The Management of Lymphoma

J. E. Ultmann, M.D.

Introduction

In 1832, Thomas Hodgkin published a paper entitled "On Some Morbid Appearances of the Absorbent Glands and Spleen," describing seven patients who had enlargement of lymph nodes, spleen and liver.1 In 1865, Wilks reviewed Hodgkin's seven cases, added 15 patients of his own, and named the disorder "Hodgkin's disease." At the turn of the century, Sternberg as well as Reed described the giant cell characteristic of Hodgkin's disease and thus permitted clear delineation of this disorder from the other lymphomas.2

*Of parenthetical interest is the fact that in 1926, Fox located the seven specimens originally described by Hodgkin in the Hunterian Museum and discovered that in three of these, Hodgkin's disease was not present and tuberculosis was the cause of the lymphoid enlargement. Ann. Med. Hist. 8: 370-374, 1926.

Incidence and Presentation

It is estimated that in the United States 22,000 new cases of lymphoma are discovered each year and that 17,000 patients die of lymphoma. Whereas lymphosarcoma and reticulum cell sarcoma are confined to the older age groups, occurring with increasing incidence after the age of 50, Hodgkin's disease appears to have 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. Hodgkin's disease is more common in men than in women.

The majority of patients with lymphoma present with enlargement of a peripheral lymph node. Others present with multiple peripheral lymph node enlargement or deep-seated lymph nodes, with organomegaly or with symptoms suggesting involvement of other sites. In Hodgkin's disease, fever and pruritus are the initial symptoms in a significant number of patients; in the other lymphomas, however, initial symptoms may be minimal.

The differential diagnosis of solitary lymph node enlargement requires the elimination of a number of possible local causes: for example, cervical lymphadenopathy may stem from tonsillitis, cancer of the mouth or pharynx, tinea capitis or dental disorders; and inguinal lymph node enlargement from venereal disease or athlete's foot. If the lymph node enlargement is more wide-
TABLE 1 — HISTOLOGIC CLASSIFICATION OF MALIGNANT LYMPHOMA

| Predominating component cell(s) | Rappaport classification | "Old classification" |
|--------------------------------|---------------------------|----------------------|
| Primitive reticular cell        | Malignant lymphoma, reticulum cell type, undifferentiated* | Large cell lymphosarcoma; reticulum cell sarcoma |
| Histiocyte                     | Malignant lymphoma, reticulum cell type, histiocytic* |                     |
| Histiocyte and lymphocyte      | Malignant lymphoma, Hodgkin’s type* |                     |
| Lymphocytic cells              | Malignant lymphoma, mixed cell type (histiocytic-lymphocytic) | Large cell lymphosarcoma; lymphoblastic lymphosarcoma |

*Malignant lymphomas with follicular pattern have been integrated into this classification and are designated by adding follicular to the cytologically appropriate term.

†See Table 2.

spread, the physician must consider infectious diseases, such as infectious mononucleosis, tuberculosis, syphilis or fungal disorders; he must also consider collagen disorders, sarcoid, carcinomatosis, leukemia, as well as lymphoma. Blood smears, chemical tests of blood and other studies may diagnose conditions other than lymphoma; however, an enlarged lymph node which is not diagnosed by complete work-up and is still present after four to six weeks must be biopsied. The lymph node biopsy should be performed by a surgeon experienced in this procedure. It should be done at the site that appears to be most involved and the incision should permit the surgeon to remove not only the easily accessible lymph nodes but also those that seem most enlarged and most likely to be involved. Often it will not be the first lymph node reached by the surgeon but the second or third that will give the diagnosis.

TABLE 2 — HISTOLOGIC CLASSIFICATION OF HODGKIN’S DISEASE

| Lukes and Butler | Jackson and Parker |
|------------------|--------------------|
| Lymphocytic predominance | Paragranuloma |
| (diffuse or nodular) | Granuloma |
| Nodular sclerosis | Sarcoma |
| Mixed cellularity | Diffuse fibrosis |
| Lymphocyte depletion | Reticular type |
| (1) Diffuse fibrosis | Sarcoma |
| (2) Reticular type | Sarcoma |

Histologic Classification of Lymphomas

The histologic classification of lymphomas recommended at this time is based upon the identity of the predominating component cells. Tables 1 and 2 summarize the current schemes of histologic classification compared with previous histologic nomenclatures. Precise histologic diagnosis permits
prognostication regarding course and comparison of results between treatment centers.

In patients with disseminated lymphoma, differences in histology appear to predict both the course of the disease and the response to chemotherapy. Thus in patients with malignant lymphoma, lymphocytic type, well differentiated, the disease will progress in a relatively more benign manner than in patients with the diagnosis of malignant lymphoma, reticulum cell type, mixed cell type or lymphocytic, poorly differentiated type. Malignant lymphomas with a follicular pattern appear to have

| TABLE 3 – HODGKIN’S DISEASE: STANFORD MODIFICATION OF THE RYE STAGING SYSTEM 1970 |
|--------------------------------|
| 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 more lymphoid regions, but limited to one side of the diaphragm. (A subscript -n indicates the number of regions involved) or solitary involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (I-E). |
| 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 side (III-E) or both (III-SE). |
| 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, all patients are subclassified A or B to indicate the absence or presence, respectively, of documented unexplained fever, night sweats, or generalized pruritus.

