Medical Progress

Hodgkin's Disease and Other Malignant Lymphomas

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● *Systematic studies of the patterns of anatomic distribution, pathways of probable spread, and prognosis of the malignant lymphomas have been greatly aided by the development of new histopathologic classifications and the introduction of more sophisticated and precise diagnostic techniques, such as lymphangiography and laparotomy with splenectomy and retroperitoneal node biopsy. Concomitantly, megavoltage radiotherapy apparatus has made total-lymphoid radiotherapy feasible and practical, and the availability of a widening spectrum of chemotherapeutic agents has ushered in a new era of combination chemotherapy. Collectively, these diagnostic and therapeutic advances have already begun to yield a dramatic improvement in the prognosis of Hodgkin's disease and the other malignant lymphomas.*

DURING THE PAST FIFTEEN YEARS there have been significant advances in our understanding of the nature, pathogenesis, diagnostic evaluation, clinical course, treatment, and prognosis of Hodgkin's disease and the other malignant lymphomas. It seems timely to review these contributions, to summarize our present concepts and to offer recommendations concerning the management of patients with such lymphoid neoplasms in the light of our own experience.

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Pathogenesis and Pathology

Although the non-Hodgkin's group of lymphomas have long been accepted as having all of the essential attributes of neoplasms, there has been long and vigorous controversy about the essential nature of Hodgkin's disease. The bizarre pleomorphism of its histologic appearance, coupled with the frequent clinical occurrence of febrile manifestations, has strongly suggested to many that Hodgkin's disease was an infectious process, perhaps of granulomatous nature. Indeed, Sternberg himself thought for a considerable time that it was an aberrant form of tuberculosis, and others have indicted various other microorganisms as the

TABLE 1.—*Histopathologic Classification of Hodgkin's Disease*

Jackson and Parker	*Rye, 1965*	*Distinctive Features*	*Relative Frequency*
PARAGRANULOMA	LYMPHOCYTE PREDOMINANCE	Abundant stroma of mature lymphocytes and/or histiocytes; no necrosis; Reed-Sternberg cells may be sparse. (Figure 1).	10-15%
	NODULAR SCLEROSIS	Nodules of lymphoid tissue, partially or completely separated by bands of doubly refractile collagen of variable width; atypical Reed-Sternberg cells in clear spaces ("lacunae") in the lymphoid nodules (Figure 2 and 3).	20-50%
GRANULOMA	MIXED CELLULARITY	Usually numerous Reed-Sternberg and atypical mononuclear cells with a pleomorphic admixture of plasma cells, eosinophils, lymphocytes, and fibroblasts; foci of necrosis commonly seen (Figure 4).	20-40%
SARCOMA	LYMPHOCYTE DEPLETION	Reed-Sternberg and malignant mononuclear cells usually, though not always numerous; marked paucity of lymphocytes; diffuse fibrosis and necrosis may be present (Figure 5).	5-15%

etiologic agents. However, none of these claims has withstood the test of time and more careful investigation. Conversely, the view that Hodgkin's disease is a neoplasm has had its proponents for an equally long period. Until recently, however, the arguments advanced for its neoplastic nature did not rest on a very firm foundation and were all open to alternative interpretations.

Recent technical advances have now made it possible to study involved tissues from patients with Hodgkin's disease in a more critical frame of reference. It is now widely accepted that the most essential and fundamental distinction between infection and neoplasia relates to their respective modes of propagation in the body. Infection is transmitted horizontally by passage of the etiologic agent from one cell to another, either immediately adjacent or by movement through body fluids to some other part of the body. In contrast, neoplasms are propagated by the mitotic division of altered cells themselves, and are thus derived clonally. It is also now well established that aneuploidy, the presence of an abnormal number and distribution of chromosomes, is a hallmark of many types of neoplastic cells and that distinctive "marker" chromosomes are not infrequently encountered in the karyotype of such cells.

Accordingly, the recent demonstration by a number of investigators that lymph nodes from patients with Hodgkin's disease frequently contain aneuploid cells constitutes *per se* strong evidence for the neoplastic character of Hodgkin's disease. Even more convincing, however, was the

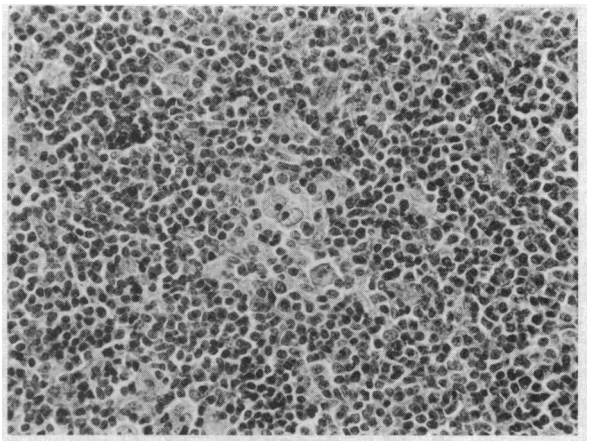

Figure 1.—Hodgkin's disease, lymphocyte predominance (Magnification 360 X). Note the abundance of mature lymphocytes, occasional atypical histiocytes and rare typical Reed-Sternberg cells.

discovery by Seif and Spriggs[1] of distinctive marker chromosomes in two of seven cases of Hodgkin's disease; one of these cases revealed the same two marker chromosomes in ten of eleven aneuploid cells studied, proving that they must have been derived from a common precursor cell by clonal proliferation. Although more such studies will be needed to document these findings convincingly in other cases, we seem finally to be approaching the time when clear and unambiguous evidence favoring the neoplastic hypothesis will finally be at hand.[2]

However, the picture in Hodgkin's disease is further complicated by the fact that many of the patients appear to have a peculiar immunological

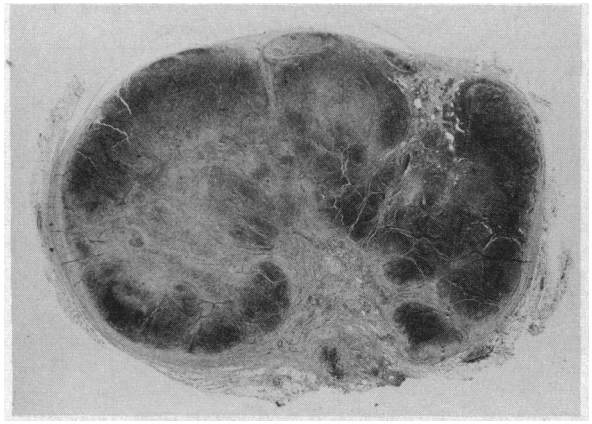

Figure 2.—Hodgkin's disease, nodular sclerosis (Magnification 7 X). Note the extensive fibrosis separating nodules of lymphoid tissue, as seen under very low magnification.

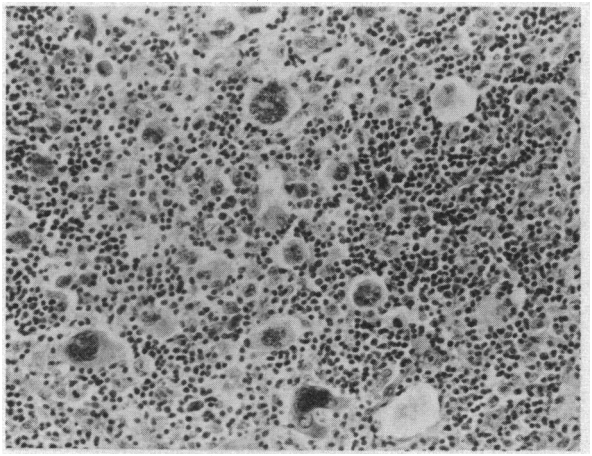

Figure 3.—Hodgkin's disease, nodular sclerosis (Magnifiication 250 X). Note the abundant atypical histiocytes and atypical Reed-Sternberg cells in "lacunar spaces".

