Dr. Marvin J. Stone

MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

17 May 1973

[MARVIN J. STONE]

HODGKIN'S DISEASE

I. Definition and Historical Aspects

II. The Reed-Sternberg Cell and Histopathologic Classification

III. The Nature of Hodgkin's Disease

- A. Etiology and Pathogenesis
- B. Epidemiology

IV. The Immunologic Defect

V. Clinical Evaluation

- A. Initial Presentation and Natural History
- B. Laboratory Features
- C. Staging
  - 1. Classification
  - 2. Mode of Spread
  - 3. The Role of Lymphangiography
  - 4. The Role of Laparotomy and Splenectomy

VI. Therapy and Prognosis

- A. Radiotherapy
- B. Chemotherapy

VII. Summary

VIII. Case Protocols

I. Definition and Historical Aspects

"There is no completely satisfactory definition for Hodgkin's disease: Its pathogenesis is unknown; transmission of the disease by transplantation or inoculation of diseased tissue into other species has not been possible; and the histologic features on which diagnoses are based are pleomorphic, variable, and subjective. In descriptive terms Hodgkin's disease (HD) is a malignant neoplasm which ordinarily arises in some lymph nodes and spreads to involve other lymph nodes. Neoplastic and reactive elements are intermingled in a uniquely complicated way which makes their identification and separation difficult. A common denominator in all types of Hodgkin's disease, however, is the presence of atypical, malignant-appearing reticulum cells, some or many of which are the multiple or multilobed Reed-Sternberg (RS) cells. The diagnosis of HD cannot be made in the absence of RS cells, but their presence alone is not sufficient for the diagnosis. They must be present in an appropriate cellular and architectural environment. Criteria for the identification of RS cells vary considerably among observers, and their relationship to the accompanying more rapidly proliferating mononuclear cells with a similar nuclear structure is uncertain."

1. Rundles, R. W. Hodgkin's disease. In: Hematology (Williams, W. J., Beutler, E., Erslev, A. J., and Rundles, R. W., editors), New York: McGraw-Hill, 1972, ch. 109.

In 1832, Thomas Hodgkin described 7 patients with tumorous enlargement of the lymph nodes, spleen and liver. His paper, entitled "On Some Morbid Appearances of the Absorbent Glands and Spleen" was the first report identifying splenomegaly and diffuse nonsuppurative adenopathy as components of a chronic and eventually fatal disease. The paper received little attention until 1865 when Samuel Wilks reviewed Hodgkin's cases and added 15 more of his own to which he attached the eponym, "Hodgkin's disease". Langhans (1872) and Greenfield (1878) were the first to describe the histopathology and both commented on the characteristic binucleate or multinucleate giant cells of HD. However, Sternberg (1898) and Reed (1902) made a more thorough and definitive study of the giant cells (which were subsequently named after them) and emphasized that HD constituted a distinct histopathologic entity.

2. Kaplan, H. S. Hodgkin's Disease. Cambridge: Harvard Univ. Press, 1972.

The first monograph on the subject in 25 years, this book is a comprehensive review written by one of the foremost experts in the field. It contains a wealth of information and is well written, profusely illustrated, extensively referenced and relatively inexpensive.

II. The Reed-Sternberg (R-S) Cell

The presence of these cells is essential for the dx of HD. In H & E stained sections, they are large cells, 15-45 μ in diameter, with abundant pale cytoplasm and either multiple or multilobed nuclei. The nuclear membrane is well-stained and frequently thickened. The nuclear chromatin

structure is delicate and the nucleoli are large, sometimes enormous, with smooth margins and a strong affinity for acid dyes. Mononuclear cells having identical nuclear and nucieolar appearance are usually also present in most sections but these may be found in reactive and inflammatory states and are, therefore, nonspecific. The definitive diagnosis of HD requires the unambiguous identification of one or more R-S cells, the two most distinctive and diagnostically reliable features of which are the huge inclusion-like nucleolus and the multilobate, binucleate or multinucleate nucleus. Both the mononuclear and the classic R-S cells of HD are thought to be abnormal reticulum (histiocytic) forms; these two kinds of cells have collectively been termed "Hodgkin's cells" (Seif and Spriggs).

Mitotic figures are infrequently seen in HD. Since the nucleolus and nuclear membrane disappear during mitosis, the characteristics on which an unambiguous identification of R-S cells depends are not present. Autoradiographic studies (with tritiated thymidine) of lymph node biopsies have shown that only a relatively small fraction of the abnormal reticulum cells actively synthesize DNA (labeling indices of 8-35%). No labeling was detected in classic R-S cells. It thus appears that only a small minority of Hodgkin's cells actively proliferate and that the R-S cell is a nonproliferating end stage derivative. The DNA content of Hodgkin's cells is increased in amount and such cells frequently display aneuploidy - i.e., they contain a chromosomal number which is not an even multiple of the haploid number. Aneuploid DNA content, a generally accepted cytologic marker of malignancy, is often seen in the abnormal mononuclear cells and is usually found in classic R-S cells. Moreover, a mitotically active subpopulation of aneuploid, hypotetraploid cells is present in lymph nodes obtained from approximately 50% of HD cases. These data, together with fragmentary evidence that some of the hypotetraploid cells are clonally derived, provide the most compelling evidence that the abnormal reticulum cells characteristic of HD are, in fact, neoplastic.

3. Rappaport, H. Tumors of the Hematopoietic System. Atlas of Tumor Pathology, Section III, Fascicle 8, AFIP, Washington, D. C., 1966.

4. Seif, G. S. F. and Spriggs, A. I. Chromosome changes in Hodgkin's disease. J. Nat. Cancer Inst. 39:557, 1967.

5. Peckham, M. J. and Cooper, E. H. Proliferation characteristics of the various classes of cells in Hodgkin's disease. Cancer 24:135, 1969.

6. Petrakis, N. L., Bostick, W. L. and Siegel, B. V. The DNA content of Sternberg-Reed cells of Hodgkin's disease. J. Nat. Cancer Inst. 22:551, 1959.

7. Dorfman, R. F. Biology of malignant neoplasia of the lymphoreticular tissues. J. Reticuloendothel. Soc. 12:239, 1972.

R-S cells have been identified in thoracic duct lymph and peripheral blood. In the latter instance, the cells are found in patients having generalized, advanced disease (particularly with intra-abdominal involvement). Very rare cases of true R-S cell leukemia have also been documented.

8. Engeset, A., Brennhord, I. O., Christensen, I., Hagen, S., Hoeg, K., Host, H., Liverud, K., and Nesheim, A. Sternberg-Reed cells in the thoracic duct lymph of patients with Hodgkin's disease. A preliminary report. Blood 31:99, 1968.

9. Bouroncle, B. A. Sternberg-Reed cells in the peripheral blood of patients with Hodgkin's disease. Blood 27:544, 1966.

10. Scheerer, P. P., Pierre, R. V., Schwartz, D. L., and Linman, J. W. Reed-Sternberg cell leukemia and lactic acidosis. Unusual manifestations of Hodgkin's disease. New Eng. J. Med. 270:274, 1964.

11. Sinks, L. F. and Clein, G. P. The cytogenetics and cell metabolism of circulating Reed-Sternberg cells. Brit. J. Hematol. 12:447, 1966.

Histopathologic Classification

In addition to the distinctive R-S cells, HD differs from other malignant lymphomas in that the apparently malignant cell type constitutes only a minor and variable component responsible for the histopathologic features observed in an involved lymph node. The enlargement of the node and obliteration of normal architecture is predominantly due to the entry and proliferation of several classes of normal or reactive stromal cells in varying proportions. The principal cell types seen include lymphocytes of various sizes, transformed lymphocytes ("immunoblasts"), normal reticulum cells (histiocytes), eosinophils, plasma cells and fibroblasts. The role of these cellular elements is obscure but their presence suggests an immunologic response by the host to the as yet unidentified etiologic agent of HD. In addition to these cellular infiltrates, necrosis may be seen in HD node biopsies, especially in the more aggressive histopathologic forms.

Jackson and Parker made the first attempt to classify HD histologically in the 1940's. Although their scheme was widely used by pathologists for nearly 20 years, it lacked utility since the favorable paragranuloma and unfavorable sarcoma subtypes accounted for only ≅ 10% of cases, the other 90% falling into the granuloma category. This grouping has been replaced by the Lukes-Butler classification which was subsequently adopted in a simplified form at a conference on "Obstacles to the Control of Hodgkin's Disease" held at Rye, N. Y. in 1966 (see Tables 1 and 2).

Table 1. Interrelationships of the Major Histopathologic Classifications of Hodgkin's Disease (from Ref. 2)

Jackson and Parker	Lukes, Butler, and Hicks	Rye	Distinctive features	Relative frequency, percent
Paragranuloma	Lymphocytic/histiocytic, diffuse Lymphocytic/histiocytic, nodular	Lymphocytic predominance	Abundant stroma of mature lymphocytes and/or histiocytes; no necrosis; Sternberg-Reed cells may be sparse	10–15
Granuloma	Nodular sclerosis	Nodular sclerosis	Nodules of lymphoid tissue separated by bands of doubly refractile collagen; atypical "lacunar" Hodgkin's cells in clear spaces within the lymphoid nodules	20–50
	Mixed	Mixed cellularity	Usually numerous Sternberg-Reed cells and mononuclear Hodgkin's cells in a pleomorphic stroma of eosinophils, plasma cells, fibroblasts, and necrotic foci	20–40
Sarcoma	Diffuse fibrosis Reticular	Lymphocytic depletion	Sternberg-Reed cells usually, though not always, abundant; marked paucity of lymphocytes; diffuse nonrefractile fibrosis and necrosis may be present	5–15

Table 2. Histopathologic Classification of Hodgkin's Disease*

Subtype	R-S cells	Lymphocytes	Collagen Bands	Diffuse Fibrosis	Eosinophils, Plasma Cells, Necrosis
1) Lymphocyte predominance (LP)	1+	5+	0	0	0
2) Nodular sclerosis (NS)	1+ - 3+ (Lacunar)	1+ - 3+	1+ - 4+	1+	1+
3) Mixed cellularity (MC)	2+ - 3+	1+	0	2+	2+
4) Lymphocyte depletion (LD)					
a) Diffuse fibrosis	2+	0	0	5+	1+
b) Reticular	5+	1+	0	1+	2+

* Modified from ref. 14.

The Rye Classification, a major improvement on the old Jackson and Parker scheme, is based on two previously known but largely neglected findings:

1) the importance of the relative proportion of abnormal reticulum cells and R-S cells to all other cells, especially lymphocytes. Previous workers had commented on the fact that survival in HD correlated with the ratio of lymphocytes to R-S cells in pre-treatment biopsies.

