# MALIGNANT LYMPHOMA *

## A Clinico-Pathologic Survey of 618 Cases

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Many generic terms have been utilized to designate those maladies of the lymphatic system which are characterized clinically by progressive tumor-like enlargement of lymphoid tissue with eventual fatality, and histologically by multiplication of one or more of the elements normally present in lymph nodes to the point of destruction of the nodal architecture. Of these, "malignant lymphoma" seems to have won most general usage in this country, at least, and has the advantage of being noncommittal as to pathogenesis.

Numerous attempts to subdivide this group of diseases have been complicated by an extraordinary confusion of terminology and controversial theses. In recognition of the complexity of the problem, The American Association of Pathologists and Bacteriologists established a "Registry of Lymphatic Tumors." Although no official classification has been promulgated, the publication in 1934 [1] by the registrar at that time, George R. Callender, of a review of the Registry material tacitly set the seal of the Registry's approval upon the schematization and terminology employed. This represented in fact an attempted fusion of three classifications: (1) cytologic, based upon morphologic recognition of component proliferating cells; (2) gross anatomical, depending upon the distribution of the process throughout the organs of the body; and (3) clinical, contingent upon physical signs and hematologic manifestations. In the intervening years no revision or amplification has appeared.

In the face of such authority it is with no little hesitation that we have the temerity to offer a somewhat different classification. An honest attempt over a period of years to apply the Registry terminology to our material has convinced the staff of this laboratory that it is in many respects impractical for routine use. Any considerable experience with malignant lymphoma makes it apparent that there is no necessary correlation between cytology and distribution. Any type of cell may be associated with a localized process, with a generalized disease involving multiple organs without blood manifestations, and, in all probability, with the presence of significant numbers of the type cell in the circulating blood—leukemia, in fact. It must be conceded, however, that

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many authorities will fail to recognize such relations in some of the subtypes, notably Hodgkin's disease, though Warthin [2] has recorded well documented instances. Nothing in the histologic character of an individual lesion will permit a reliable forecast as to the distribution of the process in other parts of the body. Moreover, determination of the extent and character of organ involvement is beyond the scope of ordinary clinical examination in many instances and must frequently await postmortem study, thus establishing a significant limitation, to say the least, to its clinical utility. Furthermore, another fallacy is introduced by dependence upon the results of necropsy. This shows only a single stage of the process, ordinarily, it is true, the terminal one, but not necessarily, since mechanical and surgical accidents or infection may have contributed to a lethal outcome at a comparatively early period in the evolution of the disease. More specifically, in regard to invasion of the blood stream, no constant histologic substrate permits one to predict whether or not the blood picture will prove "leukemic." Though diffuse bone-marrow involvement will be found in the great majority of leukemic patients, the marrow may be normal.[3,4] Conversely, diffuse marrow change is not infrequently found with normal blood pictures.[5,6] Still less reliable are the "leukemic" types of organ infiltration without tissue destruction such as are commonly seen in the liver, spleen and kidneys. They are frequently absent in leukemia and may be seen in typical form without leukemia. Moreover, continued observation of patients over a period of years shows significant variation in the blood picture, leukemic pictures alternating with non-leukemic ones, often quite irrespective of roentgen therapy. This feature will be dealt with in more detail in the body of this publication. Classification based upon distribution has therefore only a limited value; temporally limited because it is valid only for a given stage of the disease and must be altered from time to time in the same individual; practically limited in many instances by the impossibility of accurately determining distribution during life.

The alternative form of classification, cytologic, depends for its validity and applicability upon: (1) the constancy over months and years of observation of the reacting cell types, and (2) the possibility of histologic distinction in routine biopsy material. The first point, which is fundamental, will be made a subject for further analysis later in this paper. It is sufficient to state at this point that great constancy does in fact prevail and though variations occur they are practically limited to degree of differentiation without significant shifts between one major group and another. In respect to the second point, the applicability to routine biopsies, distinction between the well differen-

tiated lesions is simple; with less differentiation it becomes somewhat more difficult but is still feasible, and in a small number (6 per cent) of poorly differentiated lesions it becomes exceedingly difficult.

To those who may share our beliefs and regard all members of this group of diseases as neoplastic entities, the proposed classification has the advantage of conformity with the accepted usages of oncology. Classification of neoplastic disease is fundamentally cytologic, resting primarily on identification of the type cell with secondary qualification dependent on degree of differentiation rather than upon the distribution of metastasis. If such classification has more than academic value in the field of malignant lymphoma, it should show a reasonable degree of correlation with the clinical course of the disease. Such correlation is, we believe, demonstrated in Part II of this study.

The material included in this survey consists of all examples of malignant lymphoma passing through the Pathology Laboratory of the Massachusetts General Hospital in the 20-year period from January, 1917, to December, 1936, from which satisfactory histologic sections were available for personal study. This comprised 135 autopsies and 580 biopsies obtained from a total number of 618 patients. The results of a histologic survey constitute the first part of this paper. Clinical data from 545 of these have been analyzed and form the basis for Part II (Text-Fig. 1).

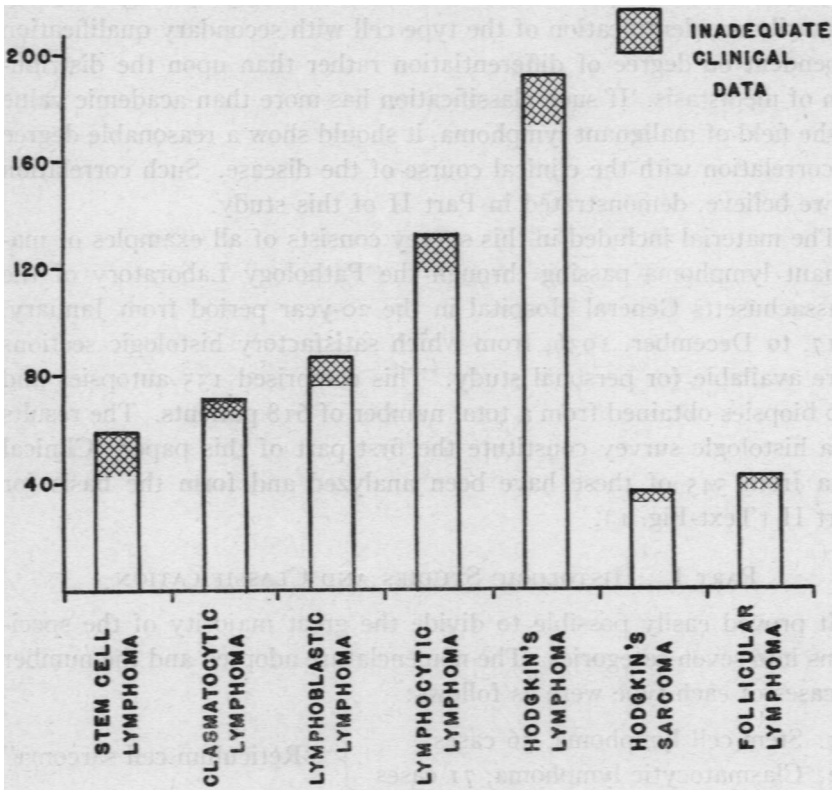
## Part I. Histologic Studies and Classification

It proved easily possible to divide the great majority of the specimens into seven categories. The nomenclature adopted and the number of cases of each type were as follows:

1. Stem cell lymphoma, 56 cases } "Reticulum cell sarcoma"
2. Clasmatocytic lymphoma, 71 cases }
3. Lymphoblastic lymphoma, 85 cases
4. Lymphocytic lymphoma, 135 cases
5. Hodgkin's lymphoma, 193 cases
6. Hodgkin's sarcoma, 36 cases
7. Follicular lymphoma, 42 cases

A distinct division can be made between the first four types and the last three. The histologic pattern of the former is comparatively simple whereas that of the latter is relatively complex. Except in the cytologic peculiarities of the type cell the general structure of members of the first four categories is so similar that many features can best be described commonly for the entire group. Common to all is the tendency of proliferating cells to encroach upon, obscure and finally replace the

normal nodal architecture, reconstructing the stromal framework more or less completely in the process. Tendencies to invade marginal and medullary sinuses, to migrate through the capsules and invade perinodal tissues are representative of all four and are found irrespective of the degree of localization or generalization of the disease. In nodes showing an early stage of involvement it is frequently possible to ob-




TEXT-FIGURE 1. Frequency of the subgroups by number of cases.

serve invading strands of tumor cells projecting from an established focus into the residual normal tissue of the node. Under such conditions the reticulum fibrils of the original tissue appear to be pushed aside rather than disrupted by the invading cells, resulting in a stromal condensation which occasionally simulates encapsulation. This, however, is but a transient phase and eventually, with complete invasion, all evidence of this condensed reticulum disappears and a delicate fibrillar network completely replaces the preëxisting stroma (Fig. 20).

A problem in histologic interpretation common to all members of the lymphoma group is the significance of mature lymphocytes and clasmatocytes frequently scattered in considerable numbers throughout the

tissue. Three possibilities for their origin must be considered: (1) they are persistent elements of the original nodal tissue; (2) they represent evidences of successful, complete differentiation of tumor cells, and (3) they constitute components of an exudative reaction to the products of disintegrating tumor cells. It is probable that each of these possibilities is, on occasion, an actuality and all efforts at interpretation must be guarded.

A problem offering equal difficulty is the correct interpretation of multinucleated cells in these tumors. On the one hand is the knowledge that multinucleated "tumor giant cells" may occur in almost all types of malignant, and in a few benign, neoplasms. On the other hand is their peculiar frequency in Hodgkin's disease. We have felt that occasional multinucleated cells do not necessarily predicate a classification as Hodgkin's disease.