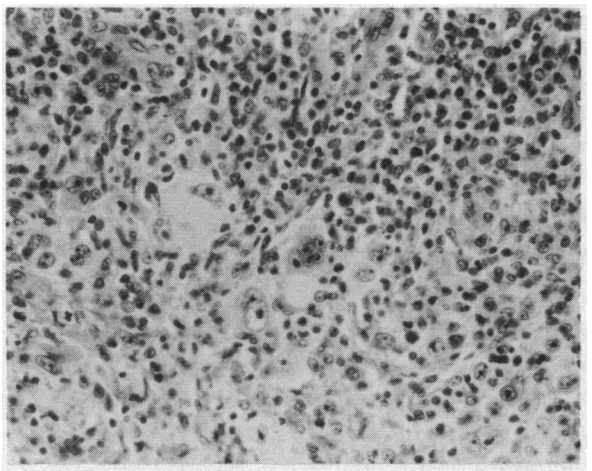

Figure 4.—Hodgkin's disease, mixed cellularity (Magnification 360 X). Note the pleomorphic cellular infiltrate and frequent Reed-Sternberg cells.

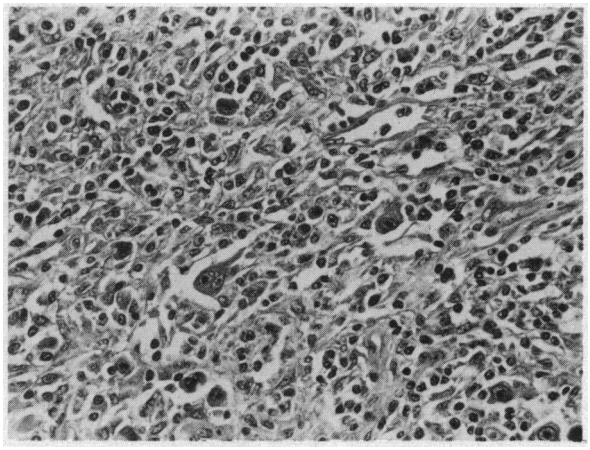

Figure 5.—Hodgkin's disease, lymphocyte depletion (Magnification 360 X). Note the paucity of lymphocytes and the numerous malignant appearing histiocytes and Reed-Sternberg cells.

disorder characterized by a hyporesponsive state of cell-mediated immune responses.[3] It is still not established whether the immunological disorder precedes or follows the development of the disease. Any ultimate theory of the nature of Hodgkin's disease must not only take into account the neoplastic character of its cellular component but must account in some satisfactory way for its immunologic manifestations.

More than 30 years ago, Jackson and Parker put forward their classical histopathological classification which divided Hodgkin's disease into three categories: paragranuloma, granuloma, and sarcoma (Table 1). Unfortunately, this classification proved of little value in clinical practice, since nearly 90 percent of all cases were found to fall in the granuloma category, leaving only a small and essentially negligible group at each fringe. More recently, principally as a result of the work of Lukes and his colleagues,[4] an important subgroup of the former granuloma category, designated nodular sclerosis, has been delineated. This and other refinements have permitted the development of a new histopathologic classification,[5] the essential features of which are summarized in Table 1 and Figures 1-5. Although this classification has become available too recently to have withstood the test of time with respect to its clinical and prognostic relevance, preliminary analyses[6,7] strongly suggest that the four categories of the new Rye classification do bear a realistic relationship to prognosis in Hodgkin's disease. Moreover, the predilection for mediastinal involvement in nodular sclerosis ver-

sus cervical-supraclavicular or abdominal involvement in the lymphocyte predominance and mixed cellularity forms seem to represent valid distinctions in the pathogenesis and mode of spread of these histopathologic types. Nonetheless, these patterns are not yet established convincingly enough to persuade clinicians to alter their therapeutic programs for patients with Hodgkin's disease on the basis of the histopathologic features alone.

The pattern of spread of Hodgkin's disease is another topic on which new light has been shed in recent years. Gilbert,[8] Peters[9] and Kaplan[10] had all noted the frequent occurrence of initial extensions of disease to lymph node chains immediately adjacent to those known to be involved at the time of diagnosis. Indeed, it was this observation that led to their advocacy of extended-field "prophylactic" radiotherapy of apparently uninvolved neighboring lymph node chains. During the past eight years, we have made systematic and detailed mapping studies of the distribution of involved nodes at the time of diagnosis and at the time of the first relapse after treatment. These data, which have been detailed elsewhere[11,2] provided strong support for the view that Hodgkin's disease usually (perhaps invariably) arises in a single lymph node chain and then spreads secondarily, at a variable rate, probably influenced by the histopathologic type and the immunologic status of the patient, contiguously via lymphatic channels to other lymph node chains, predominantly along the central axis of the body.

The concept of contiguity of spread has been extended[2] to include spread via the thoracic duct, in either direction, leading to a high frequency of joint or sequential involvement of the lymph nodes in the upper lumbar paraaortic chain and those in the lower cervical-supraclavicular region, especially on the left side. This view has recently been reinforced by data derived from our laparotomy, splenectomy, and biopsy studies[12,13] on the correlation of right versus left sided cervical-supraclavicular adenopathy and mediastinal versus paraaortic involvement, respectively. Accordingly, there is a reasonably high degree of predictability in the pattern of spread of Hodgkin's disease, and data to be presented below indicate that this distinctive feature of its pathogenesis can now be exploited to significant therapeutic advantage.

It must be emphasized that the non-Hodgkin's group of lymphomas is a diverse one, requiring expert pathologic consultation. The new classification of these neoplasms proposed by Gall and Rappaport[14] may identify sub-types more meaningfully with respect to clinical course and prognosis (Table 2 and Figures 6 and 7). However, this classification has not yet been applied critically to large series of unselected cases in which complete diagnostic evaluation, modern staging, and optimal therapeutic management were also employed. Accordingly, the clinical correlations available to date leave a good deal to be desired. In the past, patients in whom biopsy of nodes revealed a nodular or so-called "giant follicular" pattern have been grouped together without regard to cytologic type. Conversely, if the patterns were diffuse the tendency has been toward indiscriminate labelling as "lymphosarcoma" or "reticulum cell sarcoma," depending on whether the dominant cell type was a lymphocyte or histiocyte, without due regard to its degree of differentiation. Moreover, the fact that both nodular and diffuse histiocytic lymphomas were formerly identified by the single, poorly defined category "reticulum cell sarcoma" undoubtedly accounts in large part for the wide differences in clinical course and prognosis of cases to which this diagnosis has been applied.