2) Within the granuloma group, there existed a large subgroup of patients with better survival who displayed fibrosis (sclerosis) in their biopsies. Thus a new category called nodular sclerosis was established which is characterized by a) trabecular bands of collagen coursing through the node and subdividing the lymphoid tissue into nodules, and b) the presence of variants of typical R-S cells (lacunar cells).

Subsequent studies have confirmed the unequivocal correlation of the 4 histopathologic subtypes with a variety of clinical parameters as well as survival. Thus certain generalizations may be made:

1) The most favorable prognostic groups are LP and NS while LD is the least favorable.

2) Usually, LP and NS are associated with localized (Stage I or II) disease whereas LD is associated with disseminated (Stage III or IV) disease.

3) MC may be seen in any clinical stage but indicates a poorer prognosis than LP in Stage I or II and perhaps in Stage III.

4) MC or LD tend to occur in elderly patients while NS is most commonly seen in individuals 15 to 35 years of age, particularly women.

5) NS tends to be localized primarily to the neck and mediastinum; intra-abdominal disease occurs less frequently than in patients whose initial biopsies show either MC or LD.

12. Lukes, R. J. and Butler, J. J. The pathology and nomenclature of Hodgkin's disease. Cancer Res. 26:1063, 1966.

13. Lukes, R. J., Craver, L. F., Hall, T. F., Rappaport, H. and Ruben, P. Report of the nomenclature committee. Cancer Res. 26:1311, 1966.

14. Aisenberg, A. C. Malignant lymphoma. New Eng. J. Med. 288:883, 935, 1973.

15. Lukes, R. J. The pathologic picture of the malignant lymphomas. In: Proc. of the International Conf. on Leukemia-Lymphoma (Zarafonetis, CJD, editor), Philadelphia: Lea and Febiger, 1968.

16. Lukes, R. J. Criteria for involvement of lymph node, bone marrow, spleen and liver in Hodgkin's disease. Cancer Res. 31:1755, 1971.

17. Butler, J. J. Relationship of histological findings to survival in Hodgkin's disease. Cancer Res. 31:1770, 1971.

18. Berard, C. W. Histopathology of the lymphomas. In: Hematology (Williams, W. J., Beutler, E., Erslev, A. J. and Rundles, R. W., editors), New York: McGraw-Hill, 1972, ch. 108.

19. Sheehan, W. W. and Rappaport, H. Morphological criteria in the classification of the malignant lymphomas. In: Proc. Sixth National Cancer Conference, New York: J. B. Lippincott, 1970, p. 59.

20. Strum, S. B., and Rappaport, H. Interrelations of the histologic types of Hodgkin's disease. Arch. Path. 91:127, 1971.

21. Berard, C. W., Thomas, L. B., Axtell, L. M., Kruse, M., Newell, G. and Kagan, R. The relationship of histopathological subtype to clinical stage of Hodgkin's disease at diagnosis, Cancer Res. 31:1776, 1971.

22. Editorial, The Hodgkin maze, Lancet 2:728, 1969. Also see: Editorial, Further in the Hodgkin maze, Lancet 1:1053, 1971.

23. Neiman, R. S., Rosen, P. J., and Lukes, R. J. Lymphocyte-depletion Hodgkin's disease. A clinicopathological entity. New Eng. J. Med. 288:751, 1973.

Despite the advantages of the Rye classification, the histopathologic diagnosis of HD is not simple. Differentiation from inflammatory and other non-neoplastic reactive conditions may be extremely difficult and interpathologist disagreement in interpretation appears to be in the range of 10%, even among experts. Many errors are due to technically unsatisfactory biopsy slides. Typical R-S cells may be sufficiently sparse so as to be missed in the initial section. To further compound the problems of diagnosis, cells having the appearance of classic R-S cells have been described in other malignancies and, more importantly, in some benign conditions (Table 3). These findings emphasize that although a definitive diagnosis of HD cannot be made in the absence of R-S cells, the diagnosis depends on the total histologic picture.

Table 3. Reed-Sternberg Cells in Conditions Other Than Hodgkin's Disease*

Malignant	Benign
Breast carcinoma	Infectious mononucleosis
Lung adenocarcinoma	Rubeola
Malignant melanoma	Postvaccinial lymphadenitis
Malignant fibroxanthoma	Proliferative myositis
Malignant lymphoma, mixed cell type, nodular	Hydantoin-induced pseudolymphoma
Malignant lymphoma, poorly differentiated lymphocytic type, nodular	Thymoma
Panmyelosis with pronounced megakaryocytic proliferation	
Mycosis fungoides	
Multiple myeloma	

* Modified from ref. 27.

In the case of infectious mononucleosis, the situation is even more complex in light of the documentation of HD following infectious mono in some 30 instances and by the reports of positive mono spot tests and elevated EB virus titers in patients with HD. The status of hydantoin pseudolymphoma is no less confusing. Cases of true HD and other malignant lymphomas have now been reported in some individuals originally thought to have hydantoin-induced lymphadenopathy. Thus it appears that there are at present no consistent histologic or clinical criteria on the basis of which reliable differentiation between benign and malignant lymphoid reactions in hydantoin-treated patients can be made.

24. Symmers, W. S. C. Survey of the eventual diagnosis in 600 cases referred for a second histological opinion after an initial biopsy diagnosis of Hodgkin's disease. J. Clin. Path. 21:650, 1968.

25. Coppleson, L. W., Factor, R. M., Strum, S. B., Graff, P. W. and Rappaport, H. Observer disagreement in the classification and histology in Hodgkin's disease. J. Nat. Cancer Inst. 45:731, 1970.

26. Lukes, R. J., Tindle, B. H. and Parker, J. W. Reed-Sternberg-like cells in infectious mononucleosis. Lancet 2:1003, 1969.

27. 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, 1970.

28. Wolf, P., Dorfman, R., McClenahan, J. and Collins, F. False-positive infectious mononucleosis spot test in lymphoma. Cancer 25:626, 1970.

29. Levine, P. H., Ablashi, D. V., Berard, C. W., Carbone, P. P., Waggoner, D. E. and Malan, L. Elevated antibody titers to Epstein-Barr virus in Hodgkin's disease. Cancer 27:416, 1971.

30. Salvador, A. H., Harrison, E. G. and Kyle, R. A. Lymphadenopathy due to infectious mononucleosis: Its confusion with malignant lymphoma. Cancer 27: 1029, 1971.

31. Stevens, D. A. Infectious mononucleosis and malignant lymphoproliferative diseases. JAMA 219:897, 1972. Also see ref. 2, ch. 3.

32. Saltzstein, S. L., and Ackerman, L. V. Lymphadenopathy induced by anti-convulsant drugs and mimicking clinically and pathologically malignant lymphomas. Cancer 12:164, 1959.

33. Doyle, A. P. and Hellstrom, H. R. Mesantoin lymphadenopathy morphologically simulating Hodgkin's disease. Ann. Int. Med. 59:363, 1963.

34. Gams, R. A., Neal, J. A. and Conrad, F. G. Hydantoin-induced pseudo-pseudolymphoma. Ann. Int. Med. 69:557, 1968.

35. Editorial, Is phenytoin carcinogenic? Lancet 2:1071, 1971.

Finally, it is worth pointing out that differentiation of megakaryocytes from R-S cells may be quite difficult as dramatically illustrated in a recent CPC.

36. Case records of the Massachusetts General Hospital. New Eng. J. Med. 288:570, 1973.

III. The Nature of Hodgkin's Disease

A. Etiology and Pathogenesis

The cause of HD has remained an enigma. Many investigators have believed that the disorder resembles an infection more than a neoplasm but infectious agents have never been reproducibly incriminated though long sought. The lack of a suitable animal model of the human disease has undoubtedly hampered progress in this regard. Since other lymphomas and leukemias in many species of animals are known to be caused by viruses, these agents are likely possibilities. Evidence

for the viral etiology of HD has received support from 2 recent studies: 1) a new tumor antigen has been found in spleens from 3 patients with HD using a rabbit antiserum prepared against HD tissue; the antigen was apparently shared by the 3 patients studied; 2) continuous culture of HD tissue has shown that blastoid transformation occurs accompanied by release into the medium of an RNA virus and also a novel DNA herpes-like agent. Extension and confirmation of these studies are necessary before their significance can be assessed.

Immunologic and genetic factors have also been implicated in the etiology of HD. Kaplan and Smithers first called attention to the similarity between the lymphoid depletion noted in HD and that seen in animals with graft-versus-host disease. They as well as others have suggested that autoimmune (or perhaps altered immune) mechanisms play a significant role in pathogenesis. As mentioned previously, the tissue reaction observed histologically displays many features in common with an immune response. Similar suggestions have been made for the peripheral blood changes seen in HD. The ability to respond to certain antigens is known to be influenced by genetic factors and an increased incidence of some HL-A antigens has been reported in patients with HD. As noted above, certain drugs (hydantoins) appear to be occasionally responsible for lymphoid changes that closely resemble malignant lymphoma and may, in fact, participate in the induction of true lymphomatous neoplasms. Finally, the proposal that prior tonsillectomy increases the susceptibility to HD by removal of a "lymphoid barrier" remains controversial.

Two recent hypotheses attempt to explain the etiology and pathogenesis of HD by relating oncogenic viruses to an altered host immunologic response in a manner which ultimately leads to the neoplastic proliferation of lymphoreticular cells.

37. Order, S. E., Porter, M. and Hellman, S. Hodgkin's disease: Evidence for a tumor-associated antigen. New Eng. J. Med. 285:471, 1971.

38. Eisinger, M., Fox, S. M., Dettarven, E., Biedler, J. L. and Sanders, F. K. Virus-like agents from patients with Hodgkin's disease. Nature 233:104, 1971.

39. Kaplan, H. S. and Smithers, D. W. Auto-immunity in man and homologous disease in mice in relation to the malignant lymphomas. Lancet 2:1, 1959.

40. Schwartz, R. S. and Beldotti, L. Malignant lymphomas following allogenic disease: Transition from an immunological to a neoplastic disorder. Science 149:1511, 1965.

41. Hoffbrand, B. I. Hodgkin's disease, autoimmunity and the thymus. Brit. Med. J. 1:1592, 1965.

42. Smithers, D. W. Hodgkin's disease. Brit. Med. J. 2:263, 337, 1967.

43. Crowther, D., Fairley, G. H. and Sewell, R. L. Significance of the changes in the circulating lymphoid cells in Hodgkin's disease. Brit. Med. J. 2:473, 1969.