Cytologically, two broad lines of division in malignant lymphoma have long been recognized: Hodgkin's disease with its complicated structure, described independently by Sternberg [7] and by Reed;[8] and the simpler proliferative conditions of the lymphocytic series of cells variously termed, according to their distribution, lymphatic leukemia, aleukemic leukemia and lymphosarcoma. More recently, Roulet [9,10] has added a third type, named by him "Retothelsarkom" and generally entitled in this country, reticulum cell sarcoma. The justification of such further subdivision was immediately attested by the prompt and wide acceptance of the term throughout the world. Whether or not this last group represents a single entity may, however, legitimately be doubted in view of the wide discrepancies in the descriptions and theories of its origin which various authors have offered. A complete bibliography would be profitless, but let us examine a few examples. Ewing [11] implied that reticulum cell or large round cell sarcoma is a tumor composed of cells less mature than the lymphocyte derived from the germinal centers or pulp cords. Klemperer [12] stated that the reticulum cell is totipotential and similar to cells observed in the embryonic mesenchyme. Medlar [13] used the expressions reticulum cell and stem cell interchangeably. Rhoads [14] derived the tumor from elements of the phagocytic cell series, a view followed by Parker and Jackson.[15] The latter authors clearly distinguished reticulum cell sarcoma from the malignant type of Hodgkin's disease, but Callender [1] stated that reticulum cell sarcoma is Hodgkin's sarcoma. Roulet, himself, included under the heading of Retothelsarkom a group of lesions with a morphologic range which, judging from his descriptions and his illustrations, extends almost from one extreme to the other of the malignant lymphomas.

It is apparent that various authorities regard the type cell of this

tumor (1) as an immature cell of the lymphocyte series, (2) as a pluripotential cell of variously assumed potentialities of development including the formation of lymphocytes, phagocytes and of reticulum and collagen, and (3) as a relatively well differentiated cell of the monocyte or clasmatocyte series. When such variation of opinion exists it seems probable that the individual authors cited cannot be describing the same tumor; that, in fact, reticulum cell sarcoma, as the term is at present used, represents not an entity but a blanket-term covering all primary tumors of lymph nodes not otherwise classifiable. Our own observations lead us to believe that so-called reticulum cell sarcoma must be divided into two types: (1) tumors composed of relatively well differentiated wandering cells with phagocytic propensities resembling monocytes or clasmatocytes, and (2) tumors made up of highly undifferentiated, presumably pluripotential cells which we have chosen to call stem cells. The justification of such a step will, we hope, be made apparent in the descriptive sections to follow. For those who hesitate to accept such identification, this "stem cell" group may simply be regarded as consisting of those tumors of the lymphocytic series too undifferentiated to classify. With this single exception our classification does not deviate from generally accepted cytologic lines.

### 1. *Stem Cell Lymphoma*

There is general agreement concerning the existence in lymph nodes of an undifferentiated cell of mesodermal origin which, as a result of unknown stimuli, develops the ability to differentiate into various forms of blood cells.[16-19] A structurally indistinguishable cell is to be found throughout the remainder of the hematopoietic system. The extent of its pluripotentiality in lymph nodes and elsewhere is still unsettled and cannot be discussed in this paper. Such cells have variously been termed lymphoidocyte,[20] primitive blood cell,[21,27] hemohistioblast,[22] hemocytoblast,[23] reticular [24,25] and reticulum cell [12,13,26] and common lymphoid stem cell.[27] The last term seems to us simplest and most appropriate and will be used throughout the article.

The lymphoid stem cell is a large cell, 15 to 35 $\mu$ in diameter, with variably abundant, pale-staining, amphophilic cytoplasm possessing a poorly defined, often imperceptible outline. When closely packed, as in the center of a hyperplastic follicle, the cells may appear fused as if constituting a syncytium. Where the cells are more discrete, intercellular bridges are sometimes noted. The nucleus is large, two to four times that of a normal lymphocyte, is usually round and its border is thin but distinct. Chromatin is extremely delicate, irregularly distributed and generally lacks points of condensation. There is, however,

usually a single prominent vesicular nucleolus. We have been able to observe no unequivocal evidence of reticulum formation by these cells under either normal or neoplastic conditions.

Cells of this type, or at any rate cells morphologically indistinguishable from them, are found in small numbers in all tumors of the lymphoma group, just as they are present in normal lymphoid tissue. In the majority of lymphomas, however, they are so rare as to escape notice unless specifically searched for. In a limited group they constitute the predominant element and it is for this group that we have proposed the name "stem cell lymphoma."

Tumors of this type occur in two forms clearly described by Ehrlich and Gerber [24] under the heading of reticular and intermediary types of lymphosarcoma. In one the neoplasm appears to consist of homogeneous syncytial sheets (Fig. 1) and in the other of discrete cells (Fig. 2). In general, however, the fundamental similarity is so great and the two forms of growth appear simultaneously with sufficient frequency to warrant combining them as a single histologic unit. In the discrete cell type (Fig. 4) the individual cells conform closely to the description given for the stem cell of the normal lymph node, tending, however, to be larger and in a given lesion to be very uniform in size. One variation is the usual presence of a single, large, densely basophilic nucleolus. The cytoplasm is homogeneous, poorly outlined and occasionally, but rarely, exhibits particulate phagocytosis. The syncytial type which occurs much less frequently exhibits exactly similar cytologic characteristics but lacks almost entirely the separation of one cell from another (Figs. 1 and 3).

Moderate numbers of lymphocytes and monocytes are noted in some of the tumors, very few in others, particularly those of the syncytial type. Fibrosis is observed in a few of the cases but is an unusual occurrence. Reticulum is comparatively sparse and its distribution is irregular in all the tumors of this group, particularly in those of the syncytial type.

### 2. *Clasmatocytic Lymphoma*

In contrast to the preceding group, with which, in our estimation, it has been widely confused, the cells in these tumors simulate more or less closely normal clasmatocytes or monocytes. Distinction between the last named types of cells has been somewhat overemphasized.[28-30] We are in agreement with the belief [31,32] that they are closely related and often indistinguishable from each other. They tend to be smaller than the stem cells of the preceding group but are distinctly larger than lymphocytes, varying from 14 to 22 $\mu$ in diameter. The cytoplasm is abundant, generally eosinophilic, and its borders, though distinct, tend

to be irregular in outline, suggesting ameboid propensities (Fig. 5). Phagocytic qualities are marked and, though usually limited to particles, engulfment of whole cells occurs. Nuclei are frequently eccentric in position; a few are round, more are oval and still others are reniform or even horseshoe shaped (Fig. 6). Chromatin forms a moderately fine network and nucleoli are rarely evident. The rate of growth and degree of differentiation varies over considerable limits, but in most tumors sufficient numbers of apparently mature monocytic or clasmatocytic elements are present to aid materially in identification.

In the less differentiated examples the distinction from stem cell lymphoma is difficult and in some neoplasms, which by all other criteria appear to belong in this group, the presence of multinucleated cells makes confusion with Hodgkin's sarcoma possible. Small numbers of lymphocytes are occasionally found sparsely and irregularly sprinkled, presumably evidence of exudative reaction. Reconstruction of reticulum is relatively scanty. Scattered fibrils without regular network are observed in most lesions. There is little evidence to support the contention that fibrils arise from the tumor cells.[1,9,33] A few of the specimens exhibit a coarse latticework of collagen but none is actually scirrhous in appearance.

### 3. *Lymphoblastic Lymphoma*

The predominant cell in these lesions is a lymphoblast. It is a spherical cell which, however, frequently exhibits irregularity of outline with pseudopod-like protuberances. It is larger than a mature lymphocyte, varying ordinarily within the range of 10 to 20 $\mu$ in diameter, and possesses a relatively uniform, narrow, basophilic rim of cytoplasm (Figs. 7 and 8). The nucleus is likewise larger than that of the lymphocyte, is centrally placed, round or slightly indented. The nuclear border is sharp, the chromatin rather evenly distributed and much less clumped than in the mature elements, giving the nucleus as a whole a vesicular appearance. Nucleoli are infrequently observed. As would be expected in a relatively undifferentiated tumor, mitotic figures are usually numerous.

Though the lymphoblast is always the predominant cell in specimens included in this group, stem cells are present in moderate numbers and in some cases considerable numbers of lymphocytes can be found. The nodal architecture is characteristically obscured. Many specimens exhibit a homogeneous appearance as the result of the uniformity of component cells and the even distribution of the reticulum framework. The majority, however, are somewhat irregular in appearance because of incomplete stromal revision.

### 4. *Lymphocytic Lymphoma*

The predominating cell in this lesion is indistinguishable from a normal lymphocyte (Fig. 10). Stem cells and lymphoblasts are present in small numbers scattered indiscriminately, but usually are too infrequent to cause diagnostic difficulties. Mitotic figures are sparse and no multinucleated cells appear. Nodal architecture, including sinus and follicle structure, is characteristically obscured by the relatively uniform infiltration of small lymphocytes (Fig. 9). As in the preceding group, however, stromal revision is frequently incomplete and some irregularity remains as the result of persisting portions of uninvolved nodal tissue or of small focal collections of less mature cells. The nodal capsule is usually intact but invasion may occur. Extension into perinodal tissues simulates closely the appearance of the original nodal lesion.

*Leukemia.* Upon completion of both the clinical and histologic studies an attempt was made to predict the presence or absence of clinical leukemia on the basis of the nodal morphology in both this group and the lymphoblastic lymphomas. No criterion for distinction held. Nodes with apparent blood-vessel invasion were obtained from patients without leukemia, and many with pericapsular invasion or large invasive tumors simulating Kundrat's lymphosarcoma[34] were accompanied by leukemia. It was necessarily concluded that it is impossible to distinguish the leukemic from the non-leukemic lesion by means of lymph node morphology.