Fig. 1. This radioisotope scan of the liver demonstrates replacement of a portion of the left lobe by Hodgkin’s disease as well as a widened porta hepatis, presumably due to a mass of lymph nodes. Autopsy confirmed these findings.
a more benign course than those with a diffuse pattern. In Hodgkin's disease, the categories established in the classification proposed by Lukes, et al. appear to correlate better with response to therapy and with the rate of progression of the disease than do the three groups originally proposed by Jackson and Parker. Recently, Rappaport and Strum have pointed out the significance of vascular invasion in Hodgkin's disease, stressing the important prognostic value of this histopathologic feature since it may indicate that hematogenous dissemination has occurred.7

**Clinical Staging**

When the clinician is confronted with histologic evidence that his patient has lymphoma he must proceed to clinical staging to assess the extent of disease and plan optimal therapy. Over the last few years, approaches to clinical staging have undergone important developments mainly because of two factors: (1) Radiotherapeutic techniques have improved and now permit therapy encompassing wider fields and better dosimetry; and (2) new techniques of delineating disease have been developed. Rosenberg and Kaplan have proposed the "Stanford modification" of the "Rye staging system" for Hodgkin's disease.* (Table 3.) More recently, a similar classification has been applied to the other lymphomas.

Accurate clinical staging of Hodgkin's disease and other lymphomas requires rigorous investigation which should include: History, physical examination, blood count, erythrocyte sedimentation rate, evaluation of the mediastinum by chest film as well as whole lung tomography in the presence of hilar adenopathy are required in all cases. A skeletal survey with emphasis on the thoracolumbar and pelvic spine should be performed, along with special studies which have been developed for investigation of the retroperitoneum (see below). Smears of aspirated bone marrow and histologic section of marrow clot should be examined and open marrow biopsy should be done in Hodgkin's disease. Evaluation of the liver includes liver scan, bromsulphalein retention and serum alkaline phosphatase. Renal function is evaluated by urinalysis, blood urea nitrogen, creatinine and intravenous pyelography. Finally it is important to document cutaneous anergy if present.

What are some of the tools that have been developed to make staging more precise? Evaluation of the retroperitoneum and of the contents of the abdominal cavity is most difficult and radiologic examination (for example, gastrointestinal series or intravenous pyelography) is usually not sufficient to rule out disease below the diaphragm. Radioisotope scanning may be employed to demonstrate enlargement of the liver, involvement of the liver by discrete masses, involvement of the porta hepatitis, splenic enlargement and, occasionally, splenic masses. (Figs. 1 and 2.)

Fig. 2. Liver and spleen scan employing technetium 99m sulfur colloid and an Anger camera. The patient is a six-year-old boy with lymphoma. The figure demonstrates the anterior view of liver and spleen and shows massive splenomegaly. (Reproduced by permission of Dr. A. Gottschalk, Department of Radiology, The University of Chicago.)
Studies indicated for delineation of retroperitoneal involvement are the inferior vena-cavogram and bilateral lymphangiogram. (Figs. 3 and 4.) Lee, et al. studied 226 patients with Hodgkin’s disease by lymphangiography. Of those thought to have inguinal involvement Stage I before lymphangiography, he found that 100 percent had retroperitoneal involvement as demonstrated by lymphangiograms. Of those who had cervical Hodgkin’s disease Stage I, approximately 20 percent were found to have retroperitoneal disease. In patients with regional disease above the diaphragm (Stage II) lymphangiography demonstrated retroperitoneal involvement in approximately 30 percent of the asymptomatic patients (Stage II A) and in 90 percent of the symptomatic patients (Stage II B).

Over the past few years it has become clear that the radioisotope techniques of assessing hepatic and splenic involvement, as well as the techniques of inferior vena-cavography and lymphangiography, could not clearly determine whether or not the infradiaphragmatic lymph nodes or organs were involved. Because of this, a number of lymphoma centers began to use exploratory laparotomy, including splenectomy (as well as lymph node, liver and bone marrow biopsies) in the staging of lymphoma.