44. Vianna, N. J., Greenwald, P. and Davies, J. N. P. Nature of Hodgkin's disease agent. Lancet 1:733, 1971.

45. Falk, J. and Osoba, D. HL-A antigens and survival in Hodgkin's disease. Lancet 2:1118, 1971.

46. McDevitt, H. O. and Bodmer, W. F. Histocompatibility antigens, immune responsiveness and susceptibility to disease. Amer. J. Med. 52:1, 1972.

47. Vianna, N. J., Greenwald, P. and Davies, J. N. P. Tonsillectomy and Hodgkin's disease: The lymphoid barrier. Lancet 1:431, 1971.

48. Johnson, S. K. and Johnson, R. E. Tonsillectomy history in Hodgkin's disease. New Eng. J. Med. 287:1122, 1972.

49. Order, S. E. and Hellman, S. Pathogenesis of Hodgkin's disease. Lancet 1:571, 1972.

50. Schwartz, R. S. Immunoregulation, oncogenic viruses, and malignant lymphomas. Lancet 1:1266, 1972.

B. Epidemiology

HD accounts for 25-30% of all malignant lymphomas and is more common in men. During the period from 1945 to 1970 the incidence rate was 2.4/100,000 in Olmsted County, Minnesota. Whereas lymphosarcoma and reticulum cell sarcoma occur predominantly in individuals over age 50, HD has a bimodal age curve with a high incidence in young people between the ages of 18 and 35 and a second peak in the older age group. The same bimodal character has been observed in the U. S., Germany, Denmark and Israel and is also apparent in age-specific mortality rates for both sexes (Fig. 1).

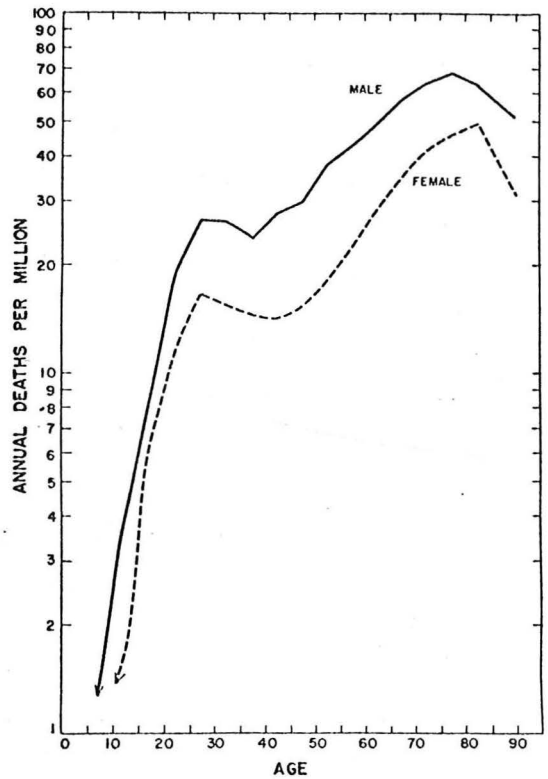

Figure 1. Age-specific mortality rates from Hodgkin's disease by sex, United States, 1958-62. From ref. 52.

Such a distribution has suggested to some that the disease may not be a single entity but a syndrome comprising at least 2 entities with distinct etiologies. Thus in 1966 MacMahon postulated that HD in young adults was a chronic granulomatous inflammation while in the elderly it was a neoplasm. This concept has been challenged for several reasons - the principal one being that nodular sclerosis, which tends to localize and therefore carries a good prognosis, is confined almost totally to the younger age group, particularly women. An alternative view (Smithers) holds that HD represents a single progressive neoplastic disorder from lymphocyte predominance through mixed cellularity to lymphocyte depletion in which host resistance may develop and that when this occurs, the disease is seen histologically as the nodular sclerosis pattern and clinically by a tendency to become arrested when localized. If true, then host resistance to the tumor is more effective in women and younger patients.

Intriguing but debatable support for an infectious etiology of HD has also come from scattered reports of "clustering" of patients with the disease. Close relatives of patients are said to have a two to three-fold chance of developing the disease as compared with that of the general population. Moreover, HD has been reported in husband and wife as well as in 6 pairs of siblings. The most impressive report suggesting that HD may be transmitted to susceptible subjects by case-to-case as well as by case-to-contact-to-case routes has come from Vianna et al. who examined the incidence of HD in Albany, N. Y. from 1950 to 1970. The study centered on a group of students who entered Albany High School in 1950. From 1950 to 1970, 34 linked patients with lymphoma were documented, 31 of whom had HD! These were found among the students, their friends and household relatives. Nine cases appeared to be case-to-case associations while the remaining twenty-five were case-to-contact-to-case associations. There was no evidence of geographical clustering and there was only one family in which two members were affected. Such startling results are difficult to evaluate statistically but imply that infection may be one of the factors favoring the development of HD and that carriers of such infection may be the means of transmission of the disease to susceptible individuals.

51. Nobrega, F. T., Kyle, R. A. and Harrison, E. G. Malignant lymphoma including Hodgkin's disease occurring in the vicinity of a large medical center (Olmsted County, Minn., 1945 through 1969). Cancer 31:295, 1973.

52. MacMahon, B. Epidemiology of Hodgkin's disease. Cancer Res. 26:1189, 1966.

53. Cole, P., MacMahon, B. and Aisenberg, A. Mortality from Hodgkin's disease in the United States. Evidence for a multiple-etiology hypothesis. Lancet 2:1371, 1968.

54. Smithers, D. W. Hodgkin's disease: One entity or two. Lancet 2: 1285, 1970.

55. MacMahon, B. Epidemiological considerations of staging in Hodgkin's disease. Cancer Res. 31:1854, 1971.

56. Cole, P. Epidemiology of Hodgkin's disease. JAMA 222:1636, 1972.

57. Vianna, N. J., Greenwald, P., Brady, J., Polan, A. K., Dwork, A., Mauro, J. and Davies, J. N. P. Hodgkin's disease: Cases with features of a community outbreak. Ann. Int. Med. 77:169, 1972.

58. Editorial, Clustering in Hodgkin's disease. Lancet 2:907, 1972.

59. Klinger, R. J. and Minton, J. P. Case clustering of Hodgkin's disease in a small rural community, with associations among cases. Lancet 1:168, 1973.

In summary, the etiology and pathogenesis of HD are unknown. Although controversy over whether it is inflammatory or neoplastic in nature has existed since the disease was first described, no clear-cut resolution has been forthcoming. Although the viral etiology of lymphoma and leukemia in many animal

species has been established and indirect virologic and epidemiologic evidence supports such a mechanism in patients with HD, the causative agent(s) has not been identified nor isolated. It appears likely at least some cases of HD result from the protracted influence of an oncogenic virus on the lymphoreticular cells which eventually leads to neoplastic transformation. There is some evidence suggesting that HD may be at least two processes, each with a distinct etiology. However, the possibility remains that the apparent heterogeneity results from variations in host response to a single etiologic factor. Further information about the structure and function of the normal lymphoid system, the effect of oncogenic viruses on lymphoid tissue and the role of genetic factors in susceptibility to virus infections should aid considerably in elucidating the cause of HD.

IV. The Immunologic Defect

Recent advances in knowledge of the differentiation and heterogeneity of the lymphoid system aid greatly in understanding the pathogenesis of immune defects which occur in patients with lymphoreticular malignancies. Normally, 70-80% of peripheral blood lymphocytes as well as those situated in the deep cortical (paracortical) areas of lymph nodes are derived from the thymus (T cells) and are responsible for mediating cellular immune responses. These include delayed hypersensitivity skin reactivity, solid tissue allograft rejection and graft-versus-host (GVH) reactions. The T cell system may also serve in a surveillance capacity to detect and destroy malignant cells. The major function of T cells, however, is to provide a defense against many viruses, fungi and facultative intracellular bacterial pathogens (mycobacteria). The other principal subpopulation of lymphoid cells normally consists of 20-30% of peripheral blood lymphocytes and the lymphocytes located in the far (or outer) cortical areas and along the medullary cords of lymph nodes. These cells are derived from the bursa of Fabricius in birds and the bone marrow (B cells) in mammals. B cells mediate humoral immunity by virtue of their ability to proliferate and differentiate into immunoglobulin-producing plasma cells after contact with antigen. B cells and their antibody products thus constitute the major protective mechanism against encapsulated high-grade pyogenic bacteria - pneumococci, streptococci, meningococci, Hemophilus influenzae and Pseudomonas aeruginosa. It is therefore possible to predict the likely consequences of primary (congenital) or secondary (acquired) derangements of T and B cell function. Bruton agammaglobulinemia and multiple myeloma are classic examples of B cell defects while the DiGeorge syndrome and Hodgkin's disease are prototype T cell deficiencies (Table 4).

Table 4. Distribution and Deficiency of Immunologically Competent Cells

Lymphoid Subpopulation	Distribution	Consequences of Deficiency	Clinical Examples of Deficiency	
			1°	2°
T cells	PBL: 70-80% LN: Deep cortex	Viral, fungal &/or acid-fast infections Anergy Fatal GVH Retention of skin grafts ↑ malignancies	DiGeorge syndrome	Hodgkin's disease
B cells	PBL: 20-30% LN: Outer cortex and medullary cords	Infections with encapsulated pyogenic bacteria	Bruton agamma-globulinemia	Multiple myeloma

PBL = peripheral blood lymphocytes; LN=lymph nodes

The array of infections observed in patients with HD reflects the pattern of immunologic deficiency. Thus zoster-varicella infections occur in 15-20% of patients. Tuberculosis, cryptococcosis, nocardiosis, cytomegalovirus and a variety of other opportunistic infections are also seen in Hodgkin's patients, particularly in the late stages of the disease. Moreover, infection with multiple organisms occasionally occurs.

Many studies in the literature report cutaneous anergy (inability to manifest delayed hypersensitivity reactions to standard intradermal antigens or after contact sensitization with certain chemicals) in 45-100% of patients with active HD. This high incidence and wide range probably reflects at least two variables in addition to the presence of HD: 1) many studies were performed in patients previously treated with radiation, alkylating agents and/or corticosteroids - each of which is itself immunosuppressive as well as lympholytic; 2) only a small number of test antigens were employed in most series. The study of Young et al. at the NCI is one of the few to assess cutaneous reactivity in untreated patients with HD. These workers determined delayed skin responses to a battery of antigens (PPD, Candida, mumps, histoplasmin, coccidioidin and DNCB) and attempted to correlate the results with stage and prognosis. Their findings in 103 patients indicated that -

1) Anergy was uncommon - only 12% of patients who had the full battery of skin tests were unreactive to all.