### 5. *Hodgkin's Lymphoma*

Hodgkin's disease (the eponymic terminology is still more widely accepted than any of the suggested synonyms such as malignant lymphadenoma or lymphogranuloma) constitutes the commonest and most readily recognizable lesion among the malignant lymphomas. Its range of clinical and histologic variation is so great that subdivision appears necessary and the two terms, Hodgkin's lymphoma and Hodgkin's sarcoma, have been employed to designate the two divisions which we have recognized. Of the utility of a third subdivision, Hodgkin's granuloma,[35,36] we are still unconvinced. In contrast to the preceding groups, in each of which proliferation of a single type of cell completely dominates the picture, Hodgkin's lymphoma is essentially polycellular (Fig. 11). The majority of the constituents; *i.e.*, granulocytes (usually eosinophilic but frequently neutrophilic), lymphocytes, plasma cells, clasmatocytes and fibroblasts, are the usual components of various inflammatory reactions. Other elements, however, the only elements, moreover, which can be regarded as pathognomonic and whose pres-

ence is universally admitted essential for diagnosis of the lesion, are not found in any inflammatory process of established etiology. They consist of stem cells, frequently indistinguishable from those of "stem cell lymphoma," which tend strongly to develop large multilobed or multinucleated forms (Fig. 12). It is important from the diagnostic point of view, moreover, to recall that both Sternberg [7] and Reed [8] noted mononucleated as well as multinucleated "giant cells" in this disease. Although their names are commonly applied to the multinucleated forms, cells with single or mirror-image double nuclei are equally characteristic of the process.

The specific cells are quite variable in size, ranging from 10 to 40 $\mu$, or more, in diameter. The cytoplasm is abundant and its staining reactions, though usually intense, are variable, ranging from acidophilia to basophilia in different cases, though relatively constant in the same case. Single nuclei are large and round, oval, or slightly indented; they are vesicular in appearance and contain chromatin without characteristic distribution. Within the majority, single nucleoli are found which differ from those noted in the stem cell tumor in that they are not densely stained but are actually vesicular in appearance.

In the multinucleated forms the nuclear masses may show narrow connecting bridges or may be entirely discrete. In either case large nucleoli are usually evident in each nuclear mass and the nuclear masses are characteristically dissimilar in size and shape. Even where each of the many nuclei is discrete they tend to overlap and remain clustered in the center of the cell. Unipolar mitotic figures are easily found and multipolar mitoses are not unusual. Mitotic activity is unusual, however, in any of the other cells composing the lesion.

A great variety of other elements are always to be observed in varying frequency and abundance. Although general trends are apparent, no constant chronologic sequence can be made out for the appearance of each type of cell. It is necessary to remember that the disease does not run a simultaneously parallel course in each node of a given patient. Early lesions may be evident in one region while the process is advanced in another area. The approximate age of an individual lesion may be roughly estimated from the histologic appearance but not the duration of the disease in the patient.

Lymphocytes are always present. They are most abundant in the early stages and their relative numbers diminish later with progression of fibrosis or with dedifferentiation of the lesion. Plasma cells are frequently encountered although they are more evident in advanced stages. In no other lymphoma subgroup do they appear with an equal degree of frequency.

Granulocytes, both eosinophilic and neutrophilic, are usually but not invariably present. They bear no constant relation to the occurrence of necrosis. Eosinophils are more common and in some cases constitute the predominant cell. Monocytes and clasmatocytes are present in variable numbers. Hodgkin's lymphoma exhibits more tendency to focal necrosis than the other types of lymphoma and in lesions showing this phenomenon phagocytes are quite numerous. In a few cases, however, in the absence of evident necrosis, phagocytic cells were so abundant that distinction from clasmatocytic lymphoma was difficult.

Collagen production is roughly proportionate to the duration of the lesion and is comparatively scanty in the early phases. This stage, however, is transient; and wavy, non-argentophilic, interlacing strands soon appear, progressing steadily by fusion of the strands until broad fibrous septa separate the foci of cellularity into islands in the scirrhous tumor (Fig. 13). Still later, if the disease is sufficiently prolonged, the entire node becomes replaced with dense fibrous tissue. Nodes of this type are found as frequently in areas not subjected to roentgen therapy as they are in regions so treated. Such a lesion is not then necessarily significant of the effect of irradiation.

### 6. *Hodgkin's Sarcoma*

It has been stated that Hodgkin's lymphoma may, after following a comparatively benign, prolonged course, undergo both clinical and histologic transformation into a rapidly progressive, highly malignant tumor.[35,37,38] Only a few cases in this series have exhibited histologic metamorphosis of this type (Table I), although many clinical histories have suggested that such a change has taken place. Most of the cases of Hodgkin's sarcoma have shown the characteristic morphology of this type at the outset.

Hodgkin's sarcoma retains the fundamental background of Hodgkin's lymphoma, the basic cell being the tumor stem cell or Sternberg-Reed cell. The peculiar difference is the marked preponderance of these cells over all other elements comprising the tumor (Fig. 14). Characteristically, the lesion consists of large numbers of these cells without syncytial relations, exhibiting marked variability in size and nuclear configuration (Fig. 15). Multinucleated cells predominate and mitotic figures are very numerous. Lymphocytes, plasma cells and eosinophils, though present, are minimal in numbers and fibrosis rarely proceeds beyond the early background of strandlike collagen. Densely scirrhous tumors do not occur. Monocytes and clasmatocytes are present, many of the latter attaining features simulating neoplastic change. In certain of the tumors this is so striking that distinction from undifferentiated forms of clasmatocytic lymphoma becomes difficult.

### 7. *Follicular Lymphoma*

This unusual subgroup was originally segregated as "giant lymph follicle hyperplasia" by Brill, Baehr and Rosenthal [39] but later classified as a manifestation of malignant lymphoma.[40,41] It has been implied by Ewing [11] and Jackson [36] that it constitutes an inconstant borderline group, evidently a developmental phase of variable duration ultimately becoming one of the other types of lymphoma. Callender [1] attributed a relatively high degree of malignancy to this type while Symmers at first [42] did not believe that the condition was neoplastic at all and later [43] conceded this point with considerable reservation. Although there is evidence that with a sufficiently prolonged course the structural arrangement of the follicular lymphomas may eventually approximate that of one of the other types of lymphoma, there can be little question relative to either the individuality or the ultimate malignancy of the lesion.[44]

Fundamentally, it manifests itself by complete replacement of normal lymph node architecture by multiple follicle-like nodules of varied size and approximation (Fig. 16). These are also present in regions of extranodal invasion. The structure of nodal reticulum is characteristically revised. Trabeculae are obscured. Surrounding each follicular nodule the reticulum meshwork is obviously distorted and condensed by the expanding follicle, and the normally loosely arranged network with broad, polygonal pulp spaces (Fig. 19) becomes compressed and the inter-reticular spaces markedly elongated and narrowed (Fig. 21). Such stromal rearrangement does not occur in ordinary hyperplasia of lymph nodes and may therefore be considered to be of some diagnostic value. Despite this condensation of interfollicular fibrils, actual fusion with the production of collagen does not occur. The sinuses are evidently obscured by displacement of condensed fibrillar material into them. The sparse, stretched attachments of follicles to the surrounding framework allow for separation of the follicles from surrounding tissues in the process of sectioning. This seeming "cracking off" of follicular from nodal substance is due to artefact but is sufficiently constant to serve as a differentiating criterion (Figs. 16 and 18). It is observed relatively uncommonly in other lymph node conditions.

In sections stained in the usual fashion with phloxine and methylene blue several types of follicular nodules are observed. These vary in different cases, apparently with the duration of the ailment, but are type-constant in a given specimen. Detailed description of this phenomenon has been recorded elsewhere [44] and will not be further elaborated here. Although these intrafollicular variations represent features characteristic of this form of lymphoma, the general morphologic

peculiarities deserve greater emphasis in a presentation of this nature.

Significant numbers of multinucleated cells do not appear, nor are there evidences of necrosis or inflammatory exudation. Invasive qualities are noted infrequently. In two cases in which focal skin involvement occurred the cutaneous lesions also manifested follicle formation.

Nodal substance intervening between follicles varies considerably with the degree of follicular contiguity. Fusion of two or more impinging follicles occurs occasionally and when these contain "germinal centers" the latter become confluent and the separating rims of small lymphocytes are lost (Fig. 17). In general, the internodular tissue consists of closely packed normal lymphocytes and the compression and obliteration of sinus spaces simulates the appearance of lymphocytic lymphoma. Such similarity is dispelled, however, by reticulum stains and by lower power examination under which the follicular structure becomes obvious.

Since isolated follicle fusion is observed, it is conceivable that, if the course were sufficiently prolonged, fusion would become quite general and the end result indistinguishable from other types of lymphoma. In eight cases in which histologic studies were possible 1 to 11 years after an initial biopsy, transformation into lymphoblastic lymphoma was observed in one case. In all of the others there was persistence of recognizable follicular structure. In these, although a few regions showed coalescence with loss of nodular structure, reticulum stains exhibited the residuum of the characteristic framework described above.

## PERSISTENCE OF HISTOLOGIC TYPE

At this point the question of persistence of histologic form in malignant lymphoma in general naturally arises. In 84 cases in this series biopsies were made on two or more occasions, or specimens from both biopsy and subsequent necropsy were available. In 56 of these cases a period of at least 1 month intervened between the two specimens. The average interval in this group was 2.3 years and the range up to 15 years. As shown in Table I, the original histologic structure was maintained in 43, or 76.8 per cent, of the cases. In the remaining 23.2 per cent (13 cases) the lesion became less differentiated in appearance and would, therefore, have been placed in another lymphoma group had the original biopsy not been available. It is believed reasonable to expect this degree of dedifferentiation in any group of malignant tumors followed over an extended period of time. In this particular instance the occasional transition from one form to another is a feature lending credence to the belief that these tumors are essentially of common origin.

