Malignant Lymphoma

Malignant Lymphoma:

NODAL AND EXTRANODAL DISEASES

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Preface

In the past decade, great progress has been made in our knowledge of the natural history and treatment of malignant lymphoma, especially Hodgkin's disease. Supravoltage radiotherapy is curative for patients with local and regional lesions and combination chemotherapy has greatly improved the outlook for those with advanced disease. Under these circumstances, why should two surgeons write a book about malignant lymphoma?

Statistically, malignant lymphoma accounted for less than 5 percent of all the cancers in this country. Histologically, Hodgkin's disease can be classified into four subtypes; and non-Hodgkin's lymphoma, more than six. Each subtype has its own pattern of involvement and natural history. Extranodal malignant lymphoma can present as lesions of a great variety of unusual sites, each with its unique clinical manifestations. Such cases offer special challenges and surgeons are more likely to be consulted.

Since the experiences of most physicians, even those who specialize in oncology, are limited to isolated cases, it is difficult for individual clinicians or even institutions to formulate a rational and standardized approach to specific problems. A good scientific guideline to follow when one does not have the answer is to read and ask others. Therefore, in addition to a detailed review of our own clinical experiences of over 30 years at the Ellis Fischel State Cancer Hospital (EFSCH) in Columbia, Missouri, we have incorporated many of the important papers published in the past 10 to 15 years. Many of the data have not been published before. Current literatures, including findings reported in 1973, are reviewed extensively.

The purposes of this book are to present broad and comprehensive views of malignant lymphoma including Hodgkin's disease and

non-Hodgkin's lymphomas. Conditions affecting both nodal and extranodal tissues are covered. The contributions of radiation therapy and chemotherapy are emphasized. The changing roles of surgery are discussed in their proper perspective. The radiobiological changes in normal tissues that affect surgical evaluation, decisions and techniques are reviewed in detail. The clinical and pathological aspects of malignant lymphomas involving different organs and systems are presented. The pertinent diagnostic and therapeutic approaches are discussed. It is hoped that the information and references will be of value for students of neoplastic disease in all medical and surgical specialties, but the orientation is primarily toward surgeons.

Since case material presented here are taken from the record of Ellis Fischel State Cancer Hospital, the contribution of all the professional staff members and residents who participated in patient care are gratefully acknowledged. Particular appreciation is expressed to Dr. Jose M. Hori who reviewed all the pathological slides and to Dr. Carlos Say who assisted in abstracting the patients' records. The cooperation of the Social Service Department under the direction of Mrs. Miriam G. Hoag and Record Room personnel under the direction of Mrs. Freda Tarr was vital in gathering follow-up information and making all charts readily available. Mr. Robert Hahn, the Cancer Research Center librarian, provided invaluable service in gathering necessary references and in checking the bibliography lists. Mrs. Linda Wilson contributed to the graphic illustrations and photography. The computer programs for life tables were developed by the Biomathematics unit of the Cancer Research Center under Dr. Francis R. Watson. Mr. Richard LeDuc, chief programmer under Dr. Watson, provided valuable consultations. Many of the statistical tables were compiled by Dr. Jean E. Holt. Mrs. Mary Lou Kaltenbach completed proofreading and final editing. Many secretaries, all hereby acknowledged collectively, contributed to the typing.

During the final stage of preparation of this book, one of the authors (Y.N.L.) spent a year of her sabbatical leave at the Division of Oncology, Department of Surgery, University of California at Los Angeles. The kindness of Dr. William P. Longmire and Dr. Donald L. Morton is much appreciated. We are indebted to the editors and publisher of the American Journal of Roentgenology, Radium Therapy and Nuclear Medicine for their permission to reprint many of the figures used in Chapter 1. Finally, Miss Janet Feller and the staff of Grune & Stratton deserve all the credit for making the final product a reality.