2) Skin test reactivity declines as stage of the disease advances; thus anergy was rare with localized disease (Stages I and II) but was present in about 25% of subjects with disseminated disease (Stages III and IV).

3) Mumps and DNCB were the antigens most reliable in ruling out anergy.

4) Patients with favorable histology (LP and NS) tended to maintain skin test reactivity while those with the unfavorable subtypes (MC and LD) exhibited a higher incidence of anergy. Maintenance of skin test reactivity also correlated with absence of constitutional symptoms.

5) Absolute peripheral blood lymphocyte counts reflected staging and skin test reactivity. Profound peripheral lymphocytopenia (< 1000/mm^3) correlated with widespread disease, the lymphocyte depletion subtype and poor prognosis.

Although the NCI study disclosed a lower incidence of anergy in untreated HD patients than was previously supposed, it did substantiate many previous reports suggesting that the defect progresses with the pathologic process. Anergy appears to be an unexplained accompaniment of the disease rather than a primary factor in its cause.

Additional evidence of defective T cell function in HD is given by the variable depression in in vitro lymphocyte reactivity as assessed by 1) response to phytohemagglutinin and 2) the mixed lymphocyte reaction. Also, it should be apparent from the above discussion that the T cell defect may be worsened by therapeutic agents which can be both immunosuppressive and oncogenic. Approximately 20 cases of granulocytic leukemia have been reported in HD - almost all in irradiated patients. Similarly, there appears to be an increased risk of developing nonlymphoreticular neoplasms in patients with HD, particularly those who receive intensive treatment (radiation and chemotherapy).

B cell function in HD is well maintained; immunoglobulin levels are usually normal or elevated and antibody formation is intact (though perhaps not maximal) until the late stages of the disease. Hypogammaglobulinemia has been reported on rare occasions and homogeneous monoclonal components very rarely.

60. Good, R. A. Structure-function relations in the lymphoid system. Clin. Immunobiol. 1:1, 1972.

61. Miller, D. G. Immunological disturbances in lymphoma and leukemia. In: Immunological Diseases (Samter, M., editor). Boston: Little, Brown & Co., 1971, ch. 27.

62. McGee, Z. A., Schaffner, W. and Koenig, M. G. Superinfection in lymphoreticular diseases. Ann. Rev. Med. 22:25, 1971.

63. Goffinet, D. R., Glatstein, E. J. and Merigan, T. C. Herpes zoster-varicella infections and lymphoma. Ann. Int. Med. 76:235, 1972.

64. Wilson, J. F., Marsa, G. W. and Johnson, R. E. Herpes zoster in Hodgkin's disease. Clinical, histologic and immunologic correlations. Cancer 29:461, 1972.

65. Levine, A. S., Graw, R. G. and Young, R. C. Management of infections in patients with leukemia and lymphoma: Current concepts and experimental approaches. Sem. Hematol. 9:141, 1972.

66. Aisenberg, A. C. Lymphocytopenia in Hodgkin's disease. Blood 25:1037, 1965.

67. Young, R. C., Corder, M. P., Haynes, H. A. and DeVita, V. T. Delayed hypersensitivity in Hodgkin's disease. A study of 103 untreated patients. Amer. J. Med. 52:63, 1972.

68. Hersh, E. M. and Oppenheim, J. J. Impaired in vitro lymphocyte transformation in Hodgkin's disease. New Eng. J. Med. 273:1006, 1965.

69. Lang, J. M., Oberling, F., Tongio, M. M., Mayer, S., Waitz, R. Mixed-lymphocyte reaction as assay for immunological competence of lymphocytes from patients with Hodgkin's disease. Lancet 1:1261, 1972.

70. Frenkel, E. P. and Stone, M. J. The rationale and approach to immunosuppressive therapy. Adv. Int. Med. 17:1, 1971.

71. Leibowitz, S. and Schwartz, R. S. Malignancy as a complication of immunosuppressive therapy. Adv. Int. Med. 17:95, 1971.

72. Arseneau, J. C., Sponzo, R. W., Levin, D. L., Schnipper, L. E., Bonner, H., Young, R. C., Canellos, G. P., Johnson, R. E. and DeVita, V. T. Nonlymphomatous malignant tumors complicating Hodgkin's disease. New Eng. J. Med. 287:1119, 1972.

73. Aisenberg, A. C. and Leskowitz, S. Antibody formation in Hodgkin's disease. New Eng. J. Med. 282:1269, 1963.

74. Goldman, J. M. and Hobbs, J. R. The immunoglobulins in Hodgkin's disease. Immunology 13:421, 1967.

Also see ref. 2, ch. 6 and ref. 14 (part one).

V. Clinical Evaluation

A. Initial Presentation and Natural History

Patients characteristically give a history of good health prior to the onset of the disease, which is usually manifested by lymphadenopathy with or without systemic manifestations. Occasionally, a history of a brief antecedent URI or of infections about the head or neck is obtained. The most common presenting symptoms are those of painless, progressive enlargement of a superficial lymph node or group of lymph nodes, especially in the neck and various constitutional manifestations including malaise, anorexia, weight loss, nausea, vomiting, fever or pruritus (Table 5).

Table 5. Presenting Symptoms and Initial Findings in 135 Patients

	Cases	%
Symptoms		
Malaise, anorexia, weight loss, nausea or vomiting	66	49
Fever	53	39
Pain	25	19
Pruritus	20	15
Initial Findings		
Peripheral lymphadenopathy	125	93
Mediastinal and/or retroperitoneal lymphadenopathy	57	42
Hepatomegaly	32	24
Splenomegaly	29	21
Respiratory tract or lung	8	6
Bone involvement	8	6
Central nervous system involvement	8	6

Modified from ref. 75.

The site of initial node involvement is not random - the superficial nodes of the neck appear to be the site of origin in 60-80% of patients. The axillary nodes are the first to be involved in 6-20% of patients, the mediastinal nodes in 6-11% and the inguinal nodes in 6-12%. In contrast to non-Hodgkin's lymphomas, initial involvement of extranodal sites is quite rare in HD. The duration of symptoms and of physical findings before diagnosis is quite variable. The usual careful and thorough physical exam is modified only by a greater emphasis on a search for peripheral lymphadenopathy. The consistency of involved nodes in HD (and most other malignant lymphomas) is typically firm but not stony hard. The firmness tends to have a characteristic resilient quality, similar to the feeling of a solid rubber ball. Such "rubbery" nodes are seldom tender or painful to palpation. Almost any anatomic structure from cranium to popliteal fossa may become involved with lymphoid tumors. In some patients the lymph nodes may enlarge rapidly and produce pain or other obstructive phenomena while in others they increase in size gradually and painlessly over a period of months or even years. Localized pain in the involved nodes after the ingestion of alcohol is a well-documented but rare occurrence (1.6% of Stanford series); the pathophysiologic mechanism of alcohol-induced pain in HD is unknown.

Certain constitutional symptoms, particularly fever, night sweats, weight loss and perhaps pruritus are associated with a significantly poorer prognosis and frequently indicate the presence of widespread disease. When present at the time of initial diagnosis, fever is usually low-grade and smouldering in character. Occasionally, the patient experiences only night sweats without awareness of the fever with which they are usually associated. The cyclic bouts of high fever, each lasting 1 to 2 weeks and separated by afebrile periods of similar duration (Pel-Ebstein), are classically characteristic of the disorder but are seldom seen except in patients with far-advanced disease. HD should always be given careful consideration in the differential diagnosis of FUO. When, as is commonly the circumstance, peripheral lymphadenopathy is not present in such cases, it should be recalled that significant fever in HD is usually associated with the presence of intrathoracic and/or intra-abdominal lymph node involvement. The pathophysiologic mechanisms responsible for fever are unclear.

Signs and symptoms in HD tend to fall into two overlapping patterns, depending somewhat on the age of the patient at time of diagnosis. Younger patients (up to age 40) tend to present with well-defined local tumors and, except for modest intermittent fever or symptoms of a mild anemia, appear healthy. The disease in these individuals may be unifocal in origin or confined to a significant degree by host resistance. By contrast, older patients often display less or virtually no evidence of disease localization and present with pronounced constitutional manifestations. These individuals appear to have multifocal or widespread disease at the outset with minimal evidence of host resistance.

The natural history of the disease in most patients follows a course such that one group of peripheral nodes after another becomes involved as well as those in the retroperitoneal, paraspinal, iliac, inguinal and femoral regions. As the disease advances, the spleen is involved and then the liver. Hodgkin's tissue may also grow in the bone marrow and may produce sclerotic or destructive lesions in the surrounding bone. Ultimately, the disease begins to grow in parenchymal organs in which lymphoid tissue is ordinarily sparse - the lung, liver, gastrointestinal tract, leptomeninges, dura, pleura, thyroid, breast, kidneys, urinary tract and gonads (see ref. 78). It is clear, therefore, that clinically as well as histologically, HD behaves as a malignant neoplasm.

B. Laboratory Features

1. Lymph node biopsy

Although HD may sometimes be diagnosed with almost absolute certainty on clinical grounds alone, confirmation ALWAYS requires histologic verification. The choice of biopsy site in superficial areas is of considerable importance. Large, centrally located, originally involved nodes are preferable and one or more should be gently removed in toto. Biopsy of inguinal or posterior cervical nodes and areas draining infections should be avoided. Rarely, adequate tissue can be obtained only by mediastinal exploration, thoracotomy or laparotomy.

2. Anemia

Decreased red cell values are present in approximately one-third of patients at the time of initial diagnosis and develops in most individuals with severe systemic manifestations. The anemia tends to worsen with advancing disease and improves with remission thus providing some measure of disease activity. The red cells are often microcytic, hypochromic and hypoferremia is characteristic. Although chronic blood loss may account for these findings, an iron reutilization defect is more common. Hemolysis occurs in some patients with Hodgkin's disease and may be due to hypersplenism or to ill-defined mechanisms associated with advanced disease. The Coombs test is usually negative. Finally, anemia may result from decreased marrow production by mechanisms noted below (see section 4).