TABLE 2.—*Histopathologic Classification of the Non-Hodgkin's Lymphomas

A. TOPOGRAPHIC
   1. Nodular (Figure 6)
   2. Diffuse (Figure 7)

B. CYTOLOGIC
   1. Lymphocytic, well differentiated
   2. Lymphocytic, poorly differentiated
   3. Histiocytic
   4. Mixed lymphocytic and histiocytic

*Rappaport, H., et al. Cancer 9:792, (1956)
Rappaport H., Tumors of Hematopoietic System AFIP. Washington, D.C., (1966)

Clinical Considerations In Hodgkin's Disease

Experience with lymphangiography,[15] laparotomy with splenectomy,[12] and other diagnostic studies[16] has provided ample evidence that the anatomical extent of involvement is likely to be much greater than that which is clinically apparent on physical examination. It is therefore essential that all patients with Hodgkin's disease be evaluated completely before therapeutic de-

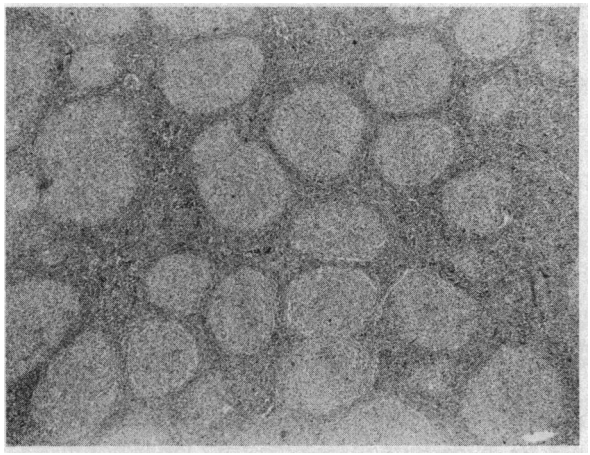

Figure 6.—Nodular lymphoma, histiocytic type (Magnification 25 X). Note the distinct nodules of atypical cells separated by mature normal lymphocytes.

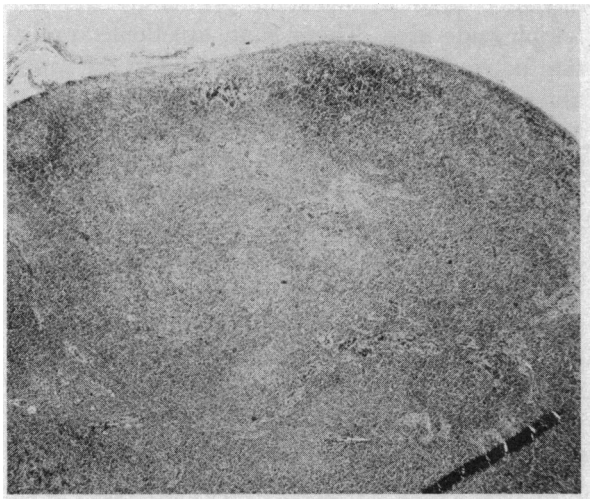

Figure 7.—Diffuse lymphoma, histiocytic type (Magnification 25 X. Note the total loss of nodal architecture.

cisions are made. Once a definite diagnosis is made by competent pathologists, it is the responsibility of the attending physician to determine within the limits of current diagnostic capabilities the complete extent of the disease. A careful history and physical examination to uncover the characteristic systemic symptoms of fever, night sweats and pruritus and to describe all of the lymph node areas of the body is essential. Special attention must be directed to the cervical, supraclavicular, infraclavicular, axillary, epitrochlear, iliac, inguinal and femoral lymph node areas. More rarely, pectoral, popliteal and pre-auricular lymph nodes may be present when the patient is first seen. Not all palpable lymph nodes are pathological in the sense that they contain lymphoma. However, if there are suspicious lymph nodes which, if involved, would change the therapeutic approach, biopsy of them should be done for confirmation. The size of the liver and spleen must be determined as carefully as possible, and examination should be done to find areas of bone tenderness. The lymphoid tissues in the oropharynx and nasopharynx should be evaluated by a skillful examiner.

Radiological examinations should include routine chest films and whole lung tomography to identify mediastinal and hilar lymphadenopathy and pulmonary parenchymal involvement.[16] Lower extremity lymphangiography is essential in all patients unless pulmonary function is seriously limited or bone marrow or other disseminated extralymphatic involvement has been documented. A skeletal survey complemented by skeletal scintigraphy is desirable to detect osteoblastic or, less commonly, osteolytic lesions, most often first seen in the vertebrae and pelvis. Routine blood cell counts and determination of sedimentation rate, serum alkaline phosphatase, and bromsulphalein retention are the minimum of laboratory studies required for evaluation. Bone marrow biopsy using a Westerman-Jensen needle or an open technique will occasionally uncover Hodgkin's disease in patients with advanced lymph node involvement in whom a bone marrow aspirate is almost always negative.[17] Bone marrow involvement is most often found in the setting of widespread lymph node disease with systemic symptoms, anemia and elevation of alkaline phosphatase. However, occasionally none of these findings will be evident.[17]

In recent years we have resorted to exploratory laparotomy and splenectomy in selected patients who have had equivocal evidence of Hodgkin's disease below the diaphragm. This experience, analyzed by Glatstein,[12] demonstrated that approximately half of the patients with clinical enlargement of the spleen did not have histologic involvement of that organ, and conversely, in approximately one case in three in which the spleen was of normal size, the organ contained demonstrable foci of Hodgkin's disease.

In these selected patients, we demonstrated the inability to identify patients with involvement of the liver when using the usual liver function tests, hepatic size, hepatic scan, or needle

TABLE 3.—*Results of Laparotomy in 100 Consecutive Untreated Patients with Hodgkin's Disease*

Site	Preoperative Assessment	A Systematic Symptoms Absent	B Systemic Symptoms Present	Total
Liver	Clinically positive	0/ 4*	1/11	1/15
	Clinically negative	1/53	1/32	2/85
Spleen	Clinically positive	2/ 6	6/10	8/16
	Clinically negative	11/51	9/33	20/84
Abdominal Nodes	Positive lymphangiogram	8/11 (1)**	10/12	18/23 (1)
	Negative lymphangiogram	5/33 (4)	2/24 (1)	7/57 (5)
	Equivocal lymphangiogram	3/13 (1)	1/ 7	4/20 (1)

*No. with histologic evidence of Hodgkin's disease of number examined
**Figures in parentheses are numbers with positive splenic hilar nodes, but negative para-aortic node biopsy

biopsy. False positive clinical evaluations were found in eight of twenty-one patients within the limitations of the diagnostic accuracy of hepatic exploration and biopsy. Six of fourteen patients with systemic symptoms had demonstrable hepatic Hodgkin's disease without any clinical suspicion of it before operation. There was a high degree of correlation of hepatic and splenic involvement. Liver involvement was not found in the absence of splenic involvement, and the larger the size of the involved spleen the greater the incidence of hepatic disease.

These results have stimulated our group and others to resort to exploratory laparotomy and splenectomy routinely in the evaluation and staging of the treated patients with Hodgkin's disease. An analysis of 50 consecutive untreated patients reported by Glatstein *et al*[13] extended our earlier observations.

The results in 100 consecutive untreated patients are shown in Table 3. Liver involvement is much less frequent in the unselected group, but has not occurred in the absence of involvement of the spleen. Half of the patients with enlargement of the spleen did not have involvement of that organ when examined histologically. Seven examples of involvement of the lymph nodes in the hilum of the spleen have been observed, occasionally as the only site of disease below the diaphragm. There has been only one example of mesenteric lymph node involvement.

Of 57 patients with lymphograms reported as negative, two were shown to have paraaortic lymph node involvement. Seventeen of 23 reported as positive were confirmed. Of 20 patients with equivocal lymphograms, three were found to have and 17 not to have lymph node involvement.

It is our conclusion that an accurate assessment of Hodgkin's disease below the diaphragm cannot be made without exploratory laparotomy and splenectomy.

It is increasingly evident that involvement of the spleen with Hodgkin's disease has more significance than involvement of merely another lymph node area. There is an excellent correlation between the size of the spleen and the probability of liver involvement, as documented at laparotomy.[12] The larger the spleen, the more frequently the liver is found to have foci of Hodgkin's disease. It is extremely rare to observe involvement of the liver with Hodgkin's disease without previous or concurrent splenic involvement. In a retrospective analysis it was noted that approximately two out of three patients who had spleen involvement also had or subsequently developed involvement of the liver with the disease.[2] It would therefore appear that the avenue for extension of the disease to the liver may be via the spleen. Special efforts must therefore be made to document splenic involvement for prognostic purposes and possible modifications of therapy.