## Part II. Clinical Studies

If a cytologic classification of the malignant lymphomas such as has been outlined is to have practical value, it should be possible to demonstrate concomitant clinical variations in the subgroups which have been distinguished. An effort will be made to show that this is, within certain limits, the case. Obviously, in a group of diseases so kindred a considerable degree of similarity and of overlapping must

Table I

*Retention of Histologic Structure*

| Type | Average interval between specimens | Number of cases | Unchanged | Dedifferentiation | Differentiation |
|---|---|---|---|---|---|
| Stem cell lymphoma | 0.25 yrs. | 2 | 2 | .. | .. |
| Clasmatocytic lymphoma | 2.3 yrs. | 12 | 6 | 6 | .. |
| Lymphoblastic lymphoma | 0.75 yrs. | 4 | 2 | 2 | .. |
| Lymphocytic lymphoma | 1.9 yrs. | 9 | 9 | .. | .. |
| Hodgkin's lymphoma | 1.9 yrs. | 20 | 16 | 4 | .. |
| Hodgkin's sarcoma | 0.5 yrs. | 1 | 1 | .. | .. |
| Follicular lymphoma | 5.0 yrs. | 8 | 7 | 1 | .. |
| Total | | 56 | 43 | 13 | 0 |

be expected. Certain differential features, nevertheless, became apparent as the material was surveyed which, though of slight importance individually, seemed collectively to delineate a series of fairly distinct clinical pictures.

In 545 cases the clinical records were found to be sufficiently complete to be of value. These were abstracted in detail without reference to histologic classification, then arranged according to histologic group and the clinical data for each subdivision analyzed. Records were complete to the day of death for 413 patients. Of the remaining 132, 21 were in the terminal stage when last seen and were presumed to have died shortly after the last observation. Fifty patients were lost and 61 are still alive, the majority of them under observation in the tumor clinic of this hospital.

### *Age at Onset*

The age at which the first presumably relevant symptom was noted has been recorded as the age at onset. Undoubtedly inaccurate as such a method is, the errors should approximately balance and, consequently, comparisons between the various subgroups should be valid. Figures for the average and median ages of onset of each of the subgroups appear in Table II. For the entire group the average was 42.5 years and the median 44. The most notable deviation from these

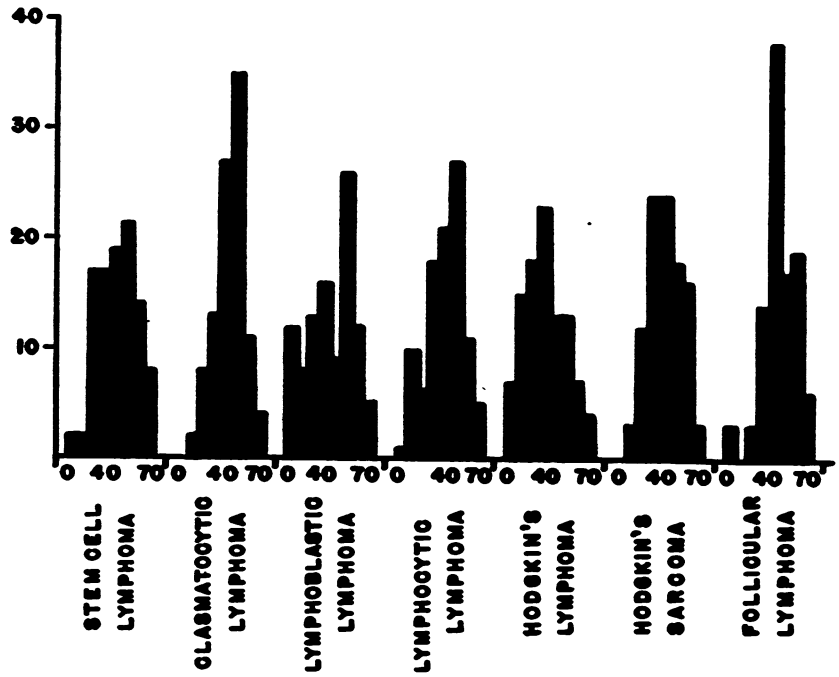
levels occurred in Hodgkin's lymphoma where both figures indicate a tendency for the disease to appear nearly a decade earlier than with any of the other subtypes. Slight deviations in the other direction above the mean level are apparent in the clasmatocytic and follicular subgroups.

TABLE II

*Age at Onset (Years)*

| Type | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| | Average | Median | Average | Median | Average | Median |
| Stem cell lymphoma | 47 | 50 | 43 | 41 | 46 | 48 |
| Clasmatocytic lymphoma | 45 | 43 | 52 | 55 | 49 | 49 |
| Lymphoblastic lymphoma | 44 | 43 | 37 | 38 | 41 | 45 |
| Lymphocytic lymphoma | 45 | 49 | 44 | 44 | 44 | 47 |
| Hodgkin's lymphoma | 37 | 30 | 34 | 34 | 36 | 34 |
| Hodgkin's sarcoma | 44 | 44 | 46 | 43 | 45 | 43 |
| Follicular lymphoma | 51 | 49 | 49 | 42 | 50 | 46 |

More convincing evidence of characteristic group variation is provided in Text-Figure 2 in which age distribution is charted. Although examples of each of the specific types were met in every age group, it is apparent that age distribution is more or less characteristically conditioned by histologic type. For all types except Hodgkin's lymphoma the disease most frequently became evident in the fifth and sixth




TEXT-FIGURE 2. Age at onset by decades, expressed as percentage of total number of cases in each subgroup.

decades, the latter usually leading by a small margin. Ordinary Hodgkin's, in contrast, showed maximal incidence in the third and fourth decades.

Only three types of lymphoma occurred with significant frequency in the first two decades. Well in the lead in development in youth was Hodgkin's lymphoma in which 24 per cent of the cases appeared before the age of 20. Most nearly comparable was the lymphoblastic type with 18 per cent of cases in this age period. In third place with 11 per cent below 20 years of age was lymphocytic lymphoma which proved unique in showing a higher percentage of occurrence in the second decade than in either the first or third, a finding reinforced by the similar observation of Jackson.[35]

At the other end of the scale come the clasmatocytic and follicular types. Both of these were extremely infrequent in youth and relatively uncommon in the twenties and thirties as shown by the fact that only 22 and 21 per cent respectively occurred below 40 years of age. Somewhat intermediate distribution was recorded for the stem cell type and Hodgkin's sarcoma. Here, too, cases were rare before 20 years of age but enough appeared in the third and fourth decades to give incidences of 38 and 42 per cent respectively below the age of 40.

### *Sex Incidence*

The greater frequency of malignant lymphoma in the male sex has long been recognized. For the entire series the proportion of men to women affected was 2.2:1. Hodgkin's lymphoma was the only subgroup strictly adhering to this mean. The other types, as may be seen by reference to Text-Figure 3, showed greater male predominance ranging up to 3 to 1 in the lymphocytic, lymphoblastic and stem cell groups whereas in the follicular and clasmatocytic types the frequency was approximately equal in males and females. It is possible that the lack of evident sex difference in these last two groups is dependent on the relatively advanced age at which they commonly occur.

None of the comparative variations in age incidence or duration of the disease in the two sexes recorded in Tables II and IV appears great enough to have significance unless the marked incidence of clasmatocytic lymphoma in older women (median for women 55 years against 43 years for men) should be substantiated in a larger series.

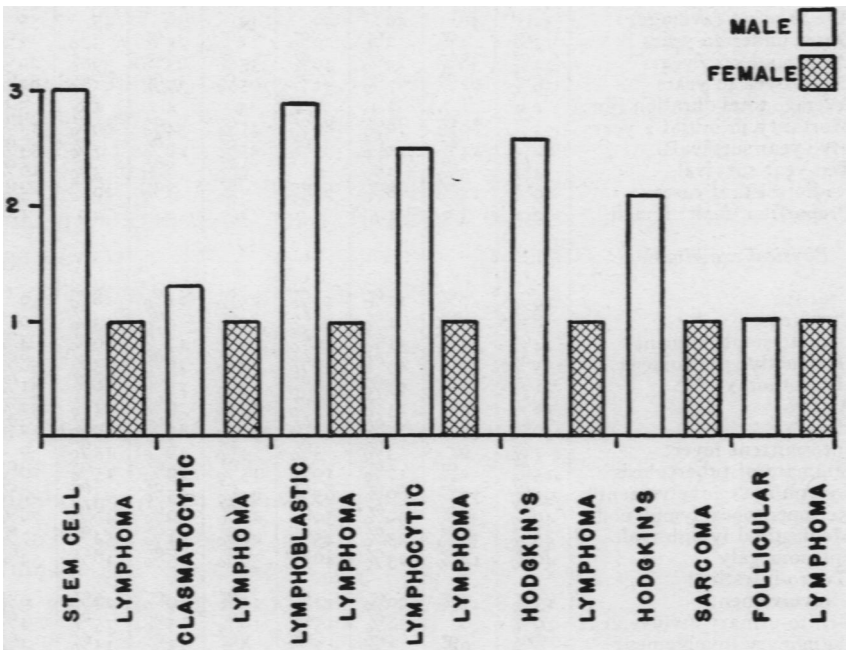
## GENERAL CLINICAL MANIFESTATIONS

In Table III a large number of clinical features have been tabulated for each of the seven subgroups. They have been selected either because they appeared to offer opportunities for noteworthy compari-

sons or contrasts, or because they have received widespread comment in the literature. In the descriptive section to follow, emphasis has been placed upon manifestations which reflect differences between the various subgroups.

### *Enlargement of Lymph Nodes and Spleen*

Palpable, visible, or presumptive lymph node enlargement was present in well over 90 per cent of the subgroups. Among only the patients with clasmatocytic and stem cell lymphoma were there 20 per cent




TEXT-FIGURE 3. Sex incidence expressed in terms of relative proportion.

without evidence of disease of lymph nodes. Peripheral lymph nodes were enlarged most frequently in Hodgkin's, lymphocytic and follicular lymphoma and retroperitoneal nodes were outstandingly prominent in the follicular type. Mediastinal nodes were enlarged in roughly the same proportions in each group although they were noted less frequently in the clasmatocytic and stem cell lymphomas. Splenomegaly was present most frequently with lymphocytoma (56 per cent) and slightly less frequently with Hodgkin's, lymphoblastic and follicular lymphoma (34 to 46 per cent). Splenic enlargement was infrequent in Hodgkin's sarcoma and in clasmatocytic and stem cell lymphoma (14 to 23 per cent).

