshoff's series were very similar to those earlier reported by Dr. Rappaport. He also mentioned that the Stanford staging system is very similar to the proposal made by Dr. Musshoff in his paper.

Dr. Carbone stated that he would agree with this change in staging if only one localized extralymphatic spread were observed, but he questioned the inclusion of multiple adjacent extralymphatic foci in the earlier stages. Dr. Musshoff claimed that treatment by radiation was not difficult even in those circumstances, and the response to treatment was excellent when mantle techniques were used.

Along the same vein, Professor Smithers introduced the problem of alloting a clinical stage to the patient with a pleural effusion. There was the consensus of the group that the finding of a pleural effusion should be ignored in the stage classification unless histological proof of involvement of the pleura can be obtained. Pleural and even pericardial effusions can be controlled during the treatment of the obvious disease.

Dr. Lukes then related an important observation. He believes that such patients and, indeed, all patients who show evidence of spread to adjacent extralymphatic tissue invariably have nodular sclerosing disease. He also believes that the extralymphatic involvement is probably disseminated in other histological types.

Dr. Tubiana introduced some caution concerning the high probability of curing the patients with direct extralymphatic spread by radiation alone. In his experience the response rates were higher in those patients treated by radiotherapy and chemotherapy. At this point, Dr. Rappaport also warned that eradication of the disease on a clinical assessment may be more apparent than real. The definition of cure is of interest to pathologists as a result of autopsy studies on patients who have survived more than 10 years without apparent disease. In an attempt to determine the cause of death, Hodgkin's disease was implicated in 14 of 29 cases reviewed but not definitely implicated in the remainder.

Returning to the definition of Stage I, there was complete agreement among all the clinicians present that Stage I should be limited to either a single lymph node region or a single extranodal site, as both shared good survival rates.

Dr. Frei's paper pointed out a discrepancy in his collected series showing the percentage risk per year of recurrent disease following the primary treatment. In the long series dating back to 1931, there was a small risk of recurrence from 5 to 10 years after treatment, but in the more recent series from other centers the risk after 5 years was minimal or absent. Dr. Rappaport offered the reminder that the late recurrence risk probably applied only to the cases prior to the era of lymphography and laparotomy investigation. This was confirmed by the chairman who had contributed the data for the long-term study, *i.e.*, that one could anticipate that the initial recurrences appearing after 5 years will, hopefully, be few in number in the future. The discrepancy shown in Dr. Frei's study might not be a true discrepancy. The chairman also reported her observations that most of the "late" initial recurrences occurred in occult sites, chiefly intraabdominal, and it is her opinion that the majority of these sites of disease would have been discovered at the time of diagnosis using present-day methods of evaluation.

Dr. Johnson's paper confirmed the moderate risk of extralymphatic extensions even when all the major lymphatic chains are irradiated. It stated that there is a fairly high risk of involvement of the spleen if the spleen is not irradiated in nonlaparotomized patients with Stage III disease.

Time did not allow discussion.

The extremely active discussion on the concepts of spread in Hodgkin's disease was informative and thought provoking but, for the most part, purely speculative as proof is not available. The papers and discussions which demonstrated possible changes in the clinical staging were indeed fruitful. Everyone agreed that Stage I should include a single extranodal site, as well as a single lymph node region.

In Stages II and III, much evidence was presented to show that these stages should also include those cases in which very localized or solitary spread to adjacent extralymphatic structures could be demonstrated during the initial evaluation.

It is true that many such cases have, in the past, been included as Stages II or III without having recognized the foci of spread, such as the patients with hilar disease accompanied by a questionable infiltration beyond the hilum into the lung parenchyma or the patients with severe lumbar pain who did not have special radiographic studies to demonstrate bone invasion. However, when these sites of limited invasion can be demonstrated initially, it is important that such cases are included in a special category within that stage in order that they can be identified and studied separately at a later date. In the T.N.M. system which I described earlier in the conference, such cases would be identified as $T_0N_{2\ or\ 3}M_1$ and could still

be considered Stage II or Stage III, but other allocations in a different system might be more acceptable at present.

When the extralymphatic spread in Stages II and III is recognized, it is important that the radiotherapist undertaking the treatment of such cases uses all the precautions necessary to avoid local radiation complications in the extralymphatic site included in the field of radiation.

The Proceedings so far have not included a proposal for the patients whose primary focus is an extranodal or extralymphatic site but disease already recognized in regional lymph nodes or beyond. In the lymphomas other than Hodgkin's disease, such presentations are common and will need to be considered in designing future classifications of the lymphomas, but not necessarily in Hodgkin's disease.