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INTRODUCTION

The term "malignant lymphoma" is used in this book to cover essentially only two conditions: Hodgkin's disease and other non-Hodgkin's lymphomas. Non-Hodgkin's lymphomas, as used here, include all the diseases formerly called reticulum cell sarcoma, lymphosarcoma, giant follicular lymphoma, lymphoblastoma, and lymphoma, unspecified. Many of these terms are still in common use. The term lymphosarcoma has often been used in a general sense to cover all of the non-Hodgkin's lymphomas. Other conditions specifically excluded here are the leukemias, histiocytosis, multiple myeloma, mycosis fungoides, myeloid metaplasia, polycythemia, and reticuloendotheliosis.

Table 1-1 gives the relative distribution of Hodgkin's disease and non-Hodgkin's lymphoma as reported in the literature. Hodgkin's disease accounted for about 40 percent of the malignant lymphomas. In the past 10 to 15 years, great progress has been made in the diagnosis and treatment of malignant lymphoma, especially Hodgkin's disease (Table 1-2). The End Result Group of the National Cancer Institute has collected information on approximately 18,000 patients with diagnosed lymphoma from 1940 to 1968. The overall 5-year survival rate for Hodgkin's disease has risen from 23 percent for the period 1940–1949 to about 40 percent for 1964–1968 (Shimkin 1973).

Similar to many other diseases, improvement in clinical management and prognosis came only after the basic pathological characteristics had been well defined and important clinicopathological correlations delineated. The Luke's classification and its modifications recommended at the Rye

Table 1-1
Relative Incidence of Various Subtypes of Malignant Lymphomas

Year	Authors	Patient No.	HD* (%)	LS* (%)	RCS* (%)	GFL* (%)
1942	Gall and Mallory	618	37.0	35.6	20.4	7.0
1947	Jackson and Parker	847	32.6	43.3	19.6	4.6
1947	Hellwig	127	20.5	61.4	16.6	1.5
1956	Hall and Olson	116	56.0	34.4	3.4	6.2
1961	Rosenberg et al	2,600†	51.2	32.0	10.2	6.6
1963	Molander and Pack	883	35.0	30.5	22.5	12.0
1966	Catlin	249	22.0	30.0	48.0	
1968	Peters et al	1,406	35.9	44.9	19.2	
1969	Lennert	218	66.5	17.4	16.1	
1972	EFSCH	527	30.9	39.8	24.7	4.6
	Total	7,591	40.9	36.3	17.6	5.2

*HD = Hodgkin's disease; LS = lymphosarcoma; RCS = reticulum cell sarcoma; GFL = giant follicular lymphoma.

†Estimated from figures given by Rosenberg et al (1961) and Molander and Pack (1963).

Conference have fulfilled this expectation for Hodgkin's disease. For non-Hodgkin's lymphomas, the terminology and descriptions of Rappaport appear to be more useful than the old classifications. Presently in our own hospital and in almost all of the cooperative oncological protocol studies involving multiple medical institutions, all the malignant lymphomas are classified according to these two new systems. Since the names lymphosarcoma and reticulum cell sarcoma are still being used quite frequently in the literature, out of necessity and for convenience, we have quoted them directly without modification in this book.

Pathologically, malignant lymphomas are tumors of the reticular tissues. Clinically, in contrast to histiocytosis and leukemias which are invariably disseminated by the time they are diagnosed, malignant lymphomas often initially affect only one lymph node group or one extranodal site. The diagnosis of malignant lymphoma can only be made by histological examination of tissue biopsies. In addition, there are many unique aspects in the clinical management of these conditions that require, and are benefited by the participation of surgeons.

In the United States for the year of 1972, there were 25,100 new cases of malignant lymphoma, and 19,800 patients died of it (Silverberg and Holleb 1972). But malignant lymphoma as defined here accounted for less than 5 percent of all the cancer cases in this country. Different subtypes of lymphoma have different natural courses, and each mode of presentation may reflect a certain pattern of involvement. And malignant lymphoma of extranodal sites includes widely scattered and heterogenous lesions, each with its unique clinical problems. It is not commonly known that extranodal