Staging of Hodgkin's Disease

Peters (1950) was the first to introduce a rational clinical staging classification. It is still widely used. When the advent of modern megavoltage apparatus brought retroperitoneal lymph node involvement within the scope of potentially curative radiotherapy, and lymphangiography made possible the earlier detection of such involvement, it became important to distinguish two subgroups within Peters' Stage III: those with widepsread disease confined to lymphatic organs, and those with spread of disease beyond the lymph nodes, thymus, spleen, and

Waldeyer's ring, to one or more extralymphatic organs or tissues. Recognition of this need[18] led in 1965 to the adoption of a new four-stage clinical staging classification at an International Symposium on Hodgkin's disease at Rye, New York.[19]

As experience with the Rye classification has increased, certain imperfections have become apparent (Table 4). Of particular significance has been the presentation of convincing data[20,21] indicating that localized involvement of extralymphatic organs or tissues, unlike disseminated involvement, does not carry the unfavorable prognosis which its allocation to Stage IV in the Rye classification would suggest. Moreover, such localized extralymphatic foci are often amenable to treatment with tumoricidal doses of radiotherapy. Accordingly, new staging classifications have been proposed by Peters et al (1968), Musshoff and Boutis (1969) and ourselves which take this distinction between localized and disseminated extralymphatic involvement into consideration (Table 4). In addition, the new classifications are readily applicable also to the non-Hodgkin's group of lymphomas, in which it is not uncommon for the neoplastic process to arise in, and be confined to, an extralymphatic organ or site. In the Rye classification, such cases would have had to be assigned to Stage IV, despite their favorable prognosis. In the new classifications, they are designated Stage I cases if truly solitary, or Stage II if accompanied by regional lymphadenopathy.

All cases of Hodgkin's disease continue in the new classifications, as in the Rye scheme, to be sub-classified as A or B to indicate the absence or presence, respectively, of one or more of the following systemic symptoms: otherwise unexplained fever, night sweats, or generalized pruritus. Fatigue, weight loss, alcohol intolerance, anemia, leukocytosis, lymphopenia, and the absence of delayed skin hypersensitivity are all important to document but not of sufficient specificity to relegate the patient to subgroup B.

One can predict, as experience is gained with newer diagnostic and therapeutic approaches, that these staging classifications will also be modified in the years to come. The major value of staging classifications is to allow comparisons among medical centers so that therapeutic programs can be meaningfully evaluated. It is essential that all reports which deal with the clinical course and therapy of malignant lymphomas carefully outline the diagnostic techniques used to arrive at a clinical staging opinion and then clearly state the definition of the staging groups. Only if this is done can workers in this field make meaningful comparisons and draw sound conclusions concerning advances in diagnosis or treatment with a view to making recommendations for their adoption by practicing physicians everywhere.

Radiotherapy of Hodgkin's Disease

The basic concepts of curative radiotherapy for Hodgkin's disease were enunciated years ago by the late Swiss radiotherapist, René Gilbert,[8] and effectively put into practice during the kilovoltage era by Vera Peters[9] and others. In the last 15 years, modern megavoltage apparatus (linear accelerators, multikilocurie cobalt teletherapy units, betatrons) has overcome the earlier technical limitations of kilovoltage x-rays and has made possible the full implementation of the concepts set forth by Gilbert.

The major technical factors which determine the efficacy of radiation therapy in Hodgkin's disease are: the total radiation dose per field; the size, shape, and number of treatment fields; and the beam energy. Permanent eradication of any given site of involvement can be achieved consistently with doses of 3,500 to 4,500 rads delivered at the rate of 1,000 rads per week. Although enlarged lymph nodes may regress completely after substantially smaller doses, such responses are likely to be temporary and recurrences are common.[22] Since re-irradiation of recurrences is hazardous because of the poor tolerance of the normal tissues, it is imperative to use optimal dose levels for all involved sites in the first course of treatment.

When multiple chains of involved or potentially involved lymph nodes must be irradiated, the use of a patchwork of multiple small treatment fields is highly undesirable because of the risk of overlapping or of excessive gaps between fields. It is therefore essential to encompass multiple lymph node chains within as small a number of very large fields as possible. Each such field must be carefully shaped to the contours of the lymph node chains, with lead shields placed to protect such vital structures as the lungs, heart, liver, kidneys and spinal cord. It is usually possible to encompass all or most of

TABLE 4.—*The Evolution of Clinical Staging Classifications in Hodgkin's Disease.*

Peters, 1950[a]	*Rye, 1965*[b]	*Peters et al, 1968*[c]		*Musshoff + Boutis, 1958*[d]	*Proposed Stanford Classification, 1970*
		Lymph Node Presentation	*Extranodal Presentations*		
STAGE I—Involvement of a single site or lymphatic region	STAGE I_1—Disease limited to one anatomic region I_2—Disease limited to two contiguous anatomic regions on the same side of the diaphragm	STAGE I—Disease limited to one anatomical region or to two contiguous anatomical regions, on the same side of the diaphragm	STAGE I—Disease in extranodal site alone *or* with involvement of one contiguous group or chain of lymph nodes	STAGE I—Lymph node involvement on one side of the diaphragm, *with* or *without localized, contiguous* extralymphatic organ or tissue involvement A—No systemic symptoms B—Systemic symptoms present	STAGE I—Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I-E)
STAGE II—Involvement of two or three proximal lymphatic regions A—With no symptoms of generalized disease B—With symptoms of generalized disease	STAGE II—Disease in more than two anatomic regions or in two noncontiguous regions on the same side of the diaphragm	STAGE II—Disease in more than two anatomical regions or in two non-contiguous regions on the same side of the diaphragm	STAGE II—Disease in single extranodal site with involvement of two adjacent lymph node chains	STAGE II—Lymph node involvement on both sides of the diaphragm, including the spleen, *with* or *without* localized *contiguous* extralymphatic organ or tissue involvement A—No systemic symptoms B—Systemic symptoms present	STAGE II—Involvement of two or more lymph node regions on the same side of the diaphragm (II) or solitary involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II-E)
STAGE III—Involvement of two or more distant lymphatic regions	STAGE III—Disease on both sides of the diaphragm, but limited to involvement of lymphoid tissues (lymph nodes, thymus, spleen, and/or Waldeyer's ring) STAGE IV—Involvement of the bone marrow, lung parenchyma, pleura, liver, bone, skin, kidneys, gastro-intestinal tract, or any tissue or organ in addition to the lymphoid tissues All Stages are subclassified *A* (no systemic symptoms) or *B* (fever, night sweats, and/or generalized pruritus)	STAGE III—Disease on both sides of the diaphragm, but limited to involvement of the lymph nodes and spleen	STAGE III—(a) Disease in single extranodal site and involvement of lymph nodes beyond limits of Stage II *without* extension to other side of diaphragm (b) Disease in two extranodal sites of different tissue origin (c) Disease in multiple extranodal sites in the same tissue of origin (b) and (c) *Without* lymph node involvement	STAGE III—Disseminated organ involvement	STAGE 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 solitary involvement of an extralymphatic organ or site (III-E) or both (III-SE)
		STAGE IV—Any lymph node region with involvement of liver, lung or bone marrow* In Hodgkin's disease, sub-divide each stage into: (a) Without systemic effects of disease (b) With systemic effects of disease *Excluding chronic lymphatic leukemia	STAGE IV—Extension of disease beyond the limits of Stage III		STAGE IV—Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement In Hodgkin's disease denote also the absence (A) or presence (B) of systemic symptoms
COMMENT—This was the first well-defined clinical staging classification, and it explicitly recognized the importance of both anatomical extent and of constitutional symptoms. Its principal disadvantage was the heterogeneity of the Stage III category	COMMENT—The main advantage of this proposal was the subdivision of the Peters' Stage III cases into new Stages III and IV, segregating the widespread lymphatic cases from those with spread beyond the lymphatic system. In practice, the criterion of "contiguity" required for the distinction between Stage I_2 and certain Stage II cases has proven troublesome to apply. Moreover, it soon become clear that many cases of localized extralymphatic disease have a relatively good prognosis, despite their being grouped here in Stage IV with other more widely disseminated and rapidly fatal cases	COMMENT—This prognostic classification recognizes the distinction between *localized* and widely *disseminated extralymphatic* disease, and is applicable to *other lymphomas* as well as to Hodgkin's disease, but is overly *complex*.		COMMENT — These authors (as well as Peters et al, 1968) present data to document the fact that survival in cases with limited lung or other localized extralymphatic involvement is not significantly different from that associated with the corresponding extent of lymphatic disease alone, and far better than that in disseminated disease. Thus the *redistribution of Rye Stage IV* is clearly necessary. However, this classification combines the Rye Stages I + II, which seems undesirable and give no clear guidelines on what constitutes "localized" or "contiguous" extralymphatic disease	COMMENT — This proposed classification attempts to combine the best features of the Rye classification and those of Peters et al, 1968, and Musshoff + Boutis, 1969. It is intended for use not only in Hodgkin's disease but also in the non-Hodgkin's group of lymphomas