3. Leukocyte Abnormalities

Neutrophilic leukocytosis is a characteristic peripheral blood finding in HD and usually coexists with absolute lymphocytopenia. Lymphocyte counts tend to be low normal or only slightly depressed at the onset of the disease (normal range:

1500-3000 per mm^3). However, profound lymphocytopenia is characteristic of widespread or terminal disease (see section IV and refs. 66 and 67). Monocytosis and eosinophilia are also seen in the peripheral blood of occasional patients. In addition to the above white cell changes which may be observed on the routine peripheral smear, the leukocyte alkaline phosphatase tends to be elevated during periods of active disease.

4. Other Findings

The platelet count may be high, normal or low. Various cytopenias may result from hypersplenism, involvement of the marrow with HD or toxic marrow suppression following therapy. The ESR is usually rapid and increased levels of α_2, β and γ globulins are frequently seen on serum protein electrophoresis when the disease is active. Serum alkaline phosphatase is elevated in many cases in which bone or liver involvement occurs. Elevation of the serum uric acid level is uncommon and hypercalcemia is rare. Low plasma zinc and elevated serum copper levels have been reported but, like most of the other laboratory tests noted above, are too nonspecific to be of any significant diagnostic aid. Liver-spleen scans may reveal organ enlargement but, as discussed below, are often unreliable for the detection of HD in these organs.

75. Ultmann, J. E. Clinical features and diagnosis of Hodgkin's disease. Cancer 19:297, 1966.

76. Kuiper, D. H. and Papp, J. P. Supraclavicular adenopathy demonstrated by the Valsalva maneuver. New Eng. J. Med. 280:1007, 1969.

77. Teillet, F., Boiron, M. and Bernard, J. A reappraisal of clinical and biological signs in staging of Hodgkin's disease. Cancer Res. 31:1723, 1971.

78. Ultmann, J. E. and Moran, E. M. Clinical course and complications in Hodgkin's disease. Arch. Int. Med. 131:332, 1973.

Also see ref. 1 and ref. 2, ch. 4.

C. Staging

1. Classification

The extent of disease, or stage, at the time of initial diagnosis is the major factor determining prognosis in HD. Because of mounting evidence for an orderly, predictable spread of the disease together with initial data indicating that some patients might be cured by aggressive radiotherapy, a standardized clinical staging classification was adopted at a symposium in Rye, N. Y. in 1966. Stage I designates disease limited to a single lymph-node group, Stage II disease limited to two or more lymph-node groups on the same side of the diaphragm, Stage III disease still limited to lymph nodes or spleen but involving nodes on both sides of the diaphragm, and Stage IV disseminated disease in lymph nodes and extranodal sites (bone, lung, liver, etc.). Each stage is subclassified to indicate the absence "A"

or presence "B" of systemic symptoms. The Rye classification has since been modified so as to permit inclusion of localized extranodal involvement in Stages I, II and III. Such limited extralymphatic disease is designated by the suffix "E". It should be noted, however, that liver and marrow involvement always indicates diffuse (Stage IV) disease. Fever and night sweats continue to be listed as prognostically significant systemic symptoms calling for the "B" subclassification. However, unexplained weight loss has replaced generalized pruritus as the third such systemic manifestation. The revised staging classification is listed in Table 6.

Table 6. Ann Arbor Staging Classification[a]

Stage	Definition
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I_E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III_S) or by localized involvement of an extralymphatic organ or site (III_E) or both (III_{SE})
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement

The absence or presence of fever, night sweats, and/or unexplained loss of 10 percent or more of body weight in the six months preceding admission are to be denoted in all cases by the suffix letters A or B, respectively.

[a]Adopted at the Workshop on the Staging of Hodgkin's Disease held at Ann Arbor, Michigan, in April 1971.

*(From ref. 2)

2. Mode of Spread

Rosenberg and Kaplan carefully analyzed the sites of involvement in 100 unselected untreated patients with HD. 89% of the patients had disease limited to the lymph nodes and spleen. The initial site of extension of disease following radiotherapy was analyzed in the 26 patients who developed new areas of involvement. It was clear that the initial areas of involvement or extension after treatment were non-random; thus 90% of the patients developed new disease in areas immediately adjacent to the initial treatment fields. These observations suggested that HD arises in a single focus and spreads in a predictable manner along contiguous lymphatic channels. This concept was a major advance in the therapy of HD and subsequent experience has confirmed its validity in the vast majority of patients. The incidence of non-contiguous spread is disputed but appears to be in the range of 10-30%. The Rosenberg-Kaplan thesis has been criticized because - 1) it suggests that spread is predominantly against the normal direction of lymph flow (i.e., retrograde), and 2) it does not account for non-contiguous spread. Although lymphatic spread does explain the dissemination of HD to many parts of the body, the involvement of certain organs (liver, bone, skin, and kidneys) cannot be easily ascribed to this mechanism. The same can be said for a certain fraction of cases in which the spleen is involved. In this regard it is now clear that HD can also spread hematogenously. Thus, as noted previously, R-S cells have been found in peripheral blood. Halie et al. have recently called attention to the presence of an abnormal basophilic leukocyte in peripheral blood concentrates from Hodgkin's patients which, they believe, indicates hematogenous dissemination to the spleen. More direct evidence for bloodstream dissemination comes from the studies of Rappaport and Strum who observed vascular invasion by R-S cells and malignant-appearing histiocytes in lymph nodes in 10% of 100 randomly-selected patients. Vascular invasion was not seen in the lymphocyte predominance type whereas the lymphocyte-depletion type accounted for six of the 10 cases in which it was present. Eight of the 10 cases with vascular invasion had Stage III or IV disease. The documentation of vascular invasion in a minority of patients with widespread disease supports the concept that HD is a true malignant neoplasm capable of metastasizing via the blood stream; moreover, the finding of vascular invasion may be a histopathological feature of important prognostic value, since it may indicate that hematogenous dissemination has occurred.

Although the relative importance of hematogenous vs. contiguous spread is argued, it is clear that involvement of the spleen is an important indicator of disseminated HD. The spleen is involved initially in about 30% of patients and in up to 80% of those with advanced disease. Isolated HD of the spleen is extremely rare. Splenic involvement does not correlate with any particular histologic subtype and is unrelated to the presence of systemic symptoms. Excluding Stage IV patients, 40% of consecutive untreated patients are found to have abdominal HD after lymphangiography and laparotomy. Of those with abdominal disease, 90% have splenic Hodgkin's (75% spleen + para-aortic nodes and 15% spleen alone). Thus the spleen appears to be an early (perhaps initial) site of intra-abdominal involvement in most patients with HD.

79. Rosenberg, S. Report of the committee on the staging of Hodgkin's disease. Cancer Res. 26:1310, 1966. See ref. 2, ch. 8 for revised classification.

80. Rosenberg, S. and Kaplan, H. S. Evidence for an orderly progression in the spread of Hodgkin's disease. Cancer Res. 26:1225, 1966.

81. Smithers, D. W. Spread of Hodgkin's disease. Lancet 1:1262, 1970.

82. Rappaport, H. and Strum, S. B. Vascular invasion in Hodgkin's disease: Its incidence and relationship to the spread of the disease. Cancer 25:1304, 1970.

83. Strum, S. B., Hutchison, G. B., Park, J. K., and Rappaport, H. Further observations on the biologic significance of vascular invasion in Hodgkin's disease. Cancer 27:1, 1971.

84. Strum, S. B., Allen, L. W. and Rappaport, H. Vascular invasion in Hodgkin's disease: Its relationship to involvement of the spleen and other extranodal sites. Cancer 28:1329, 1971.

85. Halie, M. R., Eibergen, R. and Nieweg, H. O. Observations on abnormal cells in the peripheral blood and spleen in Hodgkin's disease. Brit. Med. J. 2:609, 1972.

86. Halie, M. R., Seldenrath, J. J., Stam, H. C., and Nieweg, H. O. Curative radiotherapy in Hodgkin's disease: Significance of hematogenous dissemination established by examination of peripheral blood and spleen. Brit. Med. J. 2:611, 1972.

87. Rosenberg, S. A. and Kaplan, H. S. Hodgkin's disease and other malignant lymphomas. Calif. Med. 113:23, 1970.

88. Aisenberg, A. C., Goldman, J. M., Raker, J. W. and Wang, C. C. Spleen involvement at the onset of Hodgkin's disease. Ann. Int. Med. 74:544, 1971.

89. Aisenberg, A. C. Hematogenous dissemination of Hodgkin's disease. Ann. Int. Med. 77:810, 1972.

3. The Role of Lymphangiography

This procedure has contributed much to our understanding of lymphomas and is, by far, the most sensitive and reliable radiologic diagnostic technique for the detection of lymphomatous involvement in the para-aortic and pelvic lymph nodes. Results from several centers indicate an over-all diagnostic accuracy of about 80%. Most of the diagnostic error consists of false negative interpretations.

Although many physicians consider the lymphangiogram (LAG) a routine diagnostic procedure in patients with HD, it should be stressed that a chest film should be obtained before attempting lymphangiography. This is because the hazards of pulmonary oil embolization (which uniformly occurs but is ordinarily trivial) may be serious in the patient with extensive chronic pulmonary disease, whether due to HD or not. Likewise, lymphangiography is contraindicated in persons allergic to iodinated organic compounds.

Normally, the opacified pelvic and retroperitoneal lymph nodes vary in size but rarely exceed 2.6 cm in greatest diameter. The para-aortic nodes usually lie within 2.0 cm of the vertebral column in lateral views. Normal nodes display a finely granular but essentially homogeneous structure. Whereas carcinomatous metastases typically produce irregular filling defects, infiltration of nodes by malignant

lymphomas is usually more diffuse. A characteristic "foamy" or reticulated pattern appears in the involved nodes, which are usually enlarged as well. With further progression of the process, discrete filling defects may be observed.

About 30% of Stage I and 50% of Stage II patients with HD which is clinically localized to supradiaphragmatic sites will have positive LAG's. However, approximately 95% of individuals with apparently localized nodal non-Hodgkin's lymphoma will have demonstrable involvement of retroperitoneal or pelvic nodes. A similar incidence obtains for the occasional patient with HD who presents with involvement of nodes in the groin.

In addition to significantly increasing the over-all accuracy of clinical staging, lymphangiography is of value for the following reasons: 1) the films may aid the surgeon in choice of biopsy site in the event the patient is to undergo staging laparotomy, and 2) since the nodes remain sufficiently opacified for diagnostic purposes for one year in 50% of patients, a simple flat plate of the abdomen may be obtained in order to plan radiotherapy fields and to follow the subsequent course of the patient (response to therapy or development of new disease).