Table 1-2
History of Hodgkin's Disease

1832 Hodgkin:	Described 7 cases of lymph node disease (3 cases qualified as Hodgkin's disease today)
1898 Sternberg; 1902 Reed	Characterized the diagnostic multinucleated giant cells; correlated the pathological features with clinical findings
1902 Pusey:	First report of radiotherapeutic management
1917 Yates and Bunting:	Championed surgical removal of localized Hodgkin's disease
1946 Goodman et al:	First successful treatment with nitrogen mustard
1947 Jackson and Parker:	First histological classification: paragranuloma, granuloma, sarcoma
1950 Peters:	Devised three clinical stages according to the number of nodal regions involved (I, II, III), and separated those with or without symptoms
1962 Kaplan:	Gave high-dose prophylactic radiotherapy to all the main lymphatics using "mantle" and "inverted Y" fields; separated stage IV from old stage III for disease involving extranodal tissues
1963 Easson and Russell:	Showed that patients with localized disease could be cured by radiotherapy, because their survival curve paralleled normal population 10 years after diagnosis
1963 Lukes:	Proposed 6 histological classifications
1966 Rye Conference:	Defined 4 clinical stages (I, II, III, IV), each divided into A or B, according to the absence or presence of fever, night sweat, or pruritis; modified Luke's histological types into 4 (lymphocyte predominance, nodular sclerosis, mixed cellularity, lymphocyte depletion)
1969 Glatstein et al:	Reported on the use of laparotomy and splenectomy for more accurate staging
1969 DeVita et al:	Tried combination chemotherapy (MOPP) in the treatment of advance Hodgkin's disease
1971 Ann Arbor Conference:	Proposed changes of Rye's clinical staging system: Combine stage I_2 into Stage II, delete pruritus from substage B, add weight loss as one of the 3 significant symptoms, classify extranodal disease similar to nodal disease

lymphoma is the first recognized site(s) of involvement in nearly half of the patients with non-Hodgkin's lymphoma (Peters et al 1968).

Thus it is difficult for individual clinicians or even institutions to accumulate enough clinical experience to formulate a rational and standardized approach to specific problems. Therefore, in addition to a review of the experience at our own hospital for the past 30 years, we have incorporated all the important reports published in the literature, concentrating on findings of the last 10 to 15 years.

Within each major topic, and whenever possible, the information is

presented in chronological order to provide an historical background. Obviously there are areas of controversy, and no simple hard and fast rules can be given. Whenever pertinent, we present the exact number of patients and the results reported, in order to give the reader a greater appreciation of the "state of the art" so that he may evaluate his own opinions more intelligently.

CLINICAL MANIFESTATIONS

The most common early manifestation of malignant lymphoma of any type is a progressive, usually painless, enlargement of a single superficial lymph node or lymph node group in an otherwise asymptomatic patient. Since no physical finding nor any clinical history is characteristically reliable, biopsy is the only means of establishing a diagnosis. In some instances, especially for non-Hodgkin's lymphoma, the involvement of extranodal sites occurs early in the disease; such sites include the skin, nasopharynx, tonsil, thyroid, lung, breast, gastrointestinal tract, gonad, and bone. Whether the early involvement of any one of these organs indicates that it is a primary site for the tumor or is merely an early clinical manifestation of an already disseminated disease is often difficult to determine (Rappaport 1966). Symptoms and physical signs that are indicative of systemic malignant lymphoma, such as fever, night sweat, weight loss, weakness, anemia, enlargements of the spleen and liver, and generalized enlargement of the lymph nodes, usually appear as the disease progresses, although they may occur as early clinical manifestations of the disease.

In order to better understand the similarities and differences of the clinical courses of Hodgkin's disease and other malignant lymphomas, we have conducted a detailed retrospective and comprehensive review of 527 patients with histologically confirmed diagnosis seen at the Ellis Fischel State Cancer Hospital (EFSCH) from 1940 to 1971. The institution is a referral center and has admitted 40,610 patients during the same period, although about one-third of the patients had nonmalignant diseases. Very few pediatric cases are admitted and about six to eight percent of the new cancer cases in the state of Missouri are seen at this hospital.