TABLE III

*Distribution of Clinical Observations According to Type of Lymphoma*

| | All types | Stem cell | Clasmatocytic | Lymphoblastic | Lymphocytic | Hodgkin's | Hodgkin's sarcoma | Follicular |
|---|---|---|---|---|---|---|---|---|
| ***Miscellaneous data*** | | | | | | | | |
| Number of cases | 545 | 42 | 64 | 76 | 118 | 174 | 33 | 38 |
| Age of onset (average) | 42.5 | 46 | 49 | 40 | 44 | 36 | 45 | 50 |
| Onset under 20 years | 13% | 4% | 2% | 20% | 11% | 22% | 3% | 3% |
| Onset under 40 years | 44% | 38% | 23% | 49% | 35% | 63% | 39% | 20% |
| Onset over 40 years | 56% | 62% | 77% | 51% | 65% | 37% | 61% | 80% |
| Average total duration (yrs.) | 2.9 | 1.7 | 2.1 | 1.4 | 3.3 | 4.2 | 1.8 | 5.6 |
| Mortality in initial 2 years | 53% | 80% | 76% | 80% | 45% | 34% | 89% | 13% |
| Five-year survivals | 22% | 14% | 11% | 3% | 25% | 29% | 7% | 53% |
| Ten-year survivals | 4% | 3% | 2% | 0 | 2% | 8% | 3% | 16% |
| Radioresistant cases | 9% | 12% | 8% | 21% | 3% | 8% | 20% | 5% |
| Proportion, male: female | 2.2 | 3.0 | 1.3 | 2.9 | 2.5 | 2.6 | 2.1 | 1.0 |
| ***Physical examination*** | | | | | | | | |
| Pruritus | 14% | 7% | 11% | 12% | 23% | 21% | 18% | 0 |
| Purpura | 8% | 5% | 1% | 13% | 20% | 4% | 3% | 0 |
| Ulcerative phenomena | 24% | 42% | 31% | 29% | 23% | 17% | 39% | 4% |
| Obstructive phenomena | 35% | 49% | 49% | 39% | 28% | 26% | 33% | 58% |
| Hydrothorax | 21% | 14% | 17% | 26% | 13% | 25% | 30% | 31% |
| Ascites | 18% | 14% | 15% | 15% | 13% | 20% | 21% | 37% |
| Fever | 40% | 29% | 25% | 42% | 43% | 49% | 59% | 12% |
| Intermittent fever | 7% | 0 | 3% | 3% | 4% | 16% | 15% | 0 |
| Stigmata of tuberculosis | 15% | 2% | 17% | 10% | 15% | 19% | 15% | 20% |
| Lymph node involvement | 91% | 79% | 80% | 93% | 91% | 95% | 94% | 100% |
| Retroperitoneal lymph nodes | 49% | 30% | 40% | 50% | 46% | 50% | 48% | 79% |
| Mediastinal lymph nodes | 45% | 30% | 23% | 45% | 40% | 61% | 54% | 37% |
| Splenomegaly | 40% | 14% | 23% | 46% | 56% | 45% | 18% | 34% |
| Gastro-intestinal involvement | 13% | 27% | 20% | 14% | 11% | 9% | 24% | 6% |
| Genito-urinary involvement | 10% | 0 | 8% | 15% | 19% | 5% | 15% | 4% |
| Pulmonary involvement | 9% | 9% | 3% | 7% | 8% | 12% | 15% | 4% |
| Cutaneous involvement | 20% | 17% | 16% | 21% | 26% | 20% | 24% | 4% |
| Discrete bone involvement | 13% | 7% | 23% | 15% | 7% | 16% | 15% | 4% |
| Diffuse bone marrow involvement | 10% | 5% | 5% | 20% | 21% | 5% | 3% | 2% |
| ***Hematologic data*** | | | | | | | | |
| Anemia | 40% | 29% | 17% | 54% | 41% | 44% | 33% | 29% |
| Leukocytosis | 44% | 25% | 31% | 52% | 59% | 45% | 50% | 15% |
| Thrombocytosis | 18% | 15% | 33% | 30% | 2% | 18% | 47% | 0 |
| Thrombocytopenia | 31% | 14% | 10% | 40% | 58% | 27% | 3% | 25% |
| Monocytosis | 21% | 15% | 22% | 12% | 9% | 35% | 33% | 6% |
| Eosinophilia | 8% | 10% | 3% | 2% | 5% | 15% | 3% | 3% |
| Lymphocytosis | 31% | 13% | 16% | 62% | 70% | 14% | 7% | 18% |
| Lymphocytopenia | 8% | 0 | 2% | 2% | 4% | 19% | 13% | 0 |
| Atypical cells | 27% | 7% | 14% | 60% | 33% | 25% | 20% | 6% |
| Leukemia | 9% | 2% | 5% | 15% | 23% | 2% | 3% | 3% |
| Subleukemia | 8% | 0 | 0 | 23% | 25% | 0 | 0 | 0 |

### *Fever*

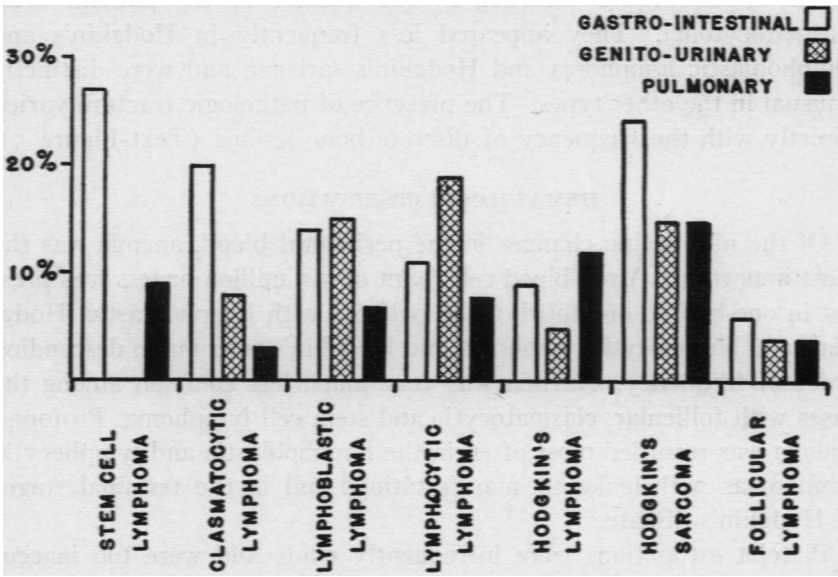
Febrile manifestations (fever of 101° F. or higher) occurred at some time during the course of the disease in cases from all the subgroups (Table III). It was rare in the follicular type (only 12 per cent), relatively uncommon (25 and 29 per cent) in the clasmatocytic and stem cell groups, appeared in 42 and 43 per cent of the lymphocytic and lymphoblastic cases, in half the Hodgkin's lymphomas and was most frequent in Hodgkin's sarcoma (59 per cent). Intermittent fever of the Pel-Ebstein type occurred with significant frequency (16 per cent) only in the two Hodgkin's types and was noted very infrequently among the others.

### *Cutaneous Involvement*

Generalized cutaneous infiltration, scattered nodular lesions of the skin, or a combination of both of these appeared in 16 to 26 per cent of the cases in all groups except the follicular lymphomas, among which cutaneous lesions were unusual. Pruritus was recorded in cases in each group except that of follicular lymphoma. Although individuals with skin lesions were prone to suffer from this symptom, it bore no constant relationship to the presence of evident cutaneous disease and was not believed to be of diagnostic value.

### *Visceral Involvement*

There appeared to be a significant group variation with regard to visceral predilection (Text-Figure 4). The gastro-intestinal tract was




TEXT-FIGURE 4. Visceral involvement by percentage of cases in each subgroup.

more often involved in patients with Hodgkin's sarcoma, stem cell and clasmatocytic lymphoma. These lesions were very unusual in follicular lymphoma. Tumor infiltration of the genito-urinary apparatus was most common among the lymphocytomas, less common in lymphoblastic lymphoma and Hodgkin's sarcoma and rare in the other types. Lymphomatous lesions of the lungs generally exhibited the histologic features of one or the other forms of Hodgkin's disease. Pulmonary foci were comparatively rare among the other subgroups.

Obstructive phenomena as the result of compression of vascular or visceral channels were particularly striking in follicular lymphoma. There was, in general, less evidence of obstruction in the clasmatocytic and stem cell lymphomas and considerably less among the remaining subgroups. Ulceration secondary to neoplastic infiltration of skin or mucous membranes occurred most frequently with stem cell lymphoma and Hodgkin's sarcoma.

Peripheral edema and ascites appeared in over one-third of the cases of follicular lymphoma and were much less common in the remaining groups. There was no differential significance in the frequency of occurrence of hydrothorax. Chylous effusion was observed in 11 per cent of the follicular lymphomas and was rarely encountered in any other type of the disease.

### *Bone Lesions*

Isolated skeletal lesions, in many instances solitary manifestations of the disease, were recorded in one quarter of the patients with clasmatocytoma. They appeared less frequently in Hodgkin's and lymphoblastic lymphoma and Hodgkin's sarcoma and were distinctly unusual in the other types. The presence of pathologic fracture varied directly with the frequency of discrete bone lesions (Text-Figure 5).