The LAG often does not opacify para-aortic nodes above the level of L2. For this reason, an inferior vena cavogram is useful in some patients since it may yield further information about nodes in the high retroperitoneal area, particularly on the right. The cavogram is also valuable in the 10-15% of patients whose LAG's are equivocal or in the occasional patient in whom a LAG cannot be performed. It should be noted that an IVP can be obtained "for free" with a cavogram thus saving patients from undergoing a separate radiographic procedure in those in whom a pyelogram is desired.

4. <u>The Role of Staging Laparotomy and Splenectomy</u>

The recent introduction of potentially curative radiotherapy together with the availability of effective chemotherapy for patients with widespread disease has made it imperative to assess the initial extent of involvement as accurately as possible. Thus an increasing number of physicians caring for patients with HD have adopted the use of staging laparotomy and splenectomy. This procedure was originally employed by the Stanford group in selected patients who had equivocal disease below the diaphragm (suspicious lymphangiograms, splenomegaly or hepatomegaly).

In general, a standardized procedure has been performed at various centers. At operation, the surgeon inspects and palpates the abdominal contents. A wedge biopsy and two needle biopsies of the liver are taken. Biopsies of lymph nodes suspicious by lymphangiography as well as by direct examination are performed. The spleen and splenic hilar lymph node are removed. Silver clips are placed at the lymph node biopsy sites, at the splenic pedicle and around any masses found. In addition, an open marrow biopsy is sometimes taken from the iliac crest and ovarian translocation is performed in young women.

The data which has emerged from the results of surgery can be summarized as follows---

1) The most significant information gained from surgery concerns involvement of the spleen. Only 50% of patients who are assessed to have splenomegaly clinically on the basis of enlargement (by PE or scan) will have HD when the organ is examined

histologically. However, very large spleens (> 400 grams in weight) uniformly contain HD. On the other hand, 25% of patients will have demonstrable HD in the spleen without any clinical suspicion preoperatively; this is so even with a spleen of normal size. 80-90% of patients with abdominal node involvement have spleen involvement.

2) The preoperative evaluation of liver involvement by determination of liver size, liver function tests and scan is unreliable. Involvement of the liver by HD is only rarely identified in untreated patients (3 of 100 at Stanford).

3) Liver involvement does not occur without splenic involvement. The larger the spleen with HD, the more likely is liver involvement (13/16 [81%] of livers involved when the spleen > 400 gm. in the Stanford series). About 20% of patients with positive findings in the abdomen have hepatic Hodgkin's.

4) Almost all patients with positive LAG's (clinical Stage III) have abdominal disease proved; some of these will be advanced to Stage IV.

5) Among patients with negative LAG's, 20% of those without symptoms (Stages IA and IIA) and 40% with symptoms (Stages IB and IIB) are found to have disease below the diaphragm. Thus the findings at surgery result in the transfer of 1 patient in 5 from Stages IA and IIA into Stage III and two in 5 from IB and IIB into Stage III.

6) A significant number of false positive and false negative LAG's do occur and surgical staging has the advantage of enabling histopathologic diagnosis which clarifies this group.

7) A correlation has been established between left neck and para-aortic node involvement and between right cervical and mediastinal disease.

Laparotomy determines the presence of disseminated HD more accurately than any other diagnostic method and has contributed significantly to our understanding of the disorder. However, its role in management is unclear. The major complications include wound dehiscence and infection, subphrenic abscess, pancreatitis, atelectasis, pneumonia, pleural effusion and pulmonary embolism and infarction. In the Stanford series (275 patients), there were 11 major and 21 minor complications during the 30 day postoperative period; no deaths occurred but a few have been reported in the literature. The splenectomized patient may be prone to develop pneumococcal of H. influenzae sepsis, particularly if the patient is a child or adolescent. However, the over-all incidence of postsplenectomy bacteremia is only 1.4%. Some direct benefits of the procedure include better radiation and perhaps chemotherapy tolerance in the splenectomized patient, elimination of the need for splenic irradiation with attendant risk to the L kidney and LLL, and preservation of ovarian function in young women by oophoropexy. Whether these advantages alone justify the risk of the procedure is questionable. Although a reasonable case can be made for surgical staging in most patients with HD, it cannot be considered as part of the routine diagnostic evaluation in every patient with Hodgkin's disease. Certainly the elderly patient with profound constitutional symptoms and an overtly positive LAG would be a poor candidate. The clinician should realize that the indications for laparotomy will be continually reassessed. More than anything else, he should remember that the major value of surgical staging is to determine the extent of disease; this is critical only if the identification of abdominal involvement would alter the planned therapeutic regimen..

In summary, the diagnostic evaluation of patients with HD is complex and requires the availability of a team of experienced internists, surgeons, pathologists, and radiologists. Current diagnostic recommendations are listed in Table 7. Through the use of sophisticated diagnostic techniques, that fraction of patients with localized disease has diminished. Aisenberg has suggested the following as an approximation---

Of every 10 newly diagnosed Hodgkin's disease patients, by simple clinical criteria 7 or 8 cases appear localized at the outset, but only 5 remain so after lymphangiography and only 3 after laparotomy (Stage I or II). Of the 7 patients with proved spread, only 1 or 2 have documented Stage IV disease (usually in liver, lung or bone), the other 5 or 6 have spread demonstrable only to the spleen or para-aortic nodes--- usually both (Stage III).

Table 7. Recommendations for the Diagnostic Evaluation of Patients with Hodgkin's Disease[a]

A. *Mandatory Procedures*
   1. Biopsy, with interpretation by a qualified pathologist
   2. History, with special attention to the presence and duration of fever, night sweats, generalized pruritus, and unexplained loss of 10 percent or more of body weight in the six months preceding admission
   3. Physical examination
   4. Laboratory tests
      a. Complete blood cell count and platelet count
      b. Erythrocyte sedimentation rate
      c. Serum alkaline phosphatase
   5. Radiographic examinations
      a. Chest (posteroanterior and lateral)
      b. Lymphangiogram
      c. Intravenous urogram
      d. Skeletal survey (spine and pelvis)

B. *Contingent Procedures*
   1. Chest tomography (frontal or lateral), *if* pulmonary, hilar, and/or mediastinal involvement is present or suspected
   2. Bone marrow biopsy (needle or open), *if* CS III, alkaline phosphatase elevated, anemia, or at time of laparotomy
   3. Laparotomy and splenectomy, *if* decisions regarding management are likely to be influenced
   4. Inferior vena cavography, *if* lymphangiogram or urogram equivocal or unsatisfactory
   5. Liver biopsy (needle), *if* there is a strong clinical indication of hepatic involvement

C. *Optional Ancillary Procedures*
   1. Radioisotopic bone scans, in selected patients with bone pain and negative or equivocal roentgenograms
   2. Radioisotopic liver or spleen scans, in selected patients; limited value
   3. Tests of immunologic function
   4. Additional blood chemistry determinations: uric acid, calcium, etc.

D. *Promising Procedures for Clinical Investigation*
   1. Radiogallium (^{67}Ga) and radioselenium (^{75}Se) scans
   2. Biological indicators of disease activity: reduced serum Fe^{++}, elevated serum Cu^{++}

[a]Adopted at the Workshop on the Staging of Hodgkin's Disease, held at Ann Arbor, Michigan, in April 1971.

(From ref. 2)

90. Glatstein, E., Guernsey, J. M., Rosenberg, S. A. and Kaplan, H. S. The value of laparotomy and splenectomy in the staging of Hodgkin's disease. Cancer 24: 709, 1969.

91. Lowenbraun, S., Ramsey, H., Sutherland, J. and Serpick, A. A. Diagnostic laparotomy and splenectomy for staging Hodgkin's disease. Ann. Int. Med. 72:655, 1970.

92. Trueblood, H. W., Guernsey, J. M. and Cohn, R. Hodgkin's disease and non-Hodgkin's lymphoma---The surgeon's role in therapy. Current Problems in Surgery, Aug 1972.

93. Goldman, J. M. Laparotomy for staging of Hodgkin's disease. Lancet 1:125, 1971.

94. Kadin, M. E., Glatstein, E., and Dorfman, R. F. Clinicopathologic studies of 117 untreated patients subjected to laparotomy for the staging of Hodgkin's disease. Cancer 27:1277, 1971.

95. Johnson, R. E. Is staging laparotomy routinely indicated in Hodgkin's disease? Ann. Int. Med. 75:459, 1971.

96. Rosenberg, S. A. Splenectomy in the management of Hodgkin's disease. Brit. J. Hematol. 23:271, 1972.

97. Piro, A. J., Hellman, S. and Moloney, W. C. The influence of laparotomy on management decisions in Hodgkin's disease. Arch. Int. Med. 130:844, 1972.

98. Desser, R. K., Moran, E. M., and Ultmann, J. E. Staging of Hodgkin's disease and lymphoma. Med. Clin. North Amer. 57:479, 1973.

99. Lowenbraun, S., Ramsey, H. E. and Serpick, A. A. Splenectomy in Hodgkin's disease for splenomegaly, cytopenias and intolerance to myelosuppressive chemotherapy. Amer. J. Med. 50:49, 1971.

100. Salzman, J. R. and Kaplan, H. S. Effect of prior splenectomy on hematologic tolerance during total lymphoid radiotherapy of patients with Hodgkin's disease. Cancer 27:471, 1971.

101. Donaldson, S. S., Moore, M. R., Rosenberg, S. A. and Vosti, K. L. Characterization of postsplenectomy bacteremia among patients with and without lymphoma. New Eng. J. Med. 287:69, 1972.

102. Desser, R. K. and Ultmann, J. E. Risk of severe infection in patients with Hodgkin's disease or lymphoma after diagnostic laparotomy and splenectomy. Ann. Int. Med. 77:143, 1972.

Also see ref. 14 (part 2) and ref. 89.

VI. Therapy and Prognosis

A. Radiotherapy

The outlook of untreated HD is dismal. Data from the period 1910-1940 indicated that 5-year survival in untreated patients was 5.8% and all patients were dead by the 10th year. Results with moderate doses of orthovoltage radiotherapy administered only to areas of known disease yielded 5-year survival of 38% and ten-year survival of 22% in the Memorial Hospital series reported by Lacher.