**TECHNIQUE OF LAPAROTOMY**

Preparation for laparotomy requires
TABLE 4 – LAPAROTOMY AND SPLENECTOMY IN STAGING OF HODGKIN'S DISEASE

| CLINICAL FINDINGS | LYMPH NODES | SPLEEN | LIVER |
|-------------------|-------------|--------|-------|
|                   | Rpln | Other | All  | + | - | + | - |
| IVC/LAG Normal    | 13   | 0     | 2    | 11 |    |    |    |
| Equivocal         | 4    | 1     | 1    | 4  |    |    |    |
| Abnormal          | 12   | 6     | 1    | 5  |    |    |    |
| SPLEEN PALPATION/SCAN |
| Not felt and neg scan | 23  |      |      | 8 | 15 |    |    |
| Splenomegaly and/or pos scan | 7   |      |      | 4 | 3  |    |    |
| LIVER FUNCTION TESTS |
| Normal            | 20   |    |      | 1 | 19 |    |    |
| Abnormal          | 12   |    |      | 0 | 12 |    |    |

a team of internists, radiologists and surgeons to meet and review all clinical data and to determine biopsy sites. At operation, the surgeon inspects and palpates the abdominal contents. A wedge biopsy and two deep needle biopsies of the liver are taken. Biopsies of lymph nodes suspicious by radiologic examination 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. After closing the abdomen, unilateral or bilateral core biopsy of the iliac bone is performed. Following this procedure, a postoperative abdominal film is taken to determine location of silver clips relative to the previously suspected lymph nodes and to determine location of splenic pedicle and masses.

**Correlation of Laparotomy Results with Other Diagnostic Tests**

**Lymph Node Biopsies**

The data regarding laparotomy are summarized in Table 4. The correlation of the inferior vena-cavogram (IVC) and lymphangiogram (LAG) with operative findings is shown for 29 patients with Hodgkin's disease. Thirteen IVCs/LAGs were considered normal; at laparotomy, no involved retroperitoneal nodes were found in 11 of these patients. However, in two patients, lymph nodes not visualized in the area of the retroperitoneum (one in the splenic pedicle and one in the porta hepatitis) were found to be positive for Hodgkin's disease. Of the four equivocal IVCs/LAGs, two were negative and one positive in the visualized area; again only positive nonretroperitoneal lymph node was found. Of the 12 abnormal IVCs/LAGs, only six were confirmed as abnormal; six were negative, but one of these six had an involved lymph node outside the retroperitoneal area. The data on 145 patients subjected to laparotomy in three medical centers, including ours, are essentially similar: the IVCs/LAGs of 74 patients were considered negative preoperatively but nine patients were found to be positive for Hodgkin's disease. Of the 24 equivocal IVCs/LAGs, 18 were negative and four were positive, with two additional lymph nodes found outside the retroperitoneum; and of 47 positive IVCs/
TABLE 5 — RESULTS OF LAPAROTOMY IN 145 PATIENTS WITH HODGKIN'S DISEASE (INVOLVEMENT OF LYMPH NODES)

| Pathologic Findings | Biopsy-proven Hodgkin's Disease | Biopsy Negative for Hodgkin's Diseases |
|---------------------|--------------------------------|-------------------------------------|
|                     | Biopsy-proven Hodgkin's Disease | Retroperitoneal Lymph Nodes | Other Lymph Nodes† | Total |
| Negative LAG/IVC:   |                                  | 57                     | 2                   | 5    |
| Stanford            |                                  | 13                     | 0                   | 2    |
| Chicago             |                                  | 4                      | 0                   | 4    |
| Total               |                                  | 74                     | 2                   | 7    |
| Equivocal LAG/IVC:  |                                  | 20                     | 3                   | 1    |
| Stanford            |                                  | 4                      | 1                   | 1    |
| Chicago             |                                  |                        | −                   | −    |
| Total               |                                  | 24                     | 4                   | 2    |
| Positive LAG/IVC:   |                                  | 23                     | 17                  | 1    |
| Stanford            |                                  | 12                     | 6                   | 1    |
| Chicago             |                                  | 12                     | 7                   | −    |
| Total               |                                  | 47                     | 30                  | 2    |
| Grand Total         |                                  | 145                    | 36                  | 11   |

†Includes: lymph nodes in porta hepatitis, mesentery, or splenic hilum. LAG = lymphangiogram; IVC = inferior venacavagram.

LAGs, 30 were substantiated but 15 were not and two positives were found in extraretroperitoneal areas. (Table 5.)

**Splenectomy**

Table 4 summarizes the results obtained in patients undergoing splenectomy. In 23 patients the spleen was not felt and the scan negative for splenomegaly; of these, eight cases of Hodgkin's disease of the spleen were discovered. (Fig. 5.) Splenomegaly was demonstrated by physical examination or positive scan in seven patients, yet Hodgkin's disease of the spleen was substantiated in only four. The data from four medical centers, including ours, are essentially in agreement. (Table 6.) The preoperative assessments of 137 cases were negative for splenic involvement, but Hodgkin's disease was demonstrated in 38 spleens; 45 patients were suspected of having Hodgkin's disease in the spleen but this was substantiated in only 28 patients.
Liver Biopsies

The liver biopsies performed in 32 patients are summarized in Table 4. In the one patient who had involvement of the liver proven on biopsy, the liver was not palpable and liver function tests and liver scan were normal. In many patients histologic abnormalities were found which were considered nonspecific. Similar nonspecific liver infiltrates are described by others. The data from three lymphoma centers, including ours, are essentially in agreement. (Table 7.) Of the 120 patients thought to have no liver involvement, only four were found to have Hodgkin's disease in the liver; however, of the 32 thought to have