[a]As modified by Peters and Middlemiss, (1958); a similar classification was also described by Jelliffe & Thompson, (1956).
[b]Rosenberg, (1966); modified from Kaplan, Bagshaw & Rosenberg, (1964).
[c]Peters, Hasselback, & Brown — pp. 357-370 in Symposium Vol. ed by Zarafonetis, (1968).
[d]Musshoff & Boutis, Sonderband 69 Z. Strahlenther., pp 59-74, (1969).

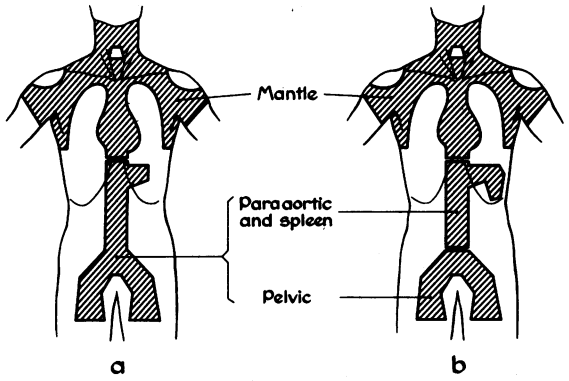

Figure 8.—Schematic representation of the "mantle" and "inverted-Y" fields for total-lymphoid irradiation: (a) a two-field technique, with small extension to include the splenic pedicle, used in splenectomized patients; (b) three-field technique; usually used when the spleen is still present.

the relevant lymph node chains within just two sets of matched anterior and posterior opposed fields (Figure 8): the "mantle" field, covering the cervical, supraclavicular, infraclavicular, axillary, hilar and mediastinal nodes down to the level of the diaphragm;[23] and the "inverted Y," covering the spleen or splenic pedicle, celiac, paraaortic, iliac, inguinal and femoral nodes.[23] It is essential to leave a gap between these adjacent fields at the skin surface; its width must be carefully calculated to permit perfect abutment of the two fields at the depth of the midplane to the body. In young female patients, surgical oophoropexy[24] with fixation of the ovaries in the midline permits ovarian function to be preserved in approximately half the attempts during intensive radiotherapy of the iliac, inguinal, and femoral lymph nodes. When cervical lymphadenopathy extends into the upper neck, the possibility of spread to the preauricular nodes or to the lymphoid tissues of Waldeyer's ring, normally rare in Hodgkin's disease, becomes sufficiently frequent to justify adding small parallel opposed lateral fields covering these areas.

The desirability of irradiating apparently uninvolved lymph node regions "prophylactically," long advanced by Gilbert and by Peters, has been under investigation at Stanford since 1962. Patients with Stages I and II Hodgkin's disease have been assigned by a random procedure to either (A) local treatment only, or (B) extended field treatment. Initially, "extended field" treatment was defined as extending only to encompass the lymph node chains immediately adjacent to those known to be involved. Accordingly,

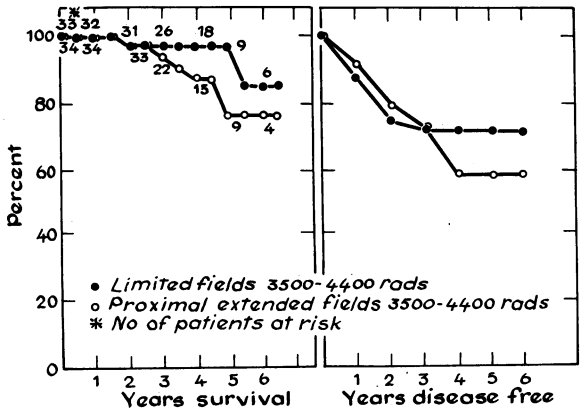

Chart 1.—Hodgkin's disease, Stages IA and IIA. Results of a randomized clinical trial, initiated in 1962, as of May 1, 1970. Actuarial analysis of survival and per cent of groups remaining continuously free of disease.

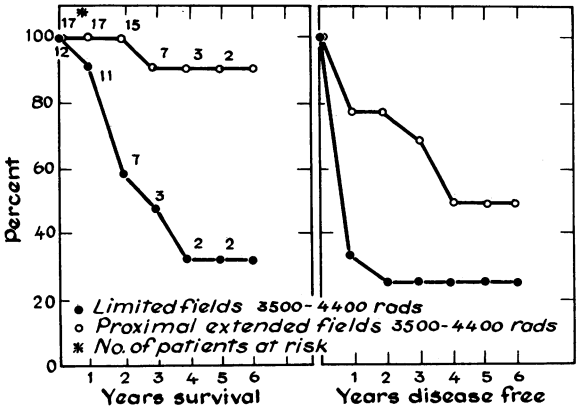

Chart 2.—Hodgkin's disease, Stages IB and IIB. Results of a randomized clinical trial, initiated in 1962, as of May 1, 1970. Actuarial analysis of survival and per cent of groups remaining continuously free of disease.

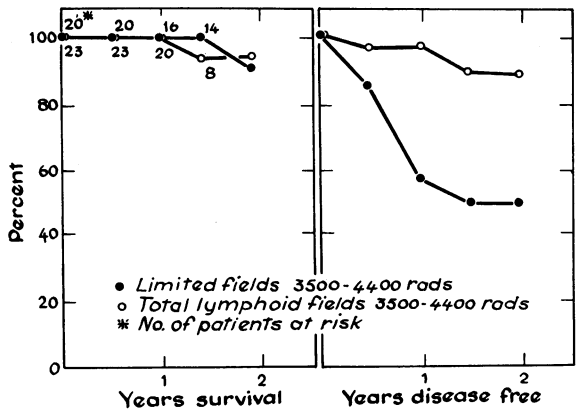

Chart 3.—Hodgkin's disease, Stages IA and IIA. Results of a randomized clinical trial, initiated in 1967, as of May 1, 1970. Actuarial analysis of survival and per cent of groups remaining continuously free of disease.

patients with disease in the neck but not in the mediastinal nodes were not treated below the diaphragm. As can be seen in Chart 1, there was no significant improvement in survival or in freedom from relapse in Stages IA and IIA with such limited extended fields. However, the extended field technique proved distinctly superior to local treatment in Stages IB and IIB (Chart 2), in part perhaps due to the fact that in most such cases there was mediastinal involvement and the patients were therefore additionally treated to the paraaortic, splenic and (in males) pelvic regions. Accordingly, three years ago a new randomized trial was initiated for Stages IA and IIA cases to compare (A) local treatment only versus (B) "total lymphoid" radiotherapy, covering all major lymph node chains. The results to date (Chart 3) clearly indicate a highly significantly reduced relapse rate with the "total lymphoid" technique, but it is still too early to know whether this will later be reflected in a significant difference in actual survival. Other clinical trials in operation at Stanford since 1962 and the N.C.I. have established the effectiveness of the "total lymphoid" radiotherapy technique for the formerly incurable Stage III cases.[2,25]

The requirement for relatively high doses and very large fields in turn dictates the use of radiation beams generated by megavoltage apparatus. Comparable doses of 200 Kv x-rays would elicit intolerably severe skin reactions over such large fields. Since the first course of radiation therapy offers the best chance for cure, it is essential to use megavoltage beams, high doses and optimal field distributions from the beginning. Extended field, "total lymphoid" megavoltage radiotherapy is technically demanding and potentially hazardous, and should not be attempted by inexperienced radiologists who do not devote their entire time to radiation therapy.