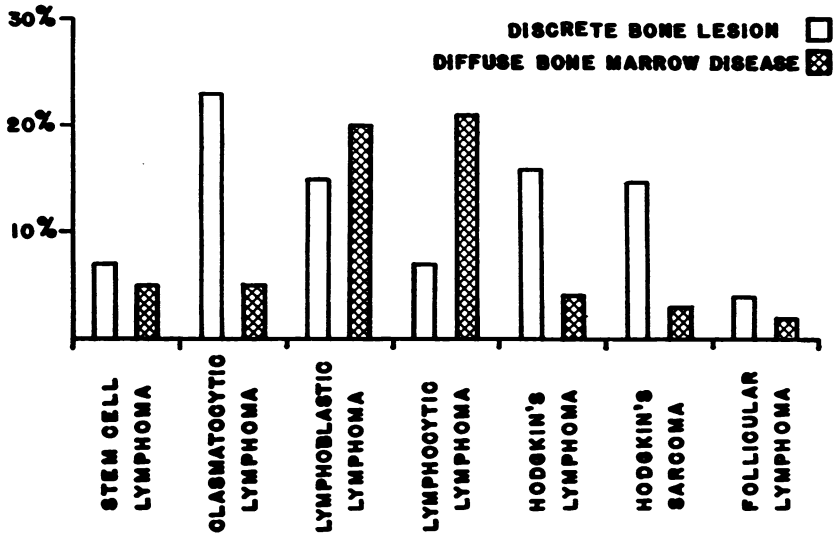
## HEMATOLOGIC OBSERVATIONS

Of the nonspecific changes in the peripheral blood, anemia was the most important. A red blood cell count of 3.5 million or less was present in one-half to one-third of the patients with lymphoblastic, Hodgkin's and lymphocytic lymphoma and Hodgkin's sarcoma in descending order of frequency. Anemia was very much less common among the cases with follicular, clasmatocytic and stem cell lymphoma. Profound anemia was recorded most often in the lymphoblastic and lymphocytic lymphomas with leukemic manifestations and in the terminal stages of Hodgkin's disease.

Platelet estimations were infrequently made and were too inaccurate for critical analysis. Thrombocytosis occurred with significant

frequency only among the patients with Hodgkin's sarcoma and thrombocytopenia among those with lymphocytic and lymphoblastic lymphoma. Purpura was noted more commonly in the two last-named groups.

A leukocytosis exceeding 12,000 per cmm. was observed in 50 to 60 per cent of the patients with lymphocytic and lymphoblastic lymphoma and Hodgkin's sarcoma. It was less common with Hodgkin's,




TEXT-FIGURE 5. Bone involvement by percentage of cases in each subgroup.

clasmatocytic and stem cell lymphoma, and was very unusual among the cases of follicular lymphoma. Leukopenia with white cells numbering less than 5,000 per cmm. was noted in 11 to 16 per cent of the patients suffering from lymphocytic, lymphoblastic and Hodgkin's lymphoma. It was rare in other types of the disease.

Monocytes in excess of 10 per cent were recorded in one-third of the cases of Hodgkin's lymphoma and sarcoma and one-quarter of those with clasmatocytomas, but rarely in the remainder. Markedly diminished monocyte values occurred with the lymphocytic and lymphoblastic lymphomas.

Lymphocytosis was observed in 62 to 70 per cent of the cases with lymphocytic and lymphoblastic lymphoma. Lymphocytopenia appeared in only 19 per cent of the Hodgkin's lymphomas and 13 per cent of the Hodgkin's sarcomas. The remaining groups generally exhibited normal values. Variations in the number of eosinophils were considered to be lacking in pertinent diagnostic value. Eosinophilia was not a prominent feature in Hodgkin's disease.

Atypical cells, "tumor cells," unidentified cells and "blast" forms appeared in the peripheral blood of almost two-thirds of the cases of lymphoblastic lymphoma, one-third of those with lymphocytoma and one-quarter of those with Hodgkin's lymphoma and sarcoma. In only 6 to 14 per cent of the remainder were such phenomena apparent.

### *Leukemia*

Peripheral blood pictures characteristic of leukemia as commonly defined occurred at some time during the course of the disease in 48 per cent of the cases with lymphocytoma and in 38 per cent of those with lymphoblastic lymphoma. They were infrequent but were encountered among each of the remaining subgroups except the stem cell type. The leukemic pictures were susceptible to division into the various phases commonly ascribed to this disease. These consisted of: true leukemia with the white cells numbering over 30,000 associated with an absolute increase and preponderance of cells of the lymphocytic series; sub-leukemic leukemia in which the total number of white cells fell between the normal range and minimal leukemic levels; and finally, aleukemic leukemia in which the total number of white cells was well below the minimal normal level of 5,000 but in which again there was a predominance of lymphocytes or "atypical" or immature lymphoid forms.

The significance of such a classification appears dubious when a series of cases is followed over a considerable period of time. Fifty patients who exhibited some phase of leukemia during their course were selected for analysis on the basis that two or more blood studies were recorded at extended intervals during their disease. Of these, 13 patients were non-leukemic when first observed but developed leukemia later in the course, six were leukemic at the initial observation but showed normal blood pictures prior to death and two other patients were leukemic at the beginning and at the end of the disease but were non-leukemic in the interval. Forty-two per cent of this group, then, exhibited marked relapse into, or remission from, leukemia. An additional 38 per cent showed a variety of shifts among the aleukemic, subleukemic and leukemic phases without reverting to normal. In only 20 per cent of the 50 patients was the blood picture entirely constant throughout the course of the disease.

Since, as has been shown in the first portion of this study, there is no difference in the histologic background of the leukemic and the non-leukemic cases, it appears evident that the development of leukemia must be regarded as an incidental occurrence in the disease—simply an overt manifestation of the underlying process. Actually nothing

is known relative to the mechanism of the delivery of the abnormal cells into the blood stream or concerning the abrupt changes in the blood picture so frequently observed.

The development of leukemia was of some prognostic import. Seventy-seven patients with lymphoblastic or lymphocytic lymphoma, with leukemia recorded at least once, showed an average life expectancy of about 1 year less than those without leukemic manifestations. Its presence at the onset or its development during the course generally implied a poorer prognosis, particularly if the leukemic cells were immature or bizarre in appearance and the causative lesion was of the lymphoblastic type.

## *"Lymphosarcoma"*

Malignant lymphoma in all its varieties tends to be a generalized disease, or to become such so rapidly that it is the exceptional case which is observed in the localized stage. From clinical study it is scarcely possible to be certain that the disease is indeed localized, but at the autopsy table isolated lesions are not infrequently met where the most meticulous examination fails to reveal any evidence of generalization. Still more convincing is the experience with surgical resection of lymphomatous tumors which may be followed by survival for many years even without postoperative irradiation; results scarcely interpretable in any other light than as the extirpation of a localized neoplasm.

Localization is not a peculiarity of any cytologic type of lymphoma but is met in all. The frequency, however, with which localized tumors are encountered varies considerably with the histologic type. In 70 of the cases in our series the lesion was limited to a single area at the time of initial examination. Their distribution is recorded in Table IV. Classified according to cytologic type, localization was observed in only 3 per cent of cases of Hodgkin's sarcoma, 6 per cent of Hodgkin's lymphoma, 10 per cent of follicular lymphoma, 11 per cent of lymphocytoma and 13 per cent of the lymphoblastic form. The frequency rose sharply to 26 per cent of stem cell and 33 per cent of clasmatocytic lymphoma.

It is of interest that over half of these lesions appeared in non-lymphoid tissues, most frequently in bones and in the gastro-intestinal tract, but occasionally in areas in which even isolated lymph follicles are not found under normal circumstances (*i.e.*, the subcutaneous fat, the bladder and the cervix of the uterus). Many of these tumors grow in a frankly invasive and destructive manner and metastases may occur in many organs without diffuse involvement of the lymphoid structures or the bone marrow.