TABLE 6 – RESULTS OF SPLENECTOMY IN 182 PATIENTS WITH HODGKIN'S DISEASE

| Preoperative Assessment | Biopsy-proven Hodgkin's Disease | Biopsy Negative for Hodgkin's Disease |
|-------------------------|---------------------------------|-------------------------------------|
| Clinically Negative     |                                 |                                     |
| Stanford                | 84                              | 20                                  |
| Chicago                 | 23                              | 8                                   |
| Baltimore               | 12                              | 7                                   |
| Iowa                    | 18†                             | 3                                   |
| Total                   | 137                             | 38                                  |
| Clinically Positive     |                                 |                                     |
| Stanford                | 16                              | 8                                   |
| Chicago                 | 7                               | 4                                   |
| Baltimore               | 8                               | 6                                   |
| Iowa                    | 14†                             | 10                                 |
| Total                   | 45                              | 28                                  |
| Grand Total             | 182                             | 66                                  |

†Approximate number.

TABLE 7 – RESULTS OF LIVER BIOPSY IN 152 PATIENTS WITH HODGKIN'S DISEASE

| Preoperative Assessment | Biopsy-proven Hodgkin's Disease | Biopsy Negative for Hodgkin's Disease |
|-------------------------|---------------------------------|-------------------------------------|
| Clinically Negative     |                                 |                                     |
| Stanford                | 85                              | 2                                  |
| Chicago                 | 20                              | 1                                  |
| Baltimore               | 15                              | 1                                  |
| Total                   | 120                             | 4                                  |
| Clinically Positive     |                                 |                                     |
| Stanford                | 15                              | 1                                  |
| Chicago                 | 12                              | 0                                  |
| Baltimore               | 5                               | 2                                  |
| Total                   | 32                              | 3                                  |
| Grand Total             | 152                             | 7                                  |

349
liver involvement clinically, only three were substantiated to have such.11

As a result of these studies, changes in staging can be made which permit logical adjustment of treatment plans. In our own series, of the seven patients considered Stage I preoperatively, four were classified Stage III postoperatively; of the eight patients considered Stage II, two became Stage III. Of the 12 patients considered Stage III preoperatively, one was advanced to Stage IV, because of microscopic liver involvement; two were staged II; and one was staged I.11

Laparotomy and Splenectomy in the Staging of Lymphomas Other Than Hodgkin’s Disease

Since laparotomy and splenectomy have proved useful in the staging of Hodgkin’s disease, we have evaluated these procedures in 12 patients with other types of lymphomas. Three of the four patients in whom contrast studies showed normal retroperitoneal lymph nodes were found to have disease in these nodes. Of eight patients with abnormal studies, only four had positive node biopsies; in two with enlarged retroperitoneal lymph nodes, the biopsied mesenteric lymph nodes were positive. In five patients, disease was detected in lymph nodes other than retroperitoneal, including splenic hilar, porta hepatis and mesenteric. Two of seven patients with no clinical evidence of splenomegaly had lymphoma in the spleen, while only three of the five with clinical splenic enlargement had disease in the spleen. Of six patients with normal hepatic evaluation, one had lymphoma in the liver; of six with abnormal studies, one had hepatic disease. One bone biopsy was positive. The staging was changed in five of the 12 patients as a result of laparotomy: four of these five changes were to more advanced stages. Laparotomy and splenectomy was well tolerated in patients with non-Hodgkin’s lymphomas, even in the elderly.12

Performance of laparotomy, splenectomy, liver biopsy and bone core biopsy in patients with malignant lymphoma offers an opportunity to define the natural history of the disease in newly diagnosed patients. This extensive staging procedure permits precise assessment of extent of disease and consideration of logical treatment plans. Laparotomy may permit removal of bulky tumor. In addition, this type of procedure accomplishes accurate port design, preventing radiation injury to vital organs such as the left kidney, diaphragm, lung and heart. The permanent silver clips permit accurate assessment of the effect of radiotherapy after the lymphangiography contrast material has disappeared. It is probable that the tolerance for radiotherapy or drug therapy is improved by removing the spleen although there are certain hazards to splenectomy which are particularly well known in pediatric practice. However, no serious complications have yet been ascribed to splenectomy in patients with lymphoma.