Mild to moderate dryness and soreness of the throat and dysphagia often occur during treatment of the "mantle" field and occasionally may be severe enough to warrant a brief interruption of treatment or a decrease in the daily dose rate. Nausea, vomiting and diarrhea are likely to occur during treatment of the retroperitoneal and pelvic nodes, but usually respond readily to medication. Leukopenia or thrombocytopenia usually reach nadir levels late in the course of treatment and may necessitate interruption of treatment for a week or two. Hematologic tolerance has been significantly better in those of our patients who had had splenectomy.[26] Temporary alopecia may be expected in the occipital regions on either side of the "mantle" field.

Hypothyroidism has been detected in about 5 to 10 percent of our patients and has been readily treated. Although some degree of radiographic radiation pneumonitis occurs in most patients after treatment to a "mantle" field, only about 10 percent of patients are symptomatic and only rarely is this serious. The usual clinical manifestations include a hacking, non-productive cough, mild to moderate dyspnea on signficant exertion, and fever. Chest films reveal accentuation of radiographic markings in the paramediastinal pulmonary zones corresponding to the treatment field contours. The clinical manifestations may persist for a few months and then gradually disappear, leaving little or no overt evidence of impaired ventilatory function, though careful physiological measurements may continue to disclose evidence of restrictive and diffusion defects.

Radiation pericarditis which occurs in about 8 percent of our cases treated to the "mantle" field[27] is usually asymptomatic and manifested primarily by the appearance of cardiomegaly on serial post-treatment roentgenograms of the chest. Diagnostic procedures will usually confirm the presence of fluid in the pericardial sac, and a friction rub may be heard transiently. Though the usual course is benign, requiring little or no symptomatic therapy in the majority of cases, careful serial observation of these patients is essential to detect the occasional case in which the condition progresses to tamponade or chronic constrictive pericarditis, necessitating more aggressive therapy including pericardiectomy.

A common but minor complication is the Lhermitte syndrome, in which numbness, tingling or "electric" sensations, without associated motor dysfunction, are experienced in the arms, legs and lower back and are characteristically exacerbated by flexion of the neck. This curious symptom-complex disappears gradually over a period of several months. Transverse myelitis is a much more serious, but fortunately quite rare, complication which can usually be traced to technical errors such as the use of an inadequate gap at the junction of the "mantle" and "inverted Y" fields.

Although isolated instances of myelogenous leukemia have been reported in patients surviving several years after radiotherapy for Hodgkin's disease,[28] conclusive proof that it is indeed radiation-induced has not yet been presented. Aplasia of the bone marrow and other major hematological complications have been quite rare; prompt recovery of peripheral blood elements to normal levels has occurred in almost all of our cases.[2]

Follow-Up Procedure

All patients must be carefully reexamined at serial intervals all their lives after the first course of radiotherapy. Relapses are most likely to occur during the first two years.[29] Visits should therefore be scheduled more often during this period, usually every two to three months, after which visits may be scheduled every six months until five years have elapsed; from then on, annual check-ups suffice. An interval history, with emphasis on the occurrence of constitutional symptoms, a careful physical examination, a complete blood cell count, serum alkaline phosphatase determinations and roentgenograms of the chest and abdomen are routinely performed at each visit. During the first five years, it is desirable to repeat the lymphangiogram whenever the amount of contrast medium remaining is no longer adequate to permit surveillance of the retroperitoneal nodes. Biopsy of any new sites of lymphadenopathy or other possible manifestations of disease should be done whenever necessary to document the occurrence of relapse. Occult involvement of the bone marrow or liver should be suspected, and biopsy done, whenever constitutional symptoms, peripheral blood count depressions, or alkaline phosphatase elevation appear in the apparent absence of lymphadenopathy.

Indications for Treatment of Relapse

In patients with initial Stage I or II disease treated with local radiotherapy in whom later relapses occur in sites other than those already irradiated, a complete diagnostic evaluation is again indicated to exclude Stage IV sites of involvement. If the restaged disease is still limited to Stage II or III, intensive radiotherapy to all previously untreated lymphoid regions is again the treatment of choice. However, if the site of relapse is in a previously heavily irradiated region, reirradiation may be prohibitively hazardous, in which case chemotherapy is the only realistic alternative. Each such decision should be made only after consultative examination by a highly experienced radiation therapist. Relapse at extralymphatic sites, adequately documented by biopsy or other reliable evidence, usually constitutes an indication for chemotherapy.

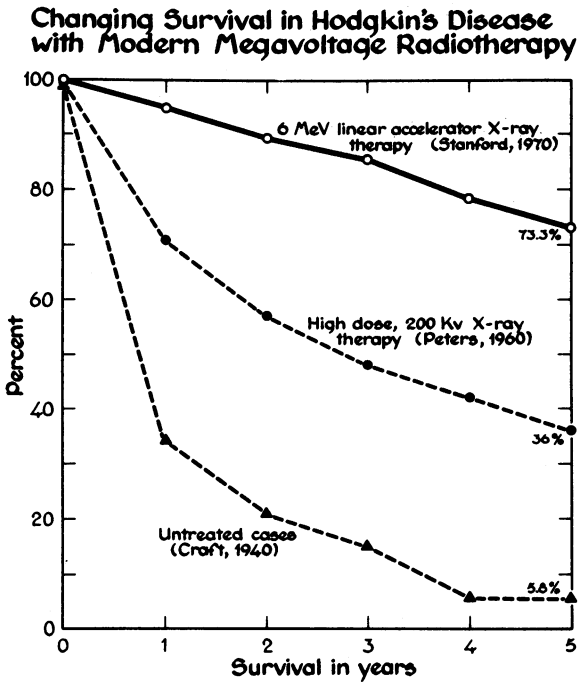

Chart 4.—Composite survival curves from three representative studies reporting results for all stages of Hodgkin's disease during various therapeutic eras: (a) untreated cases;[35] (b) high-dose (200 Kv) X-ray therapy;[36] and (c) current Stanford megavoltage radiotherapy survival data for all cases, all stages.[2]

Prognosis

Intensive, total lymphoid megavoltage radiotherapy has drastically altered the prognosis of Hodgkin's disease (Chart 4). In carefully staged and optimally treated cases the relapse-free survival rates at five years may be expected to be 85 to 90 percent in Stages I and II, 70 percent in Stage IIIA, and 40 to 50 percent in Stage IIIB, and 65 to 70 percent overall for all stages.[2] Since at least 95 percent of all primary relapses occur during the first five years, relapse-free survival for more than five years has been considered tantamount to cure.[30,2] Thus, the classical view that Hodgkin's disease is inevitably fatal is no

longer tenable. Instead, the physician should adopt an aggressive approach to early diagnosis, followed by prompt referral to highly qualified medical centers for careful staging and treatment. Only thus can he expect to offer long-term, disease-free survival to the majority of his patients with Hodgkin's disease.