In 1966, Kaplan reported that HD tends to recur in a treated field with a frequency that is inversely related to dose and approaches zero at a dose of approximately 4000 rads, delivered at a rate of about 1000 rads per week. More recently, Kaplan has employed a dose level of approximately 4400 rads; at this level the true recurrence rate is 1.3% (See Fig. 2). The high potential cure rate and danger of

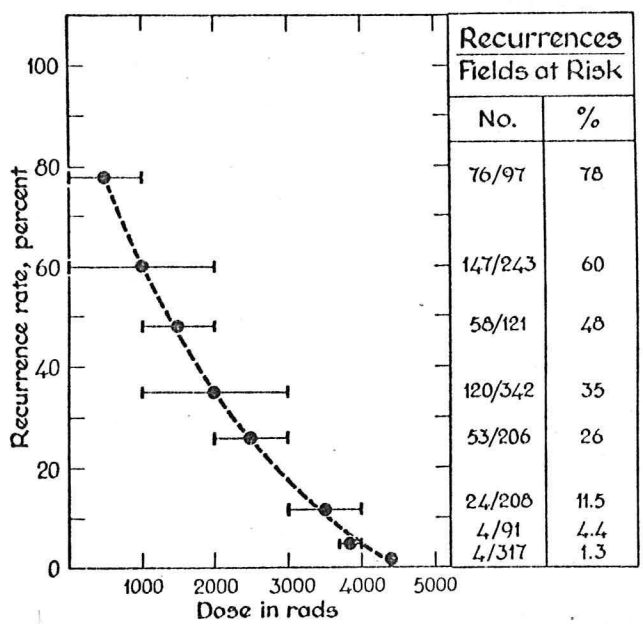

Figure 2. Influence of total radiation dose (delivered at approximately 1,000 rads per week) on true recurrence rate in Hodgkin's disease. The data are those compiled by Kaplan (1966a), supplemented by the additional point at the 4,400 rad dose level (Kaplan, 1970).

(From ref. 2)

serious damage to normal tissues make supravoltage (megavoltage) equipment mandatory and requires experienced radiotherapists employing meticulous technique. In addition to high dose radiation delivered from megavoltage sources, another cardinal principle of radiotherapy for HD involves the use of big fields. Kaplan has emphasized the importance of treating large fields in continuity to avoid missing some involved lymph nodes and devised the "mantle" extended field technique in which neck, axillae and

mediastinum to the level of the diaphragm are irradiated in continuity (Fig. 3).

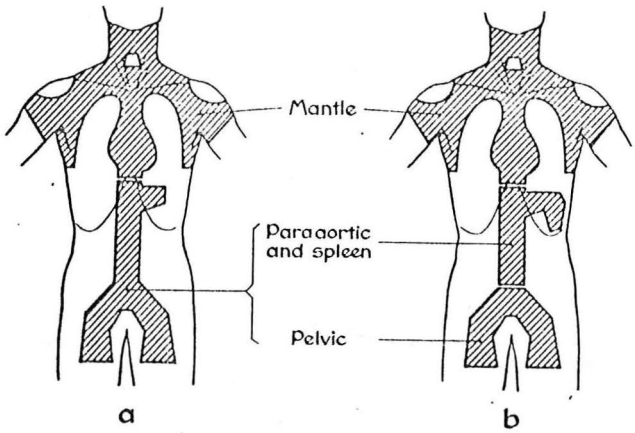

Figure 3. Diagram of the mantle and inverted-Y fields used in total lymphoid radiotherapy of Hodgkin's disease: (*a*) two-field technique, with small extension to include the splenic pedicle, used in patients who have undergone splenectomy; and (*b*) three-field technique (with full spleen extension) used when the spleen is still present or when hematologic tolerance is poor. Note the gap(s) between adjacent fields. (Reprinted by permission from the paper by Rosenberg and Kaplan, 1970.)
Ref. 87.

Extended field treatment for involvement below the diaphragm refers to the "inverted Y" technique in which splenic pedicle, celiac, para-aortic, iliac, inguinal and femoral nodes are irradiated in continuity (Fig. 3). Total nodal irradiation (TNI) refers to a combination of the "mantle" and "inverted Y" techniques.

It is generally agreed that radiotherapy using tumoricidal doses is the treatment of choice for Stages I and II. Whether total nodal irradiation is indicated for Stages IA and IIA is unclear but preliminary reports suggest that this is so. Thus the Stanford group reported 70% five-year survival with extended field therapy while Johnson has obtained 98% 5-year survival in Stages IA and IIA using TNI. For patients with Stages IB, IIB and IIIA, the treatment of choice appears to be TNI with curative intent, although optimal therapy for Stage III disease is still unsettled. Five-year survival in Stage I-IIB patients is 76% (Johnson). Kaplan has reported a 60% five-year survival in Stage III patients treated with TNI but this was a prelaparotomy series and therefore includes patients falsely placed in Stage III on the basis of misinterpreted lymphangiograms, palpable spleens and abnormal liver function tests. The NCI group has reported poor results in symptomatic patients (Stage IIIB) after TNI (17% five-year survival). Aisenberg prefers combination chemotherapy as the primary treatment of Stage III disease and uses radiation in an adjuvant role. It should be stressed that the data from laparotomy demonstrates the necessity of including the spleen in TNI fields if the organ has not been removed. If relapse occurs it usually does so within two years after radiotherapy; the probability of developing initial relapse later than five years after treatment is less than 5%.

When administered by expert radiotherapists, TNI is surprisingly well tolerated. Nevertheless serious complications do occur. Peripheral blood counts and bone marrow granulocyte reserve return to near normal levels in most patients within 6-8 months after completion of therapy. Severe spinal cord damage has been very rarely reported (1 of 592 patients) but Lhermitte's sign (numbness and tingling in the fingers and toes on flexion of the neck) develops transiently in 10% of treated individuals. Radiation-induced hypothyroidism has been described in 5 to 10% of patients. Transient weight loss associated with radiation pharyngitis and esophagitis occur in the majority of patients. The most serious and life-threatening complications result from radiation of the chest; these are especially likely when large mediastinal nodes are present. Severe radiation pneumonitis or radiation pericarditis develops in approximately 5% of patients, sometimes with a fatal outcome. Finally, I have previously alluded to the possible development of a second neoplasm in patients treated with intensive radiotherapy (and/or chemotherapy).

B. Chemotherapy

Single-agent chemotherapy has traditionally been employed in a palliative role in patients with HD, usually when the disease recurs following radiotherapy or in those who present with far advanced disease and pronounced systemic manifestations. The established drugs are listed in Table 8. BCNU and another drug recently found to be

Table 8. Major Drugs Useful in the Treatment of Hodgkin's Disease

Drug	Route	Major toxicity	Advantage
Nitrogen mustard (Mustargen)	I.V.	Bone marrow	Rapid, standardized
Chlorambucil (Leukeran)	Oral	Bone marrow	Titration for smooth control; oral
Cyclophosphamide (Cytoxan)	Oral or I.V.	Bone marrow, cystitis, alopecia, GI tract	Flexible; oral or intravenous
Vinblastine (Velban)	I.V.	Granulocytopenia	Well-tolerated, platelet-sparing
Vincristine (Oncovin)	I.V.	Neuropathy, alopecia	Rapid, marrow-sparing
Procarbazine (Natulan, Matulane)	Oral or I.V.	Bone marrow, GI tract	No cross-resistance
Corticosteroids	Oral or I.V.	Cushing's syndrome	Marrow-sparing
1,3-bis (β-chlorethyl)-1-nitrosourea (BCNU)	I.V.	Bone marrow	No cross resistance; crosses blood-brain barrier

Source: Modified from Rosenberg (1970). Ref. 2.

efficacious in HD, bleomycin, are investigational compounds. However, alkylating agents (nitrogen mustard, chlorambucil and cyclophosphamide) and the other drugs listed are generally available. The results of therapy with these agents are summarized in Table 9.

Table 9. Chemotherapy of Hodgkin's Disease

Drug	Response	Median Duration of Remission
	%	weeks
Nitrogen mustard	60	36
Chlorambucil	75	
Cyclophosphamide	55	32
Vinblastine	75	34
Procarbazine	60	12
Bleomycin	45	13
BCNU	50	17
MOPP (quadruple)	100	183+

Except for BCNU and MOPP the figures represent maintained remission. For MOPP the duration is the unmaintained remission after 6 mo. of treatment. Vincristine (Oncovin) and prednisone are of only marginal value when used alone. Modified from ref. 14.

Combination chemotherapy, first found to be effective in acute leukemia, has been recently utilized in HD and represents a major step forward. DeVita and co-workers have developed a quadruple drug regimen-MOPP (nitrogen mustard, Oncovin, prednisone and procarbazine) which results in a response rate significantly greater than that obtained with any single agent (Table 9). In the original series of 43 previously untreated Stage III and IV patients, a 100% response rate and 81% complete remission rate were achieved as compared with 60-75% responses and 15-30% complete remissions observed with single agents. The duration of unmaintained remission is even more impressive---under 3 months for single agents and in excess of three years for MOPP. Complete remissions have been longer lasting in asymptomatic patients (Stages IIIA and IVA) than in those with symptoms (Stages IIIB and IVB); 85% and 31%, respectively. Thus MOPP is not the answer for the patient presenting with advanced symptomatic HD. The response of previously treated (whether by radiotherapy or chemotherapy) patients who have relapsed is not as high although a satisfactory response may be achieved in some patients.

The ultimate role of MOPP in the management of patients with HD is unclear at present; various maintenance schedules and the addition of other drugs are currently undergoing evaluation. Thus any conclusions drawn now would be premature. In previously untreated patients with Stage IV disease, the MOPP program is the treatment of choice. As noted above, some prefer this mode of therapy for patients with Stage IIIB disease as well.

Finally, initial reports employing intensive radiotherapy (TNI) and combination chemotherapy (MOPP) in sequence suggests that the tandem program results in fewer relapses than when TNI alone is given. However, survival is not significantly different and such an ultra-aggressive approach must be regarded as highly experimental.

103. Lacher, M. J. Long survival in Hodgkin's disease. Ann. Int. Med. 70:7, 1969.

104. Kaplan, H. S. Evidence for a tumoricidal dose level in the radiotherapy of Hodgkin's disease. Cancer Res. 26:1221, 1966.

105. Johnson, R. E., Kagan, A. R., Hafermann, M. D. and Keyes, J. W. Patient tolerance to extended irradiation in Hodgkin's disease. Ann. Int. Med. 70:1, 1969.

106. Johnson, R. E. Modern approaches to the radiotherapy of lymphomas. Sem. Hematol. 6:357, 1969.

107. Johnson, R. E., Glover, M. K. and Marshall, S. K. Results of radiation therapy and implications for the clinical staging of Hodgkin's disease. Cancer Res. 31:1834, 1971.

108. DeVita, V. T., Serpick, A. A. and Carbone, P. P. Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann. Int. Med. 73:881, 1970.