Gallium-67 Scanning

Pinsky, Hoffer, Turner, Harper and Gottschalk of the University of Chicago have developed a new radiological scanning technique employing radio-

| TABLE 8 — 67GALLIUM (ATOMIC NUMBER 31) |
|----------------------------------------|
| PRODUCTION |
| 66Zn (d, n) 67Ga |
| 8 MeV. deuterons used in cyclotron to bombard zinc target |
| DECAY |
| 67Ga (e, c) 67Zn |
| half life of 67Ga = 77.9 hours |
| Gamma Energies of Decay |
| 93KeV. — 40% |
| 184KeV. — 24% |
| 296KeV. — 22% |
| 388KeV. — 7% |
| Scan — with the 296KeV. gamma photons |
active Gallium-67. This approach may further refine the clinical staging of lymphoma as it enables the clinician to identify Hodgkin’s disease or lymphoma in sites not readily assessed by other techniques. The production, decay factors and method of scanning are outlined in Table 8. Sixteen patients with Hodgkin’s disease have been studied prior to surgical staging. Normal scans were obtained in eight and in none of these was disease demonstrated outside of the original biopsy site. In eight other patients, the gallium scan showed involvement in 16 sites; 14 of these were substantiated at laparotomy; there was one false negative. The figures illustrate results obtained in two patients. (Figs. 6 and 7.)

Complications of Lymphoma

The natural history of progressive lymphoma is characterized by bursts of exacerbation and by remissions which can be achieved by radiotherapy or chemotherapy. Invariably, unless the patient is cured, the disease progresses, affecting various organs, decreasing their normal function and producing complications such as anemia; thrombocytopenia with bleeding; and failure of respiratory, gastrointestinal or central nervous system function. There may be progressive infiltration of the liver with hepatomegaly, jaundice and liver failure.

Immunological defects are among the most intensely studied complications of the lymphomas. Most patients with progressive lymphoma manifest some immunological disorder during the course of the disease. In 1911, Bunting described the blood picture of Hodgkin’s disease and noted a tendency to lymphopenia with progression of disease. Thus, long before the advent of extensive radiotherapy and chemotherapy, lymphopenia was known to occur in Hodgkin’s disease. Another historic observation was made in 1914 when Moreschi reported that a patient with bacteriologically proven typhoid fever failed to develop specific antibodies; the patient was found to have chronic lymphocytic leukemia. Moreschi subsequently challenged patients with chronic lymphocytic leukemia with typhoid vaccine and discovered that many of them were unable to develop specific antibodies.

When serum protein electrophoresis became available, it was soon apparent that a significant number of patients with chronic lymphocytic leukemia or lymphocytic lymphosarcoma, as well as patients with the other lymphomas, tended to develop hypogammaglobulinemia. Although a few patients had hypogammaglobulinemia at the onset of their illness, the number of individuals with this complication appeared to increase with the duration of the disease. (Fig. 8.) For any one patient followed over a number of years, it was possible to demonstrate that if he had normal immunoglobulin levels to start with, these fell progressively as the disease advanced.

Studies in immunoglobulin (for example, IgG) survival by radioisotopic techniques showed that the life span of the immunoglobulins in patients with hypogammaglobulinemia was prolonged. It thus appeared that the hypogammaglobulinemia was due to a defect in gamma-globulin production. Antibody biosynthesis can be measured precisely by assessing the specific antibody response to an antigenic challenge. For example, in individuals immunized for the first time with tetanus toxoid, there is a predictable response in normal controls; however, in patients with chronic lymphocytic leukemia or lymphocytic lymphosarcoma, as well as other lymphomas, the following situations are seen: a few patients have normal immunoglobulin levels and respond to the tetanus toxoid challenge; many more patients fail to respond to the specific antigenic challenge and among these are the patients with
Fig. 6. Gallium-67 Scan. Left side: anterior body scan; right side: posterior body scan. There is a large mass in the right supraclavicular area. There are periaortic nodes. The spleen is enlarged and appears involved. (Reproduced with permission of Pinsky, et al., Department of Radiology, The University of Chicago.)

Fig. 7. Gallium-67 Scan. Left side: anterior body scan; right side: posterior body scan. There is an anterior mediastinal mass. There is a mass in the left upper quadrant; this is not an enlarged spleen but mass of mesenteric lymph nodes. (Reproduced with permission of Pinsky, et al., Department of Radiology, The University of Chicago.)
hypogammaglobulinemia. A significant number of patients with normal or, in fact, increased immunoglobulin levels also failed to respond. It can be concluded that the immunoglobulin level is only a rough indication of the capacity of the host to respond to antigen stimulation with synthesis of specific antibodies. Hypogammaglobulinemia is the major immunologic complication in patients with lymphosarcoma of the lymphocytic or of the histiocytic type.

In Hodgkin's disease the immunologic defects are considerably more complicated. It is well known that patients with Hodgkin's disease are more prone to develop tuberculosis than the general population. This, however, is not the only infectious disease that occurs with increased frequency. Fungal diseases, unusual bacterial or plasmoidal diseases, and viral disorders, such as herpes zoster, may complicate the course of Hodgkin's disease. It has been known for many years that some patients with Hodgkin's disease are anergic, which, when interpreted in current immunologic terminology, would represent a marked impairment in the mechanism of cellular immunity or delayed hypersensitivity. In 1954 Schier demonstrated that patients in various stages of Hodgkin's disease have a decreased cutaneous response to antigens known to provoke a cellular immune response (for example: mumps, candida, trichophyton and tuberculin). A few years later, it was shown that not all patients with Hodgkin's disease were anergic but that those with active advanced disease were more likely to show this defect. In view of the fact that a negative skin test for a cutaneous allergen may not be due to anergy but may represent failure to have been sensitized previously, Aisenberg and others advocated active sensitization with dinitrochlorobenzene (DNCB) and subsequent testing for delayed hypersensitivity in patients with Hodgkin's disease. It could be demonstrated that in those with inactive disease only 30 percent failed to respond whereas in those with active disease all failed to respond. The National Cancer Institute conducted a study of carefully staged, previously untreated patients with Hodgkin's disease to determine

