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Formal Discussion of Robert J. Lukes' Paper, "Criteria for Involvement of Lymph Node, Bone Marrow, Spleen, and Liver in Hodgkin's Disease"

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Recently published observations by Lukes *et al.* (6) and Strum *et al.* (7) have thrown a questionable light on the specificity of the Reed-Sternberg cell in the diagnosis of Hodgkin's disease. These authors have described instances in which biopsy sections of both benign and malignant lesions other than Hodgkin's disease have revealed cells closely resembling or indistinguishable from Reed-Sternberg cells. Furthermore, they quote periodic reports since 1935 describing the presence of cells masquerading as Reed-Sternberg cells in a variety of other disease entities. Jackson and Parkers' classic description of Hodgkin's disease (2) emphasizes the fact that the diagnosis of Hodgkin's disease cannot be made in the absence of Reed-Sternberg cells, but the diagnosis must depend on the picture of the section as a whole.

We have attempted to follow these teachings to the best of our ability. Problems of identification of Reed-Sternberg cells in lymph node biopsies and other tissues relate frequently to poor fixation and to inadequate sectioning and staining procedures. We demand identification of characteristic Reed-Sternberg cells in the original biopsy and frequently request the loan of paraffin blocks from referring pathologists in order to obtain uniform staining. The finding of Reed-Sternberg cells must then be correlated with appropriate cellular and architectural patterns corresponding to those described by Lukes and Butler (5).

As described by Strum and Rappaport (8), we have recognized focal involvement of both peripheral and abdominal lymph node biopsies, with partial maintenance of the normal architectural patterns (4). The effects of lymphangiography have not interfered with our ability to detect microscopic lesions in these lymph nodes. We have also observed very small lesions involving Malpighian corpuscles of the spleen, which have necessitated the cutting of many sections in order to identify Reed-Sternberg cells. We have not yet encountered microscopic involvement of the spleen without first macroscopically observing the lesions, however tiny. On the other hand, microscopic involvement of lymph nodes in the abdomen is by no means uncommon in our experience. Furthermore, we have recently made similar observations in scalene lymph node biopsies which are now included in the surgical staging procedure at Stanford Medical Center. Scalene lymph nodes may also show lymphangiogram effect.

We have encountered most difficulties in relation to the interpretation of liver and bone marrow biopsies. In the liver, inflammatory infiltrates may be seen in the portal tracts, particularly in wedge biopsies, just beneath the capsule. These often are composed of lymphocytes, histiocytes, and occasional eosinophils. In most instances such lesions are nonspecific. However, if they are associated with the presence of atypical histiocytes possessing prominant eosinophilic nucleoli and expand the portal tract or involve periportal tissue, we examine serial sections in the search for Reed-Sternberg cells. In several instances, we have interpreted atypical lesions of this nature as consistent with Hodgkin's disease even in the absence of identifiable Reed-Sternberg cells. We will only do this in a patient who has diagnostic evidence of Hodgkin's disease elsewhere. Similar observations have been made with regard to focal lesions in the bone marrow. In some instances, bone marrow involvement in patients with nodular sclerosing Hodgkin's disease elsewhere may be associated with diffuse fibrosis, and Reed-Sternberg cells may be extremely difficult to identify. Reticulin stains are a great help in the interpretation of focal lesions in bone marrow biopsies. The presence of abnormal reticulin patterns associated with lymphocytes, atypical histiocytes, mononuclear cells with prominent nucleoli, fibroblasts, and eosinophils, in the absence of Reed-Sternberg cells, has been interpreted by us as indicative of Hodgkin's disease in patients subjected to surgical staging procedures at Stanford. Conversely, Reed-Sternberg cells in the marrow are always associated with an appropriate stromal reaction.

Comparison of lesions in peripheral lymph nodes with those encountered in the spleen and abdominal nodes has disclosed a remarkable constancy of histological patterns. However, in 13 of 137 patients with nodular sclerosing Hodgkin's disease (1), we observed lesions containing characteristic nodular aggregates of hyperlobated cells in lacunar spaces, with minimal or absent sclerosis. We have chosen to interpret such lesions as representing the cellular phase of nodular sclerosis. We do not regard this as evidence of progression to the mixed cellularity type, since involved lymph nodes elsewhere in the same patient showed characteristic nodular sclerosis. (1, 4). Strum and Rappaport (9) have confirmed this concept by examining sequential biopsies, demonstrating the development of sclerosis in these patients over a period of time.

We have recently reported the observation of isolated granulomas in a series of patients undergoing staging laparotomy and open iliac crest bone marrow biopsy at Stanford Medical Center (3, 4). While we have also recognized this granulomatous reaction in association with lesions which are diagnostic of Hodgkin's disease, we have encountered isolated sarcoid-like granulomas in lymph node biopsies,

spleen, liver, and bone marrow biopsies. These are composed of epithelioid histiocytes with or without giant cells of the Langhans type. They may be accompanied by lymphocytes and a few eosinophils. However, in many sections examined we have not been able to identify evidence of associated Hodgkin's disease. In the spleen, these granulomas occur predominantly in Malpighian corpuscles, in a paravascular and frequently subendothelial location. They may also occur in the red pulp. They are seen in both portal tracts and parenchyma of the liver, and isolated lesions have been observed in the bone marrow. Special stains for acid-fast bacilli and fungal elements have consistently proved negative. Accordingly, the observation of isolated granulomas has not influenced the clinical staging of such patients.

References

1. Dorfman, R. F. Relationship of Histology to Site in Hodgkin's Disease. Cancer Res., *31:* 1786–1793, 1971.
2. Jackson, H., and Parker, F. Hodgkin's Disease. New Engl. J. Med., *231:* 35–44, 1944.
3. Kadin, M. E., Donaldson, S. S., and Dorfman, R. F. Isolated Granulomas in Hodgkin's Disease. New Engl. J. Med., *283:* 859–861, 1970.
4. Kadin, M. E., Glatstein, E., and Dorfman, R. F. Clinico-pathologic Studies of 117 Untreated Patients Subjected to Laparotomy for the Staging of Hodgkin's Disease. Cancer, *27:* 1277–1294, 1971.
5. Lukes, R. J., and Butler, J. J. The Pathology and Nomenclature of Hodgkin's Disease. Cancer Res., *26:* 1063–1081, 1966.
6. Lukes, R. J., Tindle, B. H., and Parker, J. W. Reed-Sternberg-like Cells in Infectious Mononucleosis. Lancet, *2:* 1003–1004, 1969.
7. Strum, S. B., Park, J. K., and Rappaport, H. Observation of Cells Resembling Sternberg-Reed Cells in Conditions Other Than Hodgkin's Disease. Cancer, *26:* 176–190, 1970.
8. Strum, S. B., and Rappaport, H. Significance of Focal Involvment of Lymph Nodes for the Diagnosis and Staging of Hodgkin's Disease. Cancer, *25:* 1314–1319, 1970.
9. Strum, S. B., and Rappaport, H. Interrelations of the Histologic Types of Hodgkin's Disease. Arch. Pathol. *91:* 127–134, 1971.