109. Ultmann, J. E. and Nixon, D. D. The therapy of lymphoma. Sem. Hematol. 6:376, 1969.

110. Ultmann, J. E. Current status: The management of lymphoma. Sem. Hematol. 7:441, 1970.

111. DeVita, V. T., Canellos, G. P. and Moxley, J. H. A decade of combination chemotherapy of advanced Hodgkin's disease. Cancer 30:1495, 1972.

112. Young, R. C., DeVita, V. T., Serpick, A. A. and Canellos, G. P. Treatment of advanced Hodgkin's disease with [1,3-bis(β-chlorethyl)-1-nitrosourea] BCNU. New Eng. J. Med. 285:475, 1971.

113. Curran, R. E. and Johnson, R. E. Tolerance to chemotherapy after prior irradiation for Hodgkin's disease. Ann. Int. Med. 72:505, 1970.

114. Canellos, G. P., Young, R. C. and DeVita, V. T. Combination chemotherapy for advanced Hodgkin's disease in relapse following extensive radiotherapy. Clin. Pharmacol. Therapeutics 13:750, 1972.

115. Moore, M. R., Bull, J. M., Jones, S. E., Rosenberg, S. A. and Kaplan, H. S. Sequential radiotherapy and chemotherapy in the treatment of Hodgkin's disease. Ann. Int. Med. 77:1, 1972.

116. Rosenberg, S. A., Moore, M. R., Bull, J. M., Jones, S. E. and Kaplan, H. S. Combination chemotherapy and radiotherapy for Hodgkin's disease. Cancer 30:1505, 1972.

117. DeVita, V. T. and Canellos, G. P. Treatment of the lymphomas. Sem. Hematol. 9:193, 1972.

Also see ref. 2, ch. 10 and 11; ref. 14 and ref. 87.

VII. Summary

Much remains to be learned about Hodgkin's disease. Its etiology and pathogenesis are unknown; controversy continues regarding its basic nature (infection vs. neoplasm), origin (unifocal vs. multifocal) and spread (lymphatic vs. hematogenous). The histopathologic diagnosis is frequently difficult and it is clear that the Reed-Sternberg cell can no longer be considered pathognomonic of the disease. Diagnostic evaluation and management are still in a state of flux. Yet, by utilizing a multidisciplinary approach, major progress has been achieved during the last decade. The most important consequence of this new knowledge is the vastly improved outlook for patients with the disorder. Whether long-term survival is tantamount to true cure (i.e., eradication of all disease) is unsettled. However, it is evident that permanent cure of Hodgkin's disease is indeed possible.

118. Durant, J. R. Treatment of Hodgkin's disease: With what and by whom? Ann. Int. Med. 73:1033, 1970.

119. Strum, S. B. and Rappaport, H. The persistence of Hodgkin's disease in long-term survivors. Amer. J. Med. 51:222, 1971.

120. Editorial, Selection of treatment in Hodgkin's disease. Lancet 2:1404, 1972.

Also see ref. 2, ch. 13.

VIII. Case Protocols

1. REED-STERNBERG CELLS IN NON-HODGKIN'S LYMPHOMA

M. T. PMH #42 11 75. This 29-year-old WF veterinarian was referred in March 1972 for evaluation of a 4-month history of weight loss, fatigue and hepatosplenomegaly. Physical exam disclosed small (< 1 cm), shotty lymph nodes in the neck, epitrochlear, inguinal and femoral regions. Except for hepatosplenomegaly (confirmed by scan), there were no other abnormal physical findings. Laboratory studies: Hgb 9.5 gm%, Hct 30%, WBC 3500 with occasional atypical lymphs, platelets 185,000, ESR 13 mm/hr., hypogammaglobulinemia (0.32 gm% with ↑ IgM, ↓ IgG and no detectable IgA, IgD or IgE), BFP serology, pos ANF X 3, neg. LE prep X 2, and neg. latex. Skin tests (PPD, Histo, Candida, mumps and trichophyton) were negative. X-rays: normal chest, UGI, BE, IVP and inferior vena cavogram; LAG was nonspecifically abnormal. Bone marrow was non-diagnostic. While in the hospital, she was noted to have a tiny subcutaneous nodule over the upper right biceps. Biopsy revealed it to be a lymph node, the architecture of which was replaced by diffuse infiltrates of lymphocytes and reticulum cells. Typical R-S cells also were present and the diagnosis of HD, mixed cellularity type, was made. The patient then underwent a staging laparotomy. Despite moderate splenomegaly (385 gm), the histology was nonspecific and no R-S cells were seen in the spleen, lymph nodes or liver biopsies. She was discharged without therapy and subsequently resumed full activity. A WBC obtained in Aug '72 was WNL. She returned for a routine visit in Nov '72 at which time exam revealed several firm 2 X 2 cm axillary nodes and three subcutaneous nodules (similar to the original one) over the thorax. Her WBC was 80,000 with 95% lymphosarcoma cells seen on smear. Bone marrow exam confirmed the diagnosis of lymphosarcoma leukemia.

2. HODGKIN'S DISEASE FOLLOWING INFECTIOUS MONONUCLEOSIS

C. C. PMH #41 94 32. This 15-year-old WF was well until Nov. 1971 when she developed low-grade fever, lassitude, sore throat and bilateral swelling in the posterior neck. During the following 6 weeks the symptoms persisted and her heterophile titer rose from 1:56 to 1:1000 and subsequently declined; her local physician made the diagnosis of infectious mononucleosis. The patient was referred here in Feb. '72 because of progressive cervical adenopathy, persistent fatigue and a 20 lb weight loss. She denied chills, sweats and pruritus but had continued to have intermittent fever. Marked bilateral cervical and supraclavicular lymphadenopathy was noted on physical exam. In addition, a 2 X 2 cm firm, nontender left axillary node was present. There was no splenomegaly and the remainder of the physical exam was unremarkable. Laboratory Data: Hgb 11.6 gm%, Hct 36%, WBC 13,400 with 87% PMN's, platelets 320,000, ESR 91 mm/hr, heterophile < 1:28. Chest film revealed a huge mediastinal mass. Axillary node biopsy disclosed nodular sclerosing HD. IVP and LAG were negative. The patient underwent staging laparotomy and splenectomy; lymph node and liver biopsies as well as the spleen were normal, thus establishing her stage as II-B. She was treated with upper mantle extended field radiotherapy.

3. CLASSIC PERIPHERAL BLOOD CHANGES OF HODGKIN'S DISEASE

J. E. PMH #40 24 71. This 66-year-old LAM, a known chronic alcoholic, was admitted in Oct. 1971 for evaluation of cervical adenopathy. He denied all constitutional symptoms. Multiple discrete, nontender, rubbery nodes varying in size from 1 X 2 cm to 3 X 3 cm were present in the right cervical, submandibular and supraclavicular areas. Bilateral 1 X 1 cm femoral nodes also were palpable but there was no evidence of hepatosplenomegaly. Hgb and Hct were normal but the WBC was 14,800/mm^3. Small lymphocytopenia, monocytosis (14%), eosinophilia (22%) and thrombocytosis (510,000/mm^3) were demonstrated on peripheral smear. In addition, polyclonal hypergammaglobulinemia (3.1 gm%) was present on SPEP. Changes consistent with chronic obstructive lung disease were evident on chest film. The probable diagnosis of HD was made and confirmed by supraclavicular node biopsy (mixed cellularity subtype). Because of mild splenomegaly by scan and an equivocal LAG, the patient underwent staging laparotomy and splenectomy. The spleen weighed 330 gm and contained HD but liver and lymph node biopsies were negative (Stage III-A). He was treated with total nodal lymphoid radiotherapy (upper mantle followed by inverted-Y). In Oct. '72 he was readmitted with massive upper GI bleeding which ultimately resulted in death. No autopsy was performed.

4. MULTIPLE INFECTIONS ASSOCIATED WITH THE T CELL DEFECT OF HODGKIN'S DISEASE

R. T. PMH #43 88 36. This 61-year-old WM was admitted in Nov 1972 because of anorexia, weight loss and an abnormal chest film. He was known to have had tuberculosis in 1942 and was hospitalized then for 9 months, but he had never been treated with anti-tuberculous drugs. During the 6 months preceding his 1972 admission, he had noted weakness, a 25 lb weight loss and cough productive of small amounts of yellow sputum. He denied fever, chills, sweats, pruritus and hemoptysis. On exam, he appeared markedly wasted and chronically ill. Bilateral cervical adenopathy and a 2 X 2 cm firm, nontender node at the angle of the left mandible were present. Bronchial breath sounds were audible over the right apex and the liver was enlarged (16 cm span). The spleen was not palpable. Laboratory data:

Hgb 7.0 gm%, Hct 23%, WBC 7000 with 88% PMN's (only 9% lymphs), platelets 230,000. Total bilirubin 2.0, alk. phos. > 350, albumin 5.0, globulin 1.8. Chest x-ray showed bilateral apical infiltrates and a cavity in the RUL. Multiple sputum specimens were positive for AFB. A PPD skin test was negative. Non-caseating granulomas were seen on bone marrow biopsy. Cervical node biopsy demonstrated unequivocal HD with numerous R-S cells. The patient was begun on INH, ethambutal and streptomycin but he developed refractory GI bleeding and a superimposed bacterial pneumonia which resulted in death on the 26th hospital day. Autopsy demonstrated: 1) Stage IV Hodgkin's disease, (lymphocyte depletion subtype) with involvement of spleen and liver; 2) extensive pulmonary tuberculosis and tuberculous enteritis; and 3) disseminated cryptococcosis.

5. OCCULT SPLENIC HODGKIN'S DISEASE: CHANGE IN STAGING BY LAPAROTOMY

R. M. PMH #38 53 41. This 29-year-old WM mechanic from Odessa presented to his local physician in Aug. 1970 because of progressive bilateral neck swelling of 2 months' duration. A lymph node biopsy was performed and read as HD (nodular sclerosis subtype). He was then referred here and on admission denied all constitutional symptoms, stating that he felt perfectly well. Diffuse bilateral cervical and supraclavicular adenopathy was present; the nodes were discrete, firm, fixed and nontender. A 1.5 cm left axillary node of similar character also was noted. The remainder of the physical exam was negative. CBC, platelets, ESR, SMA and liver battery were normal. A large anterior superior mediastinal mass was seen on chest film but liver-spleen scan, inferior vena cavogram and LAG were normal. The patient underwent staging laparotomy and splenectomy; the liver and lymph node biopsies were negative but clear-cut evidence of nodular sclerosing HD was evident in the normal-size (110 gm) spleen. He received total lymphoid radiotherapy and remains well.