![Fig. 8. Hypogammaglobulinemia in lymphoma. The figure illustrates the paper electrophoresis pattern obtained in a patient with lymphoma as compared to a normal control. Hypogammaglobulinemia is seen in the patient's pattern. (Reproduced with permission of Dr. E. F. Osserman, Department of Medicine, Delafield Hospital, New York.)](image)
the relationship of anergy to the stage of disease. The study demonstrated that only among the patients with Stage III and IV disease (Rye classification) was there a significant increase in the number of anergic individuals.16,19

Aisenberg as well as Brown, et al. re-emphasized that patients with advanced Hodgkin's disease tended to have lymphopenia.16,19 Lymphopenia occurs in a significant number of untreated patients who have Stage III or IV disease, but in only a few Stage I or II disease. Patients whose initial lymph node biopsy showed lymphocyte depletion tend to have the lowest lymphocyte count in the peripheral blood. The patients with lymphopenia are the ones who are found to be immunologically unresponsive on skin testing; however, a number of patients without lymphopenia may be anergic.

It is important to elucidate why patients with normal lymphocyte levels are anergic or why patients with chronic lymphocytic leukemia or lymphocytic lymphoma have hypogammaglobulinemia. The development of in vitro techniques of studying lymphocyte transformation has made this possible. Peripheral blood lymphocytes from some patients with Hodgkin's disease fail to transform in the presence of phytohemagglutinin (PHA), whereas in normal individuals such transformation occurs readily with 70 percent lymphoblasts in PHA-stimulated cultures. The in vitro lymphocyte response to vaccinia antigen, a common immunogen, is also diminished in patients with Hodgkin's disease when compared to normal controls. The diminished response of in vitro lymphocyte transformation is confined largely to patients with Stage IV disease and only a few of the patients with Stage II and III disease have marked impairment in cellular reactivity. Studies of the relationship between the ability to transform lymphocytes (in response to
PHA) and the response to cutaneous allergen, have produced significant evidence that individuals who do not transform lymphocytes in vitro also tend to be anergic.\textsuperscript{19}

Patients with active widespread Hodgkin's disease tend to have a decreased response to delayed allergens and a decreased ability to be actively sensitized with dinitrochlorobenzene (DNFB). (Table 9.) Lymphopenia and defects in lymphocyte transformation accompany the anergy. Decreased humoral antibody production and a fall in the gamma-globulin level appear only late in the course of the disease, while in the non-Hodgkin's lymphomas the defect is largely one of decreased gamma-globulin production by the lymphocytes in vitro as well as in vivo.

The hypogammaglobulinemia seen in chronic lymphocytic leukemia or lymphocytic lymphosarcoma and the anergy seen in patients with Hodgkin's disease produce an increased incidence of infectious diseases in these patients. Casazza, et al., at the National Cancer Institute, have shown that a significant number of patients with lymphoma either succumb to infectious diseases or have their disease complicated by infectious diseases.\textsuperscript{20} Thirty-five of 51 patients with Hodgkin's disease, 28 of 38 patients with lymphosarcoma and 10 of 16 patients with reticulum cell sarcoma died from or with severe infections.

In addition to defining the immunologic basis for infectious complications in patients with lymphoma, studies of these immunologic abnormalities may also provide a clue to the pathogenesis of Hodgkin's disease and the other lymphomas. Research in our, as well as in other laboratories, is directed toward detection and measurement of tumor-specific immunity in patients with Hodgkin's disease. Dr. John Hopper (University of Chicago) believes that Hodgkin's disease may represent a malignant transformation of thymic-dependent lymphocyte stem cells. His hypothesis is that this malignant process may induce cell-membrane tumor-specific antigens (TSA) which are immunogenic in the host and elicit a cytotoxic humoral (antibody) response.\textsuperscript{21} It is further postulated that these anti-TSA antibodies may crossreact with normal thymic dependent lymphocyte stem cell antigens and thereby gradually deplete the population of normally reactive thymic-dependent lymphocyte stem cells in the host.

**The Therapy of Lymphoma**

**Radiotherapy**

Major advances have been made in the management of patients with Hodgkin's disease. Their success has led to a reexamination of the therapy in patients with the other lymphomas. In view of the fact that the data on Hodgkin's disease have been developed for a longer period of time than for the other lymphomas, results obtained in such studies will be emphasized.