TABLE IV

*Initially Localized Malignant Lymphoma (Lymphosarcoma; Kundrat)*

| No. | Type | Location | Treatment | Duration | Ultimate distribution | Result | Autopsy |
|---|---|---|---|---|---|---|---|
| 1 | Stem cell lymphoma | Mediastinum | X-ray | 1.6 years | Local | Dead | |
| 2 | Stem cell lymphoma | Cerv. l. n. | Surg., x-ray | 10.2 years | Generalized | Dead | |
| 3 | Stem cell lymphoma | Stomach | Surg. | 0.3 years | None | Dead | |
| 4 | Stem cell lymphoma | Stomach | Surg. | 2.0 years | None | Dead | |
| 5 | Stem cell lymphoma | Thigh | Surg., x-ray | 15.7 years | Generalized | Dead | |
| 6 | Stem cell lymphoma | Abdom. l. n. | X-ray | 1.2 years | Generalized | Dead | |
| 7 | Stem cell lymphoma | Dura (cord) | Surg., x-ray | 2.2 years | Generalized | Lost | |
| 8 | Stem cell lymphoma | Cecum | None | 0.4 years | Local | Dead | Yes |
| 9 | Stem cell lymphoma | Eyelid | Surg., x-ray | 1.9 years | Generalized | Dead | |
| 10 | Stem cell lymphoma | Stomach | Surg. | 3.0 years | Local | Dead | Yes |
| 11 | Stem cell lymphoma | Stomach | Surg., x-ray | 0.8 years | Local | Dead | |
| 12 | Clasmatocytic lymphoma | Abdom. l. n. | Surg., x-ray | 0.5 years | Generalized | Dead | Yes |
| 13 | Clasmatocytic lymphoma | Stomach | Surg. | 0.3 years | None | Dead | |
| 14 | Clasmatocytic lymphoma | Tonsil | X-ray | 1.1 years | Generalized | Dead | |
| 15 | Clasmatocytic lymphoma | Thyroid | Surg., x-ray | 1.3 years | Generalized | Lost | |
| 16 | Clasmatocytic lymphoma | Abdominal l. n. | X-ray | 1.1 years | Local | Dead | |
| 17 | Clasmatocytic lymphoma | Humerus | Surg. | 15.9 years | Local | Alive | |
| 18 | Clasmatocytic lymphoma | Stomach | Surg., x-ray | 7.2 years | None | Alive | |
| 19 | Clasmatocytic lymphoma | Dura (cord) | X-ray | 0.4 years | Local | Dead | |
| 20 | Clasmatocytic lymphoma | Thyroid | Surg., x-ray | 3.3 years | Generalized | Dead | Yes |
| 21 | Clasmatocytic lymphoma | Stomach | Surg., x-ray | 4.9 years | Generalized | Dead | |
| 22 | Clasmatocytic lymphoma | Stomach | None | 1.0 years | Local | Dead | Yes |
| 23 | Clasmatocytic lymphoma | Tibia | Surg. | 7.5 years | None | Alive | |
| 24 | Clasmatocytic lymphoma | Clavicle | X-ray | 4.8 years | Generalized | Dead | |
| 25 | Clasmatocytic lymphoma | Femur | Surg., x-ray | 4.7 years | None | Alive | |
| 26 | Clasmatocytic lymphoma | Stomach | Surg. | 5.5 years | None | Alive | |
| 27 | Clasmatocytic lymphoma | Thyroid | Surg., x-ray | 1.6 years | Local | Dead | |
| 28 | Clasmatocytic lymphoma | Femur | X-ray | 3.7 years | None | Alive | |
| 29 | Clasmatocytic lymphoma | Nasal sinus | X-ray | 2.6 years | None | Alive | |
| 30 | Clasmatocytic lymphoma | Sacrum | X-ray | 1.4 years | Generalized | Dead | Yes |
| 31 | Clasmatocytic lymphoma | Ing. l. n. | X-ray | 4.1 years | None | Alive | |
| 32 | Clasmatocytic lymphoma | Ileum | None | 0.3 years | Local | Dead | Yes |
| 33 | Lymphoblastic lymphoma | Abdominal l. n. | Surg., x-ray | 1.1 years | Local | Dead | |
| 34 | Lymphoblastic lymphoma | Jejunum | X-ray | 2.3 years | Generalized | Dead | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 35 | Lymphoblastic lymphoma | Rectum | Surg. | 0.3 years | None | Dead | |
| 36 | Lymphoblastic lymphoma | Frontal bone | X-ray | 2.5 years | Local | Dead | |
| 37 | Lymphoblastic lymphoma | Tonsil | X-ray | 1.7 years | Local | Dead | |
| 38 | Lymphoblastic lymphoma | Cerv. l. n. | X-ray | 0.4 years | Local | Dead | |
| 39 | Lymphoblastic lymphoma | Stomach | Surg., x-ray | 3.2 years | Generalized | Dead | |
| 40 | Lymphoblastic lymphoma | Parotid | X-ray | 1.2 years | Generalized | Alive | |
| 41 | Lymphoblastic lymphoma | Mediastinum | None | 0.1 years | Local | Dead | Yes |
| 42 | Lymphoblastic lymphoma | Mediastinum | None | 0.1 years | Local | Dead | Yes |
| 43 | Lymphocytic lymphoma | Nasal sinus | Surg., x-ray | 7.5 years | Generalized | Dead | |
| 44 | Lymphocytic lymphoma | Testis | Surg., x-ray | 0.5 years | Generalized | Dead | |
| 45 | Lymphocytic lymphoma | Nose | X-ray | 2.5 years | Generalized | Dead | Yes |
| 46 | Lymphocytic lymphoma | Parotid | None | 1.0 years | Local | Dead | Yes |
| 47 | Lymphocytic lymphoma | Tonsil | Surg., x-ray | 9.0 years | Generalized | Dead | Yes |
| 48 | Lymphocytic lymphoma | Cerv. l. n. | Surg., x-ray | 3.8 years | Local | Lost | |
| 49 | Lymphocytic lymphoma | Prostate | X-ray | 4.0 years | Local | Lost | |
| 50 | Lymphocytic lymphoma | Stomach | Surg., x-ray | 7.0 years | None | Alive | |
| 51 | Lymphocytic lymphoma | Femur | Surg., x-ray | 8.0 years | Local | Alive | |
| 52 | Lymphocytic lymphoma | Dura (cord) | X-ray | 0.7 years | Local | Dead | |
| 53 | Lymphocytic lymphoma | Intestine | Surg., x-ray | 2.4 years | Generalized | Dead | |
| 54 | Lymphocytic lymphoma | Mediastinum | None | ? | Local | Dead | Yes |
| 55 | Lymphocytic lymphoma | Bladder | None | 0.3 years | Local | Dead | Yes |
| 56 | Hodgkin's lymphoma | Abdominal l. n. | None | 1.5 years | Local | Dead | |
| 57 | Hodgkin's lymphoma | Back | X-ray | 5.5 years | Generalized | Dead | |
| 58 | Hodgkin's lymphoma | Cerv. l. n. | Surg., x-ray | 8.6 years | Generalized | Dead | |
| 59 | Hodgkin's lymphoma | Abdominal l. n. | Surg. | 0.6 years | None | Dead | |
| 60 | Hodgkin's lymphoma | Parotid | X-ray | 9.0 years | Generalized | Dead | Yes |
| 61 | Hodgkin's lymphoma | Cerv. l. n. | X-ray | 5.9 years | Generalized | Dead | |
| 62 | Hodgkin's lymphoma | Abdominal l. n. | X-ray | 3.3 years | Generalized | Dead | Yes |
| 63 | Hodgkin's lymphoma | Cerv. l. n. | X-ray | 8.9 years | None | Alive | |
| 64 | Hodgkin's lymphoma | Mediastinum | None | 0.2 years | Local | Dead | Yes |
| 65 | Hodgkin's lymphoma | Ing. l. n. | None | 0.7 years | Local | Dead | Yes |
| 66 | Hodgkin's sarcoma | Axillary l. n. | X-ray | 1.5 years | Generalized | Lost | |
| 67 | Follicular lymphoma | Abdominal l. n. | X-ray | 5.5 years | Local | Lost | |
| 68 | Follicular lymphoma | Ing. l. n. | Surg. | 6.5 years | None | Dead | Yes |
| 69 | Follicular lymphoma | Abdom. l. n. | X-ray | 2.2 years | Generalized | Dead | |
| 70 | Follicular lymphoma | Ing. l. n. | Surg., x-ray | 5.5 years | None | Alive | |

Observations of this sort have led to the concept of a special form of malignant lymphoma termed by Kundrat [34] "lymphosarcoma" and currently defined [45] as an initially circumscribed lymphoid neoplasm which breaks through its confines and invades neighboring structures by way of lymphatics. Many authors [46-49] believe such a segregation is artificial and merely represents a phase in the course of the disease. The difficulty of maintaining the concept becomes obvious in surveying a large group of cases since "sarcomatous" tumors may even appear in cases of otherwise typical leukemia. Indeed, leukemic blood pictures may develop in cases starting as apparently typical lymphosarcoma, and the confusion is hardly alleviated by the use of terms such as "leukosarcoma" [50] to describe these transitional forms. The absence of detectable bone-marrow involvement cannot be used to rule out leukemia since cases of both lymphatic and myelogenous leukemia have been observed in which marrow replacement by leukemic cells has not occurred.[4,31,51] It has been claimed that the type of cell appearing in the blood in leukosarcoma is distinctive and does not resemble that noted in other forms of lymphatic leukemia. This has not been our experience. We have found the character of the circulating cell to be identical with that composing the organic process from which it has arisen.

Of the 70 cases referred to above in which a single localized lesion was present at the outset, 27 ultimately became generalized in character and indistinguishable from other forms of malignant lymphoma. Among the remaining 43 cases, all of which were followed to the time of death or for a period of at least 1 year, 27 showed persistent localization of the process. Twenty-two of these died and only 11 were autopsied so that the evidence of failure of dissemination was purely clinical in 60 per cent. Furthermore, the duration of the disease had been only one-half as long as that in the 27 who developed the generalized condition (2.2 and 4.1 years).

In addition to these 54 cases, 16 showed no evidence of persistent tumor at all. Twelve of these had been subjected to radical surgical excision and 5 died immediately postoperatively. Ten of the 16 were still alive and an autopsy had been made on only 1 of the others. The evidence here also was therefore overwhelmingly clinical and unconfirmed by postmortem investigation.

It seems reasonable to conclude that the condition termed "lymphosarcoma" represents a transient clinical phase and in most instances might be expected to progress into a generalized process if the patient did not succumb at too early a period. Whether or not the dissemination when it does occur is the result of direct extension, metastasis or

independent foci of multicentric origin cannot be stated with any degree of certainty. It is possible that any one or all of these means may be operative.

### *Duration of the Disease*

In a group of diseases which are generally regarded as inevitably fatal, the most practical function of a classification is to aid prognosis. Review of the literature reveals that authors have accepted an extremely discouraging viewpoint regarding sufferers from malignant lymphoma, which is, to a considerable extent, borne out by the median figure of 2.0 years for our entire series. On the other hand, 116 patients, or about 20 per cent, have lived beyond a 5-year period and nearly 10 per cent have survived 8 or more years. It is therefore of importance to determine if consistent variations in survival periods can be correlated with histologic structure.