There were 163 patients with Hodgkin's disease and 364 with other malignant lymphomas. More than 200 clinicopathological factors were abstracted from patient records, including details of radiotherapy and chemotherapy. Survival data presented are adjusted for age, sex, and decade of admission and are calculated from the time of tissue diagnosis by the life-table method. All patients who had major surgical procedures or required surgical consultation were studied in detail and are discussed under appropriate topics in this book. Whenever applicable, data from this EFSCH series will be used to illustrate the clinical manifestations, pathological variations and fac-

tors important for prognosis (Lee et al 1973). Pertinent and current reports in the literature will be included in the discussion to supplement our data.

Age and Sex

In the EFSCH series, there were 99 males and 64 females with Hodgkin's disease (M : F = 1.5 : 1). The age range was 4 to 81 years (median = 40, mean = 43.3). There were 220 males and 144 females with other lymphomas. The male-to-female sex ratio is also 1.5. The age range was 4 to 88 years (median = 62, mean = 58.5). Figure 1-1 shows the age distributions. In our series, as in others, the non-Hodgkin's lymphomas appeared mainly in older patients.

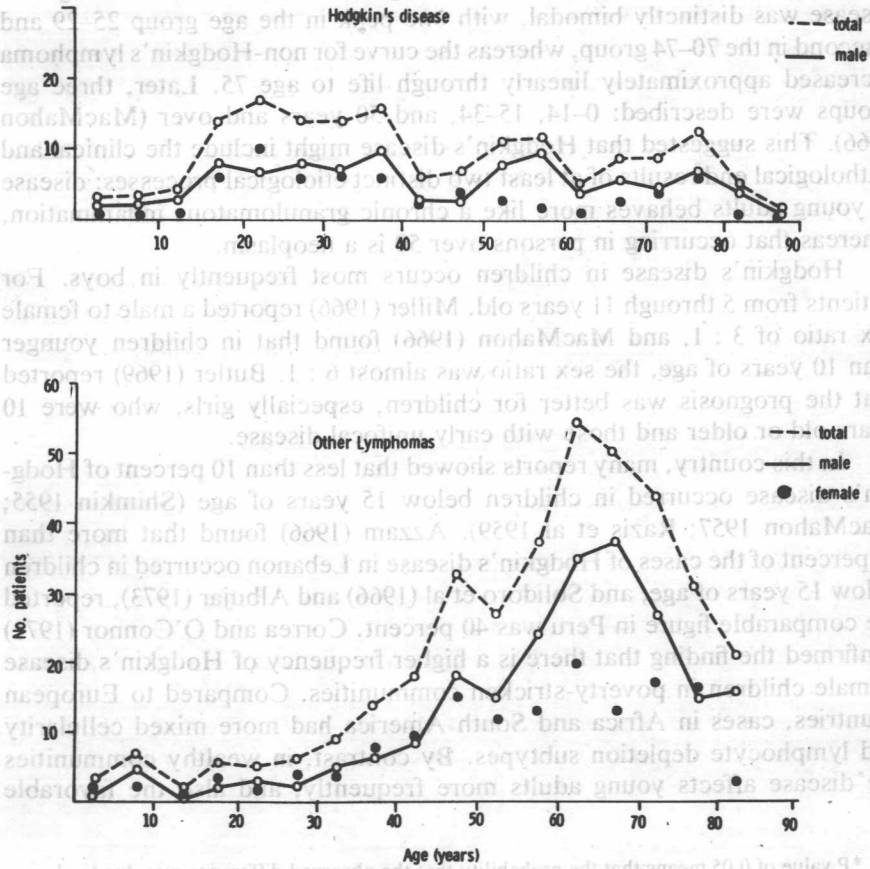

Fig. 1-1. Age and sex distribution of 163 cases of Hodgkin's disease and 364 cases of other lymphomas (EFSCH series).

