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Summary of Informal Discussion on Histological Criteria for Diagnosis of the Extent of Hodgkin's Disease

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Diagnostic Criteria

Dr. Lukes described the wide range of histological features of Hodgkin's disease and the criteria for the subclassification of the disease as previously reported on and as modified at the Rye Conference.

The principal discussion was presented by Dr. Dorfman and concerned the following: (*a*) involvement of the spleen; (*b*) the significance of "nonspecific" infiltrates in the portal tracts of the liver; (*c*) noncaseating granulomas in lymph nodes, spleen, and liver of patients with Hodgkin's disease; and (*d*) Hodgkin's disease involving bone and bone marrow. Dr. Dorfman stated that, from the Stanford experience, splenomegaly may occur in a patient with Hodgkin's disease, but the spleen when removed may be entirely free of detectable Hodgkin's disease even after meticulous gross and microscopic examination. Conversely, grossly normal spleens, even when small, may contain isolated foci of Hodgkin's disease. Sometimes these foci are minute and identifiable only by microscopic study of multiple sections.

Dr. Rappaport showed a spleen in which the Malpighian follicles were all large and hyperplastic and pointed out that a small nodule of Hodgkin's disease, which was recognized microscopically, could not be distinguished grossly from the hyperplastic Malpighian follicles.

The conclusion from this discussion was that the spleen from a patient with Hodgkin's disease must be meticulously examined grossly after it is cut into 2- to 3-mm slices and that multiple, random blocks must be taken and examined microscopically to search for occult Hodgkin's disease. Hodgkin's disease in the spleen, even when present only in microscopic foci, does not present any unusual histological difficulties for the pathologist.

By contrast, all discussants agreed that sections of needle biopsy fragments of the liver from a patient with Hodgkin's disease often present major difficulties in interpretation. An infiltration of lymphocytes may be encountered in the portal tracts. The significance of this infiltration is not known, but there was general agreement that it should be interpreted as "nonspecific" and should not be reported as suggestive of Hodgkin's disease. On the other hand, a mixed cellular infiltrate in the portal tracts, often with eosinophils, some fibrosis, and neoplastic-appearing mononuclear histiocytes, should be considered indicative of Hodgkin's disease. In such cases, multiple or even serial sections should be examined in an effort to find diagnostic Reed-Sternberg cells. (*This is one of the recommendations included in the Diagnostic Criteria Committee's report.*)

Dr. Thomas reported that in the National Cancer Institute material cases with neoplastic-appearing mononuclear cells could almost invariably be shown to contain Reed-Sternberg cells when serially sectioned. He also pointed out that Reed-Sternberg cells and other neoplastic-appearing histiocytes in the portal tracts may be smaller and more difficult to recognize in sections of the liver than in lymph nodes from the same patient. Presumably, there is more shrinkage artifact of these cells in the liver than in lymph nodes.

Following the discussion about the difficulties of finding acceptable Reed-Sternberg cells in the liver, Dr. Lukes showed photomicrographs of methyl green-pyronin-stained sections. He pointed out that the cytoplasmic RNA in Reed-Sternberg cells is very prominent with this stain, a feature which might be helpful in some instances in demonstrating Reed-Sternberg cells.

There was considerable discussion about the possible significance of nonspecific lymphocytic infiltrates in the portal tracts. Dr. Musshoff reported that he had studied 60 cases and that this type of infiltrate occurred in all clinical stages of Hodgkin's disease, and its presence and/or severity did not correlate with survival. He also reported finding some degree of infiltrate in the portal tracts of all of his patients. Dr. Rappaport and other United States pathologists found the nonspecific infiltrate in many, but not all, of their cases.

Dr. Dorfman reported recent observations concerning noncaseating granulomas in the tissues of patients with Hodgkin's disease. The principal point was that these patients should be carefully followed because these granulomas might indicate some type of immunological response to Hodgkin's disease. It was agreed by the pathologists that, when such granulomas are found, a meticulous search should be made for neoplastic mononuclear histiocytes and Reed-Sternberg cells. When such cells are present, the diagnosis of Hodgkin's disease can be established. When, however, neoplastic cells are not identified, even in multiple or serial sections, the noncaseating granulomas are not *per se* indicative of Hodgkin's disease and should be reported as nondiagnostic.