Kaplan and others have shown that megavoltage radiotherapy of Hodgkin's disease produces better survival rates than kilovoltage therapy.\textsuperscript{22-24} In reviewing the radiotherapy literature, Kaplan demonstrated that the recurrence rate is inversely related to the dosage delivered: at 3,600 r tumor dose, the recurrence rate is 10 percent; only at 4,000 r tumor dose or greater is the recurrence less than five percent. From this and similar observations a treatment strategy has evolved in which the radiotherapist delivers a minimum of 4,000 rads over a four-week period to the involved area and more often to the proximal extended field using megavoltage equipment. (Fig. 9.) In asymptomatic patients with Stage I A or II A Hodgkin's disease there is a small, probably not significant, increase in survival time as well as in disease-free interval when the extended field therapy is compared to therapy of involved
field only. In patients who are symptomatic, however, (Stage I B and II B) marked differences are noted; patients treated with the proximal extended field showed a highly significant increase in survival time as well as in disease-free interval.\textsuperscript{24} From these and other data it is currently felt that an aggressive radiotherapy approach is indicated. Recently, Rosenberg and Kaplan have compared the survival of patients with limited field therapy versus total lymphoid field therapy.\textsuperscript{35} Although there is no difference in the two-year lifespan, there appears to be a significant difference in terms of disease-free interval. Moreover, other studies\textsuperscript{25} have shown that patients who have a disease-free interval of two years have a 90 percent probability of five-year survival. We reason from these data that regardless of stage, an aggressive approach may be indicated and that a controlled clinical trial of these various therapeutic approaches is in order. These trials, as well as studies applying these concepts to the other lymphomas, are now in progress.

**CHEMOTHERAPY**

Major advances have also occurred in the chemotherapy of patients with lymphoma. Twenty-five years ago, the only agent available for chemotherapy of lymphoma was the alkylating agent, nitrogen mustard (Mustargen\textsuperscript{5}). Nitrogen mustard is administered intravenously and produces an initial remission rate of 70 to 90 percent. The remissions are brief and 90 percent of the patients relapse within 10 weeks. In the 1950's oral alkylating agents became available and one of these, chlorambucil (Leukeran\textsuperscript{5}) was used not only for the management of patients with chronic lymphocytic leukemia or lymphocytic lymphoma, but also for maintenance therapy of patients with Hodgkin's disease previously treated with nitrogen mustard. A controlled study by Frei and Gamble at the National Cancer Institute showed that of the patients with Hodgkin's disease who were given nitrogen mustard for remission induction and chlorambucil for maintenance, half had remissions that extended to 43 weeks; in contrast, those given nitrogen mustard alone had a remission duration of 10 weeks.\textsuperscript{26} When cyclophosphamide (Cytoxan\textsuperscript{1}) was developed, it was used to both induce and maintain remissions with the same success as the combination of nitrogen mustard and chlorambucil. It must be emphasized that cyclophosphamide has two toxic manifestations not shared by other alkylating agents: a tendency to hemorrhagic cystitis and alopecia.

Until about 12 years ago, the alkylating agents were the only drugs available for the management of lymphoma. With the discovery that derivatives of the Periwinkle plant have antimitotic activity, new avenues for the management of advanced lymphoma were opened. The purified alkaloids, vinblastine sulfate (Velban\textsuperscript{5}) and vincristine (Oncovin\textsuperscript{5}) were developed. Vinblastine is administered intravenously and has found application in the management of Hodgkin's disease. We have made a study of the effect of this agent in patients with advanced Hodg-
kin's disease.\textsuperscript{27-29} An initial intravenous dose of 0.15 mg./kg. is followed at weekly intervals by gradually increasing dose up to 0.25 mg./kg. or until tumor regression or toxicity occur; the patient is then maintained on a weekly or biweekly schedule. In 19 patients with advanced disease who had had previous therapy with radiotherapy, alkylating agents, procarbazine or more than one of these, we were able to induce objective and useful remissions in 13 out of 19 patients, lasting an average of 10.5 months.\textsuperscript{26} Data developed by the National Cancer Institute indicate that in patients not previously treated, vinblastine is superior as the initial agent in inducing remission when compared to cyclophosphamide.\textsuperscript{29} In patients previously treated by radiotherapy or chemotherapy, however, the two agents have equal potential in inducing objective remission.\textsuperscript{29} Vincristine when given alone appears to have less effect in Hodgkin's disease than vinblastine alone. In contrast, vincristine appears to be a useful agent in the management of malignant lymphoma, histiocytic type. The remission induction rate approached 40-50 percent with a remission duration of four months.\textsuperscript{27}

Eight years ago a new type of agent was developed. Its mode of action differs from the alkylating agents, antimetabolites and Periwinkle alkaloids in that it is believed to act by generation on intracellular peroxide. Procarbazine (methylhydrazine; Matulane \textsuperscript{8}) is administered orally in gradually increasing doses to a tolerated dose of 300 mg. per day. This is then continued on a daily basis until toxicity or tumor regression occurs. The average patient requires 9.0 grams and 50 days elapse before an objective remission is achieved. Remission is maintained with low doses of procarbazine. In a series of 14 patients, all of whom had had previous treatment including seven who had Velban, radiotherapy and alkylating agents, we were able to achieve a remission induction rate of 100 percent.\textsuperscript{28} In a larger group of patients studied by us, as well as recorded by others, the remission induction rate is approximately 60 percent.\textsuperscript{30A-30H} The duration of remission averages six months. Comparison of vinblastine with procarbazine suggests that both agents have similar remission induction rates (60 percent) but that vinblastine is superior as a maintenance agent.