In the EFSCH series, our overall survival rates were similar for the patients with Hodgkin's disease and those with other lymphomas (adjusted 5-year survival rate = 24 percent, 10-year = 16 percent; Fig. 1-2). Similar to numerous other reports, females had a better survival curve in both groups, but statistically it was not significant ($p > 0.05$).* Patients who belong to the age group of 21 to 40 years had the best survival rate (Fig. 1-3), and the difference was significant ($p < 0.05$). Within each age decade, females fared better than males, especially those who were younger than 40 years old. Within each sex group, the age factor holds equally true. Jelliffe and Thompson (1955) also found that the outlook was best in the third and fourth decades, and this was particularly marked among the female cases. Lampe and Fayos (1968) found a 5-year survival rate of 27.7 percent in males and 41.0 percent in females. Within each stage, the 5-year survival was found to decrease with increasing age.

MacMahon (1957) found that the age-incidence curve of Hodgkin's disease was distinctly bimodal, with one peak in the age group 25–29 and a second in the 70–74 group, whereas the curve for non-Hodgkin's lymphoma increased approximately linearly through life to age 75. Later, three age groups were described: 0–14, 15–34, and 50 years and over (MacMahon 1966). This suggested that Hodgkin's disease might include the clinical and pathological end results of at least two distinct etiological processes: disease in young adults behaves more like a chronic granulomatous inflammation, whereas that occurring in persons over 50 is a neoplasm.

Hodgkin's disease in children occurs most frequently in boys. For patients from 5 through 11 years old, Miller (1966) reported a male to female sex ratio of 3 : 1, and MacMahon (1966) found that in children younger than 10 years of age, the sex ratio was almost 6 : 1. Butler (1969) reported that the prognosis was better for children, especially girls, who were 10 years old or older and those with early unifocal disease.

In this country, many reports showed that less than 10 percent of Hodgkin's disease occurred in children below 15 years of age (Shimkin 1955; MacMahon 1957; Razis et al 1959). Azzam (1966) found that more than 20 percent of the cases of Hodgkin's disease in Lebanon occurred in children below 15 years of age, and Solidoro et al (1966) and Albujar (1973), reported the comparable figure in Peru was 40 percent. Correa and O'Connor (1971) confirmed the finding that there is a higher frequency of Hodgkin's disease in male children in poverty-stricken communities. Compared to European countries, cases in Africa and South America had more mixed cellularity and lymphocyte depletion subtypes. By contrast, in wealthy communities the disease affects young adults more frequently, and also the favorable

*P value of 0.05 means that the probability that the observed difference was due to change alone was one in 20. Conventionally when p value is less than 0.05, the difference seen are considered as statistically significant.