In Dr. Dorfman's discussion of Hodgkin's disease in the bone marrow, it was pointed out that the involvement is often focal but may be diagnosed with appropriate material, *i.e.*, open biopsy or with a punched-out core of bone marrow. The principal diagnostic problem concerns the histological finding of fibrosis in the marrow without identifiable Reed-Sternberg cells or neoplastic-appearing mononuclear cells. (*A recommendation regarding this problem is included in the report of the Diagnostic Criteria Committee.*)

Relationship of Histology to Clinical Stage and Survival

Following Dr. Butler's and Dr. Berard's presentations, the discussion was opened by Dr. Tubiana who presented additional information based on a study of approximately 450 patients with Hodgkin's disease. His data show that both histological subtype and clinical stage are significantly related to survival and that histological subtype is prognostically significant even within clinical stages. Furthermore, the influence of histological subtype varies with age and with sex. The analysis of information with so many contributing factors is very difficult. The principal question raised by several discussants was, "How dependent or how independent are these variables with regard to the survival of patients with Hodgkin's disease?" It was generally agreed that no single center, especially in a retrospective study, could accumulate enough data to answer this question. It was also agreed that sufficient data could be assembled if several centers cooperated in a uniform study.

Dr. MacMahon pointed out that the participants of this conference could probably collectively assemble 2000 to 3000 cases on the basis of past experience and that this data base, if properly analyzed, could answer a number of questions about the interrelationships of stage, age, histology, sex, and survival.

Relationship of Histology to Site and Significance of Vascular Invasion

These 2 subjects were presented by Dr. Dorfman and Dr. Rappaport. In the discussion it was emphasized that nodular sclerosis is apparently a very stable subtype of Hodgkin's disease, while lymphocytic predominance frequently progresses to mixed cellularity or even lymphocytic depletion. In this respect, mixed cellularity is intermediate between nodular sclerosis and lymphocytic predominance in that it may show progression to lymphocytic depletion but does not necessarily do so with regularity.

The question of the so-called "cellular phase" of nodular sclerosis was raised during this part of the discussion. Both Dr. Dorfman and Dr. Rappaport presented cases which in the initial biopsies exhibited Reed-Sternberg cells typical of nodular sclerosis but without fibrous trabecular bands and which in subsequent biopsies exhibited both criteria, *i.e.*, fibrous bands and Reed-Sternberg cells in lacunar spaces typical of nodular sclerosis. There was general acceptance of the concept that there is a cellular variant or cellular phase of nodular sclerosis. (*This subject is also included in the report of the Diagnostic Criteria Committee.*)

In the discussion about vascular invasion, Dr. Johnson pointed out that Dr. Rappaport's reported frequency of vascular invasion (about 8%) is very similar to the rate of extranodal recurrences observed in patients following total nodal radiotherapy at the National Cancer Institute. If vascular invasion can be shown to identify those patients with a high risk of extranodal relapse, it might be reasonable to use combined or sequential chemotherapy and radiotherapy in their management.

Dr. Dorfman's presentation of the pathological findings in spleen, liver, and abdominal lymph nodes in the Stanford series of consecutive patients with Hodgkin's disease undergoing laparotomy for staging produced a great deal of discussion along 2 lines: (*a*) about the concepts of contiguous spread and (*b*) about the frequency of involvement of the spleen if abdominal lymph nodes and/or liver are involved. Drs. Dorfman, Rosenberg, and Kaplan pointed out that their data show a nonrandom distribution of Hodgkin's disease in mediastinal and abdominal sites. There is a strong association between involvement of lower cervical nodes and the mediastinum, between right cervical nodes and the mediastinum, and between left cervical nodes and abdominal nodes. Dr. Smithers agreed that Hodgkin's disease is nonrandom in distribution but felt that the concept of contiguous spread is still conjectural and inadequate to explain patterns of the disease in many patients. He particularly objected to the concept of retrograde spread, against the lymphatic flow, as an explanation for frequently associated sites, *e.g.*, abdominal and left cervical lymph nodes. It was agreed that further discussion would be deferred until Dr. Kaplan and Dr. Rosenberg had presented more detailed information about the contiguity and spread of Hodgkin's disease in their patients.

Dr. Thomas presented data about the relative frequency of Hodgkin's disease in the liver, spleen, bone marrow, bone, lung, and pleura in the National Cancer Institute autopsy series. The series consists of 117 autopsies on patients treated at the National Cancer Institute from 1953 to 1969. It was pointed out that at death cases initially classified as lymphocytic predominance show less pulmonary or pleural involvement than do cases of mixed cellularity, lymphocytic depletion, or nodular sclerosis. Also, cases initially diagnosed as nodular sclerosis show at death a higher percentage of involvement of the lung and pleura than do the other types. Of the total series, 84 (71%) had splenic involvement and 72 (63%) had hepatic involvement. Of particular interest were 8 patients who had liver involvement without documented splenic disease. Dr. Musshoff reported that he has also encountered cases of hepatic involvement without splenic involvement of their laparotomy material. These observations are at variance with the Stanford series, in which the liver was never involved in a patient with a negative spleen. To some degree these differences may be due to sampling error. All agreed that, even if Hodgkin's disease can involve the liver without prior invasion of the spleen, it must do so with great rarity. A negative spleen at laparotomy is perhaps the best evidence against hepatic involvement, since the volume of hepatic tissue available for examination in needle or wedge biopsies is miniscule in proportion to the hepatic tissue at risk.