With the success of combination chemotherapy in the treatment of patients with acute leukemia, it was obvious that this approach should be tested in the management of patients with lymphoma. Leukemia studies showed that each chemotherapeutic agent has unique toxic manifestations and a combination of agents does not necessarily result in additive toxicity: for example, methotrexate, 6-mercaptopurine, cyclophosphamide and methylhydrazine are marrow depressants; prednisone effects protein, glucose and electrolyte metabolism; and vincristine has toxic effects mainly on the peripheral nerves. The leukemia studies emphasized one other point: individuals who had partial remissions tended to have shorter remissions than those who had complete remissions. Combination chemotherapy was then tried in patients with Hodgkin's disease and lymphoma. Seventy percent of the patients with Hodgkin's disease may have remissions with single agents; complete remissions, however, constitute only about a third of this number and partial remissions are the rule. As soon as one combines two agents, for example, vinblastine and chlorambucil, the complete remission induction rate increases to over 50 percent.\textsuperscript{11} Consequently, DeVita, et al., at the National Cancer Institute, investigated the effect of quadruple chemotherapy (MOPP) on Hodgkin's disease.\textsuperscript{11} The program of six cycles of a 14-day course consisted of nitrogen mustard; vincristine; procarbazine and prednisone; each two-week
cycle of therapy was followed by a two-week period of rest. The results obtained with combination chemotherapy in previously untreated patients with Hodgkin’s disease are superior to single agent therapy. (Table 10.) As expected from the protocol the mean duration of treatment was approximately six months. Six patients responded but did not achieve complete remission; on the other hand, 35 did achieve complete remission. Of these 35 patients, remission was achieved in 17 before three months had elapsed. The median duration of complete remission, from the last day of treatment ranged from 29 to 42 months. None of these patients was on drugs during the period of observation. Eighteen of 35 (51 percent) have relapsed. There were two deaths during treatment. These findings are extremely challenging for they indicated that 80 percent of patients with Stage III and Stage IV Hodgkin’s disease who are not curable by techniques of radiotherapy currently employed, may yet have complete remission and that these remissions persist without drug maintenance for a significant period of time. The patients who fail to respond to this therapy or those who eventually relapse are still able to tolerate traditional chemotherapeutic management.

Encouraged by results obtained with combination chemotherapy in patients with Hodgkin’s disease, investigations have been undertaken to determine the effect of this type of therapy in patients with other lymphomas. The data obtained so far suggest that in previously untreated patients with non-Hodgkin’s lymphoma combination chemotherapy offers remission induction rates superior to single drug therapy. Complete remissions in 40 percent of patients with lymphosarcoma for an average of 7.5 months and in 12 percent of patients with reticulum cell sarcoma for 4.5 months have been reported.

### TABLE 10 – RESPONSE TO (COMBINATION CHEMOTHERAPY) TREATMENT

|                         | 5.8 months | 2 | 6 | 35 (81%) | 3 months | 29-42 months | 18 (51%) | 11 months |
|-------------------------|------------|---|---|----------|----------|--------------|----------|-----------|
| Mean duration of treatment |            |   |   |          |          |              |          |           |
| Deaths during treatment |            |   |   |          |          |              |          |           |
| Responded but failed to achieve a complete remission | | | | | | | |
| Achieved a complete remission | | | | | | | |
| Mean time to complete remission | | | | | | | |
| Median duration of complete remission (from the cessation of all therapy) | | | | | | | |
| Number who have relapsed | | | | | | | |
| Median time to relapse | | | | | | | |

**Summary**

Major advances have occurred in the management of patients with lymphoma. These advances have been largely in the area of more precise staging, delivery of more extensive radiotherapy and the optimal use of chemotherapy. Accurate histologic and clinical staging have permitted precise definition of the clinical status of patients and, consequently, more precise application of therapeutic methods to the individual case. The pathophysiology of the complications of lymphoma is now better understood; advances in immunology, in particular, have permitted comprehension of the pathogenesis of infectious complications in patients with lymphoma. In a significant number of selected patients, aggressive radiotherapy promises cure. Although traditional means of chemotherapeutic management have led to significant advances, more aggressive approaches of combination chemotherapy in Hodgkin’s disease in particular and probably, in the other lymphomas, too, will lead to significant improvement in remission induction rates and in prolongation of survival.
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CHEMOTHERAPY

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