Chemotherapy of Hodgkin's Disease

Chemotherapy of the lymphomas has developed significantly since the initial experience with nitrogen mustard during World War II. At this time successful palliation can be obtained in the majority of patients and is among the most satisfactory in the difficult field of cancer chemotherapy.

Not infrequently chemotherapy will eliminate all evidence of malignant lymphoma. Inevitably, however, the disease recurs; no documented instance of apparent cure by single drug chemotherapy of Hodgkin's disease or lymphoma (with the possible exception of the Burkitt's tumor) is on record.[31] It is therefore not justifiable to utilize chemotherapy as initial treatment for patients with localized disease who still have a chance for cure by intensive radiotherapy. In fact, despite the definite observation in individual patients that a life-threatening situation can be reversed with chemotherapy, no adequate data has been presented which is conclusive to indicate that the average duration of life of a group of patients with malignant lymphoma has been prolonged by chemotherapy, when comparison is made with a control group.

The alkylating agents, vinblastine, and procarbazine are valuable drugs for palliation of patients with Hodgkin's disease. In addition, for patients with non-Hodgkin's lymphomas, vincristine and the corticosteroids are important drugs to be used in their management.

Alkylating Agents

The principal alkylating agents are nitrogen mustard (HN_2), chlorambucil (Leukeran®), cyclophosphamide (Cytoxan®), and thiotriethylenephosphoramide (Thiopeta®). Making a choice among them depends more on the experience of the physician and the individual patient situation than on any real superiority of one drug over the others. HN_2 has the advantage of rapid action, but it must be given intravenously and it causes brief but occasionally severe nausea and vomiting. The average duration of benefit is two to three months after a single dose. The advantage of chlorambucil is that it may be given orally, and its effect may be titrated more readily against both tumor and bone marrow response. The use of chlorambucil to maintain a response induced by HN_2 can obviate the need for repeated courses of intravenous drug. Oral maintenance therapy should be started two to four weeks after HN_2 infusion, as soon as the white blood cells and platelet counts begin to rise. If one waits for the blood cell counts to return completely to normal levels, clinical evidence of active Hodgkin's disease will often return also, and the value of smooth maintenance response is lost.

Cyclophosphamide is a good drug for Hodgkin's disease. It appears to be somewhat more predictably absorbed from the gastrointestinal tract than chlorambucil and can also be given intravenously. Its gastrointestinal toxicity is mild, allowing its use intravenously over a period of five to seven days instead of HN_2 in cases of intermediate urgency. An advantage is its lesser toxicity for blood platelet formation. However, it induces alopecia in many patients in whom administration of the drug is carried to the point of marrow toxicity; this is an especially important consideration in women and children. Cystitis is also a frequent complication which, if not recognized early, can progress to a serious hemorrhagic form which may be difficult to control. The hazard of this complication can be minimized by adequate hydration and the maintenance of a high urine volume. When cystitis is detected, it may be necessary to reduce the dose of drug or discontinue it completely. Patients who respond well to cyclophosphamide can be maintained at a dose of 50 to 100 mg per day orally. Although Thiotepa® is active against Hodgkin's disease, it offers no major advantage over the other alkylating agents.

Vinblastine (Velban®). It is of great interest that this alkaloid from the periwinkle plant is seldom effective against the other malignant lymphomas, yet provides significant objective improvement for the majority of patients with Hodgkin's disease. Though oral preparations have been tested, the clinically available form of the drug must be given intravenously. It is well tolerated, granulocytopenia being its major

has been beneficial.[31] Moreover, the routine supplementation of radiotherapy with concurrent single drug chemotherapy in Stage I, II or IIIA Hodgkin's disease seems distinctly unwise, since the drug, by lowering white blood cell or platelet counts, may jeopardize the completion of the course of radiotherapy and thus interfere with potentially curative treatment.

More recently, we have found it possible to administer the MOPP cyclic combination chemotherapy following total lymphoid radiotherapy. With a rest period of 30 to 60 days after the irradiation, amounts of the drugs comparable to those used in non-irradiated patients have been safely tolerated.[33] We have randomly allocated patients with systemic symptoms, widespread disease, or both to treatment with total lymphoid radiotherapy alone or with sequential combination chemotherapy (MOPP). To date 17 patients have completed this combined therapeutic program, with no failures of disease control and no relapses following completion of therapy. The longest follow-up period is only 12 months, which is still too short for therapeutic projections. The program, however, has proved to be feasible and encouraging.[33]

Special Clinical Considerations For Other Malignant Lymphomas

As in Hodgkin's disease, the clinical extent of involvement must be studied carefully before staging and treatment. Lymphangiography may be expected to demonstrate unsuspected disease in the abdomen in a very high proportion of patients. In various reported studies[15,34] between 50 and 90 percent of patients with apparently localized forms of non-Hodgkin's lymphoma have also had silent retroperitoneal disease as demonstrated by lymphangiography. It is especially important in these patients to perform careful bone marrow examination, using both the aspiration and the cutting needle or open biopsy techniques, since, unlike those with Hodgkin's disease, a high proportion of patients will show involvement of the marrow even when the peripheral blood elements are entirely normal.

Usually, patients present with asymptomatic lymph node involvement or symptoms referable to a local tumor mass. Systemic symptoms are not characteristic as an early feature of the non-Hodgkin's group, being present in less than 10 percent of these patients when first seen; and they are not well correlated with the extent of disease. Severe night sweats and fever may develop later in the course of the disease. Unexplained severe pruritus is seen occasionally but is not characteristic of these disorders.

Since involvement of the gastrointestinal tract is much more common in the non-Hodgkin's group, radiological examinations routinely performed for the evaluation of these patients, in addition to those utilized in Hodgkin's disease, should include barium studies of the entire gastrointestinal tract. The lymphoid structures of Waldeyer's ring are also far more frequently involved than in patients with Hodgkin's disease. They must be examined with care, and biopsy done when they are at all suspect.

The staging definitions and classifications suggested for Hodgkin's disease can be applied to the non-Hodgkin's group. However, prognostic correlations are not yet as well established for these patients, and clinical stage may well prove to be a less important prognostic indicator than histopathologic sub-type, unlike the situation in Hodgkin's disease.

Radiotherapy of Non-Hodgkin's Lymphomas

Although the fundamental concepts remain the same, the radiotherapy of this group of neoplasmas differs in certain essential respects from that for Hodgkin's disease. Since the numbers of cases available for radiotherapy with curative intent are smaller, data on the optimal dose level required to obtain local eradication of disease with comparable reliability are much less firmly established. It is generally believed that the histiocytic and some of the lymphoblastic lymphomas are somewhat more radioresistant, requiring total doses in the 5,000 rad range, whereas the nodular lymphocytic lymphomas seem more sensitive and might well be controlled with substantially smaller doses. Since this is not certain, however, and since the dose level employed for Hodgkin's disease has, on the whole, been well tolerated, it has been our practice to use the same dose (about 4,000 to 4,400 rads) for all of the other lymphomas except those of the diffuse histiocytic variety, to which a dose of about 5,000 rads is normally delivered.