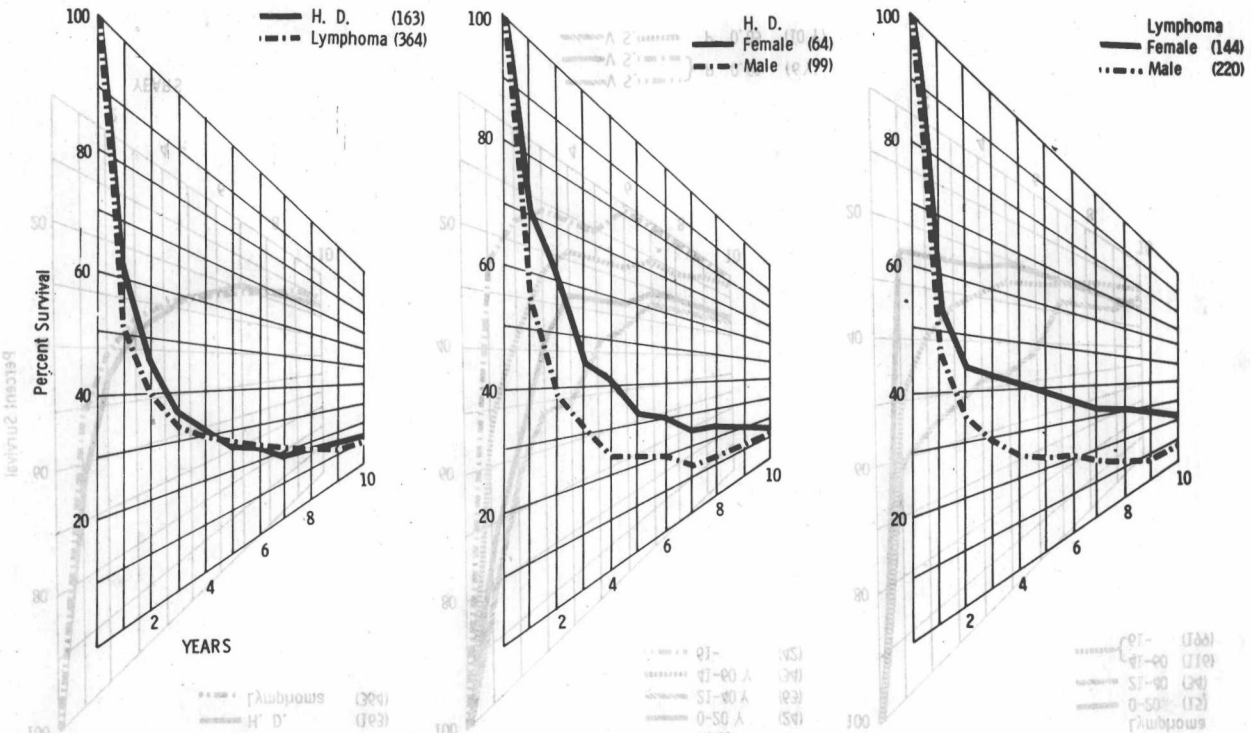

Fig. 1-2. Survival curves according to diagnosis and sex (EFSCH series).

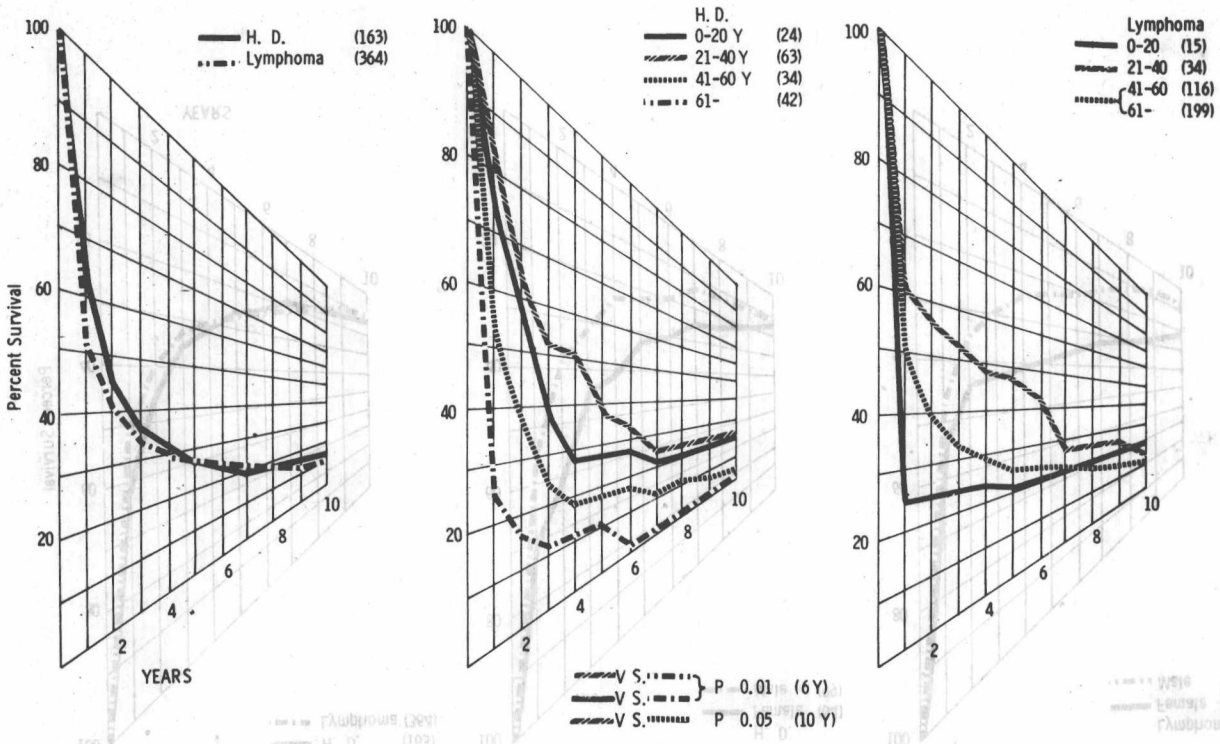

Fig. 1-3. Survival curves according to diagnosis and age (EFSCH series).

form of nodular sclerosis predominates. MacMahon (1971) has summarized many distinct clinical and pathological differences among patients of different age groups with Hodgkin's disease.