A second question relates to the need for "prophylactic" treatment of extended fields to

toxic effect. There is little or no depression of the platelet count; indeed, many patients exhibit an increase in the platelet count on vinblastine. The drug is usually given at weeklv intervals at dose levels of 0.05 to 0.20 mg per kg of body weight, titrated against the response of the disease and of the white blood cell count. Although pronounced leukopenia may develop, rapid recovery is the rule. Patients who respond well to vinblastine usually do so after the first or second injection. Occasionally, four to six doses are required before remission is observed. In some patients, injections may be spaced at two to four week intervals after the initial response is obtained. With maintenance therapy, the disease may be kept in remission for many months, occasionally for several years.

Procarbazine (Matulane®). The sole representative to date of a third class of drug for Hodgkin's disease is procarbazine. It has been used extensively in clinical trials in Europe and the United States and is now available commercially. It has definite activity against Hodgkin's disease and a high proportion of patients experience objective benefit for at least a short time. Its bone marrow toxicity is similar to that of nitrogen mustard, affecting all of the formed elements. When used as the third sequential drug for Hodgkin's disease, the responses have been relatively short in duration, averaging two or three months. It can be presumed that better results will be obtained when the drug is used earlier in the course of the disease.

Corticosteroids. There is no doubt that objective regression of Hodgkin's disease is observed in some patients when treated with corticosteroid therapy. The general experience is, however, that the responses are brief in duration and overshadowed by the serious toxic effects of steroids, which are particularly distressing in the leukopenic patients. In general, their use is indicated for patients with serious hemolytic anemia or in the near terminal stages of the illness with bone marrow function too severely impaired to allow the use of any of the myelosuppressive agents.

Cyclic Combination Chemotherapy. In recent years there has been great interest in the use of combinations of chemotherapeutic agents. It is possible to achieve a greater degree of cell destruction when drugs do not have overlapping toxicity. This principle has been applied to the treatment of acute leukemia and would appear to have provided definite improvement in the palliative use of the drugs available. The same approaches have been applied to the malignant lymphomas. The most successful and widely tested combination of drugs has been developed at the National Cancer Institute[32] and consists of six two week cycles of therapy with nitrogen mustard, vincristine, procarbazine, and prednisone, the so-called MOPP program. Since two-week rest periods intervene between successive cycles, the entire course of treatment requires six months. Though this is a difficult, prolonged, and potentially hazardous therapeutic program, complete suppression of evidence of Hodgkin's disease can be obtained in 70 to 80 percent of previously untreated patients. The value of this approach has been the high percentage of complete regression of disease and of long disease-free intervals without maintenance therapy. In one group of 43 patients with Stage III or IV disease treated in this manner at the National Cancer Institute, 35 obtained complete regression of disease and 17 remain without evidence of disease without maintenance therapy with a minimum duration of at least 36 months since completion of the treatment.

Unfortunately, there have been no adequately controlled studies to indicate that this form of therapy is superior to the more conservative use of single drug chemotherapy in terms of duration and quality of life. There is no doubt, however, that a higher frequency of complete remission is achieved with the four-drug combination than when one drug is used. It has been demonstrated that unmaintained remissions are significantly longer with the combination therapy than when one drug is given. This is true even when one drug is given to the maximum tolerance and then in repeated cycles. However, what remains to be demonstrated is that an appropriately matched control group picked at random will have a different survival when any form of single drug, sequential chemotherapy is given compared with the aggressive four-drug combination. Until this demonstration is forthcoming, such programs of combination chemotherapy must still be considered experimental.

Combination Radiotherapy and Chemotherapy. There have been numerous attempts to improve the results of radiotherapy by combining chemotherapy with it. There are to date, however, no convincing reports that such combined therapy

encompass apparently uninvolved lymph node chains. Though data on this point are still sparse for the other lymphomas, it is suggestive that contiguity of spread via lymphatic channels is more likely to occur when the histologic pattern is nodular than when diffuse. In the latter group, new sites of involvement are not infrequently quite remote and unpredictable, thus making the argument for the extended field technique much less attractive than in Hodgkin's disease.

Finally, certain specific points deserve comment. The lymphoid structures of Waldeyer's ring are much more commonly involved, either primarily or during the course of the disease, and should therefore be treated routinely whenever there is lymphadenopathy in the neck, as well as when involvement of Waldeyer's ring is actually present. These lymphomas are also much more likely to arise in an extranodal structure, such as the stomach or small intestine. In such instances, surgical extirpation of the primary lesion followed by intensive radiotherapy to an extended field, encompassing the regional lymph nodes, whether evidently involved or not, is the treatment of choice.

Chemotherapy of Non-Hodgkin's Lymphomas

The general indications for chemotherapy for patients with the non-Hodgkin's lymphomas are much the same as for those with Hodgkin's disease. When the disease has become widespread and is beyond the scope of potentially curative radiotherapy, a palliative approach is indicated. Patients with non-Hodgkin's lymphomas of the nodular and well differentiated lymphocytic types may be completely asymptomatic for prolonged periods. This may be true despite the presence of widespread disease even involving Stage IV sites such as the bone marrow. In our experience this is more commonly true for these sub-types within the non-Hodgkin's group than for Hodgkin's disease. It is our practice to withhold treatment until such systemic symptoms as weight loss, fatigue, night sweats or fever develop or there is documented progressive lymph node enlargement such that local or generalized symptoms can be anticipated in a short time. In these circumstances, palliative radiotherapy may still be preferred when the principal symptomatic manifestation is essentially local in nature. If, however, this does not seem to be the case, chemotherapy can be employed and is often very successful for palliation.

All of the chemotherapeutic agents described for Hodgkin's disease may be used in the same manner and at the same dose levels for patients with non-Hodgkin's lymphoma. Assuming a normal platelet count, nitrogen mustard or chlorambucil is usually our first choice, though we tend to favor cyclophosphamide for patients with diffuse lymphomas of the poorly differentiated lymphocytic (lymphoblastic) or histiocytic types. Its relative superiority over chlorambucil has not been established, however. When the disease becomes refractory to the alkylating agents, the second agent of choice differs depending on the histopathologic type of lymphoma. For patients with diffuse lymphoblastic or histiocytic lymphomas, vincristine is the second drug we normally employ. It produces objective regressions in the majority of patients, and occasionally these responses are dramatic. The dose of vincristine does not have to be large; often 15 to 25 gamma per kg of body weight at weekly intervals is sufficient to induce good responses. The drug is administered at weekly intervals until complete regression has occurred, and thereafter at longer intervals between injections, as necessary.

Vincristine should be used as sparingly and with as long intervals as possible, so that the inevitable complication of neuropathy can be delayed and its severity minimized. The disappearance of deep tendon reflexes and the development of peripheral paresthesias, especially in the finger tips are the first indication that neuropathy is occurring. With continuing or prolonged therapy this usually becomes more severe; motor loss of the small muscles of the hands or feet usually develops, with foot drop as one of the most serious manifestations. Alopecia is also frequently observed with vincristine therapy, and patients must be informed about it. Occasionally, for patients who are critically ill, alkylating agents and vincristine may be given in combination. Once disease control has been achieved, vincristine may be discontinued until it becomes clear that alkylating agents alone cannot maintain the response. Vincristine has much less value for treating patients with diffuse lymphocytic or nodular lymphomas. When alkylating agents have lost their effectiveness in these patients, corticosteroids may produce dramatic

and useful remissions. The side effects of corticosteroid administration are well known and distressing, so that the smallest possible dose of corticosteroid is usually sought once initial remission has been obtained.

More aggressive combination chemotherapy for the non-Hodgkin's lymphomas has been attempted by several groups of investigators, but such combinations have not yielded significant improvement in results beyond those obtained with single drugs. Combinations which have received the greatest attention have included cyclophosphamide, vincristine and prednisone in various dose schedules and the four-drug combination of nitrogen mustard, vincristine, prednisone and procarbazine as described for Hodgkin's disease. None of these combinations have shown clinical advantages in a controlled trial which would justify adopting them as routine.

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