In the United States, most of the patients with Hodgkin's disease come from the higher economic groups. And high mortality ratios in the upper social classes are characteristics of the lymphomas as a group, except multiple myeloma which is more common in nonwhites. However, "it remains to be seen, which of the several closely related variables—socioeconomic status, duration of education, intelligence, and occupational class—is most closely related to Hodgkin's disease's risk" (MacMahon 1966).

Many epidemiological aspects of Hodgkin's disease are interesting, but have not shed any light regarding its etiology (Cole 1972, Kaplan 1972, Lee 1973). Vianna et al (1972) reported an unusual cluster of cases of malignant lymphoma in a group of high school students, their relatives, and friends. There were 34 interlinked cases, 31 of Hodgkin's disease and 3 of other lymphomas, diagnosed from 1948 to 1971. Their findings suggest that Hodgkin's disease could be similar to an infectious condition, transmitted either from patient to patient or through some healthy carrier, with a long incubation period. Heath (1972) commented that many other epidemiological studies did not show very strong nor consistent evidence of such spread.

Clinical Staging

Studies on large series of patients with malignant lymphoma have shown that the important prognostic factors included age, sex, presence or absence of symptoms, histological types and clinical stages. However, Keller et al (1968) found that age and sex contributed little additional prognostic information beyond that determined by histological type and clinical stages, and Patchefsky et al (1973) showed that age, sex, and systemic symptoms were weaker prognostic variables. Thus, in talking about the natural course of patients with malignant lymphomas, we will concentrate on these two latter distinct but interrelated factors.

Clinical staging of malignant disease, in general, reflects the extent of involvement based on physical findings supplemented by standard diagnostic procedures. Progressively more advanced stages have progressively shorter median survivals. The objectives of clinical staging as stated by the International Union Against Cancer (1966) included: (1) aiding the clinician in planning treatment; (2) aiding the clinician in estimating the prognosis; (3) assisting in the evaluation of the results of treatment; (4) facilitating the exchange of information between treatment centers; and (5) assisting in the continuing investigation of human cancer.

As early as 1920, Longcope and McAlpin described seven clinical subtypes of Hodgkin's disease: (1) localized, (2) mediastinal, (3) generalized, (4) acute, (5) concealed, (6) splenomegalic, and (7) osteoperiosteal. Later

Craver (1948) used three subtypes: localized, regional, and generalized. Peters (1950) devised three stages (I, II, III) according to the number of nodal regions involved and further subdivided the stages according to those patients with and without systemic symptoms. Kaplan (1962) added a stage IV, separate from the previous stage III, to include patients who had visceral disease such as lesions of the bone marrow, bone, lungs, skin, subcutaneous area, gastrointestinal tract, or kidney.

In the 1965 Rye Conference, the Committee on Staging of Hodgkin's Disease recommended a clinical staging system which found wide acceptance (Rosenberg 1966). The criterion for involvement of the spleen was either palpable enlargement or abnormal radioisotopic scan. Liver involvement was defined as hepatomegaly and elevated alkaline phosphatase, or two abnormal liver function tests, or an abnormal liver scan and one abnormal liver function test.

Subsequently, several drawbacks of the Rye Classification were found, especially regarding the group with stage IV diseases. Excluding patients with lesions of the liver, lung, and bone marrow, Peters et al (1968) showed that patients with localized extranodal presentations fared as well as the patients whose diseases were limited to the nodal presentations. Musshoff et al (1970) suggested that survival rates of patients with organ involvement from local invasion from a node, especially those of lung, pleura, bone, and soft tissues were much better than those with visceral lesions secondary to generalized disease. Rosenberg and Kaplan (1970) also found that many localized extralymphatic foci were amenable to treatment with tumoricidal doses of radiotherapy. Thus, a new staging system applicable to extralymphatic and non-Hodgkin's lymphoma was proposed and recommended for use by the 1971 Ann Arbor Conference (Carbone et al 1971).

Table 1-3 summarizes these clinical staging systems. In order to have meaningful staging designations, the methods used to define the extent of the disease need to be standardized. The staging procedures recommended by the Committee on Hodgkin's Disease Staging Procedure are listed in Table 1-4 (Rosenberg et al 1971). They are divided into four groups: required procedures for all untreated patients; those procedures necessary under certain conditions; useful auxiliary procedures; and those promising experimental procedures to be done at selected centers. Although these procedures are recommended for the staging of Hodgkin's disease only, many of them have also been found useful in cases of non-Hodgkin's lymphomas. Details and pertinent discussions of many of the tests and procedures are given elsewhere in this book.

In the EFSCH study of 527 patients with histologically proven Hodgkin's disease and other lymphomas, we have used the Rye staging system, with the exception that hepatomegaly and splenomegaly as such were considered as involvement of the liver and spleen, respectively. The modern techniques of lymphangiogram and staging laparotomy were used rarely in the EFSCH series. The basic work-up consisted of complete blood counts,

Table 1-3
Clinical Staging of Malignant Lymphoma

A. Rye Conference (1966)
   1. 4 stages:
      Stage I. Disease limited to one anatomic region (Stage I_1) or two contiguous anatomic regions (stage I_2) on the same side of the diaphragm.
      Stage II. Disease in more than 2 anatomic regions or in 2 noncontiguous regions on the same side of the diaphragm.
      Stage III. Disease on both sides of the diaphragm but not extending beyond the involvement of lymph nodes, spleen, and/or Waldeyer's ring.
      Stage IV. Involvement of the bone marrow, lung parenchyma, pleura, liver, bone, skin, kidneys, gastrointestinal tract, or any tissue or organ in addition to lymph nodes, spleen, or Waldeyer's ring.
   2. All stages are subclassified as A or B to indicate absence or presence of the following systemic symptoms: fever; night sweats; pruritus.
   3. Anatomically, the lymphoid regions are defined as follows:
      Above diaphragm: Waldeyer's ring; neck; mediastinal or hilar; infraclavicular; axillary and pectoral; epitrochlear and brachial.
      Below diaphragm: Spleen; para-aortic; mesentery; iliac; inguinal and femoral; popliteal.

B. EFSCH Study (1940–1971)
   Same as above, except hepatomegaly or splenomegaly were considered involvement of liver and spleen, respectively.

C. Ann Arbor Conference (1971)
   1. Clinical stages same as those proposed at Rye Conference except:
      Delete symptom of pruritis from subclass B; replace with "unexplained weight loss of more than 10% of body weight in the 6 months prior to admission."
      Combining previous stage I_2 into stage II.
      Add appendix and Peyer's patches to the list of lymphoid tissues.
      Staging lesions originated from extralymphatic organ or site in the same way as lesions of lymphoid tissue, but add subscript E, e.g., stage III_E = localized lesion of extralymphatic site and involvement of lymph node regions on both sides of diaphragm.
   2. Add pathological stages to incorporate the results of histopathological findings of tissues biopsied at staging laparotomy or other procedures. Abbreviations used:
      D = skin
      H = liver
      L = lung
      M = marrow
      N = abdominal node
      O = bone
      P = pleura
      S = spleen

urinalysis, blood typing, chest x-ray, and electrocardiogram. As listed in Table 1-5, lymphangiogram and radioisotope liver scans were used in less than 10 percent of the patients. Thirty to 50 percent of the patients had gastrointestinal x-rays and about 70 percent had intravenous pyelograms. Bone marrow biopsy—the majority done by needle aspiration—was obtained for approximately 50 percent of the patients.