In surveying our figures it was at once apparent that since many of our patients were still alive, including many of the cases of notably long survival, a false impression would be created if these were excluded. It was therefore decided, somewhat arbitrarily, to include all living cases of 3 or more years' duration. Though such a procedure robs the figures of absolute value—which could only be obtained by the impractical procedure of retiring to a perspective of at least 10 years—it has been uniformly applied and therefore does not affect the validity of the comparative results. Average and median figures for the various subgroups appear in Table V. Inspection at once reveals that four types (lymphoblastic, stem cell and clasmatocytic lymphomas and

TABLE V

*Total Duration (Years)*

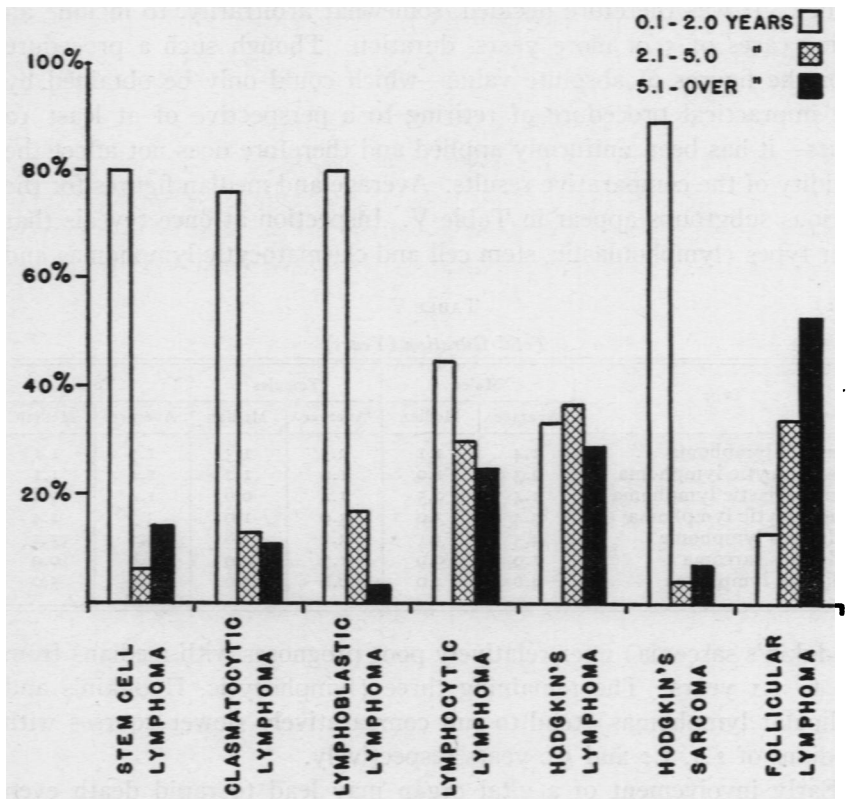
| Type | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| | Average | Median | Average | Median | Average | Median |
| Stem cell lymphoma | 1.4 | 1.1 | 2.5 | 1.3 | 1.7 | 1.1 |
| Clasmatocytic lymphoma | 2.3 | 1.0 | 1.9 | 1.2 | 2.1 | 1.1 |
| Lymphoblastic lymphoma | 1.4 | 0.5 | 1.4 | 0.6 | 1.4 | 0.6 |
| Lymphocytic lymphoma | 3.4 | 3.0 | 3.0 | 1.9 | 3.3 | 2.4 |
| Hodgkin's lymphoma | 4.3 | 3.1 | 3.7 | 3.8 | 4.2 | 3.2 |
| Hodgkin's sarcoma | 1.9 | 0.9 | 1.7 | 0.9 | 1.8 | 0.9 |
| Follicular lymphoma | 4.6 | 4.0 | 6.8 | 5.6 | 5.6 | 5.0 |

Hodgkin's sarcoma) offer relatively poor prognoses with medians from 0.6 to 1.1 years. The remaining three (lymphocytic, Hodgkin's and follicular lymphomas) tend to run comparatively slower courses with medians of 2.4, 3.2 and 5.0 years respectively.

Early involvement of a vital organ may lead to rapid death even with the relatively benign varieties. Conversely, in even the most

malignant types, occasional instances of notably long survival (8 or more years) are met. These are least frequent in lymphoblastic lymphoma and Hodgkin's sarcoma; they occur with enough frequency in the stem cell and clasmatocytic types to raise the average duration above the median and they are most frequent in the three relatively benign varieties. It is noteworthy that 25 per cent of the cases of lymphocytic, 29 per cent of those with Hodgkin's and 53 per cent of those with follicular lymphoma lived 5 or more years after the clinical onset. On the other hand, only 3 per cent of the lymphoblastomas, 7 per cent of the Hodgkin's sarcomas, 11 per cent of the clasmatocytomas and 14 per cent of the stem cell lymphomas have survived this period (Text-Fig. 6).

Analyses of the cases with the more malignant forms of the disease which had unexpectedly prolonged courses demonstrated that group prognosis apparently was altered by several factors. Patients with primary diffuse skin disease (mycosis fungoides) or single primary lesions of a bone or a viscus (intestine, stomach, thyroid) frequently




TEXT-FIGURE 6. Total duration expressed as percentage of cases in each subgroup.

belied the gloomy outlook predicated by the histologic appearance of the underlying lesion. Cases in which cutaneous, osseous or visceral lesions were secondary phenomena in the course of a generalized process obviously do not belong in this category. Among the outstanding survivals referred to, of which there were 21, 17 showed lesions primary in the regions noted above and the remaining 4 were indistinguishable from the ordinary type of ultimately generalized disease. The longest duration recorded in this series was 23 years, the patient being still alive 21 years since an initial biopsy and 5 years after another, both of which showed classical Hodgkin's lymphoma.

In several of the subgroups the duration was apparently influenced by the age at the onset of the disease. With Hodgkin's lymphoma the survival period was much shorter in those patients in whom the disease was initiated after the age of 50 years. Among the lymphocytomas the life expectancy was better during the middle decades than it was at either extreme of life and it was particularly poor in those few cases occurring in youth. Follicular lymphoma rarely occurred in the young and uniformly offered a relatively favorable prognosis as to period of survival. The four malignant types were relatively uninfluenced by age.

## THERAPY

Roentgen therapy has been the only universally accepted means of combating the malignant lymphomas.[45, 52] Indeed, lymphomatous lesions are, for the most part, so strikingly susceptible to this type of irradiation that radiosensitivity has been utilized as a diagnostic criterion for tumors not accessible for histologic study.[53] Despite this common characteristic, individual cases may fail to exhibit any favorable response to such treatment. Such failure has appeared in our experience very rarely among the Hodgkin's, follicular, lymphocytic and clasmatocytic lymphomas, although the last type occasionally required something more than the customary "lymphoma" dosage (600 r.) of deep x-ray therapy to produce subsidence of a lesion. Among the Hodgkin's sarcomas and the lymphoblastic and stem cell lymphomas, however, 20, 21 and 12 per cent, respectively, failed to show any evidence of improvement following irradiation.

It is generally agreed that the benefits of radiotherapy in the malignant lymphomas are but transitory. Moreover, it has even been claimed that although symptomatic relief might be expected, actual prolongation of the course of the disease was unusual.[54, 55] Experience in the clinic leaves the observer with the impression that in many instances roentgen therapy has snatched a patient from immediately impending

death and prolonged his life by months and even years. Acceptable statistical evidence, however, that the average duration of life is prolonged is extremely difficult to accumulate. In a group of diseases where x-ray treatment has become almost automatic once the diagnosis has been established, the collection of an adequate control series is almost impossible. Out of our entire series only 76 patients were found to whom no x-ray treatment had been administered. Most of these were not seen until they were in the terminal stages of their disease, at which time therapy of this type was deemed inadvisable. A few died as the result of surgical intervention, some refused treatment and others were not treated because of failure to recognize the nature of the disease. It is interesting to note that of these 76 patients only 4 survived beyond the average duration established for their respective subgroups. The average total duration of their various illnesses was 0.8 years in contradistinction to the average duration for the entire series of 2.9 years. The two series are by no means strictly comparable since a significant degree of selection had been brought into play.

Comparison of the survival periods among the patients observed and treated between 1917 and 1926 and those seen between 1927 and 1936 showed no noteworthy difference. No improvement in results corresponding to the obviously increased efficiency of radiotherapy in the treatment of carcinoma during the same interval could be discerned.

### *Surgery*

Surgery as a therapeutic measure in malignant lymphoma has been generally interdicted, presumably on the basis that the disease is essentially systemic.[56] In this connection it was noted that among the 135 autopsied cases in this series, 10 per cent showed localized lesions, apparently available to surgical excision and certainly not systemic in character. No evidence of the disease was found elsewhere.

In the entire series radical surgery was attempted in 77 cases, generally in ignorance of the histologic character of the lesion. In 44 cases the disease had extended beyond the limits of eradicability at the time of operation. Of the remaining 33 patients, 10 died as the immediate result of the surgical procedure. Twenty-three survivors, 12 of whom were among those listed above as exhibiting unexpectedly prolonged courses, lived or are living, an average of 7.0 years after the onset of their disease. Ten have survived an average of 6.6 years after operation without evidence of recurrence and the remaining 13 continued for an average of 5.7 years postoperatively before any evidence of recurrence appeared. Of those surviving without recurrence, one died of other causes 4.5 years after operation and at necropsy no evidence of residual tumor was found.

The number of individuals receiving radical surgical treatment was admittedly too small and the operative mortality obviously too high to allow unqualified recommendation of such a therapeutic measure. The selection of cases, however, was quite limited and the surgical approach in many was unduly delayed. Considering all of these factors we believe that among the malignant lymphomas there are certain cases with evidence of a single localized lesion, generally, though not always, affecting a bone or a viscus, which may be more successfully treated by radical surgery than by other means.

## Summary and Conclusions

A cytologic classification of the malignant lymphomas has been presented and its advantages pointed out in a clinico-pathologic survey of 545 cases (73 cases of the 618 studied histologically had inadequate clinical data). It has been shown, by multiple examinations at significant time intervals, that the cytologic type is remarkably constant, although a few cases show a progressive failure of differentiation as the disease progresses. In contrast, in a classification based largely on distribution, such features as the presence or absence of leukemia, generalization versus localization and "sarcomatous" growth are considered important. These have been shown to be inconstant and changeable, thereby requiring variation in classification from time to time in order to fit the stage of the disease.

It was found that the vast majority of the 618 cases from which histologic material was available could be readily divided into the following seven categories: stem cell lymphoma, clasmatocytic lymphoma, lymphoblastic lymphoma, lymphocytic lymphoma, Hodgkin's lymphoma, Hodgkin's sarcoma and follicular lymphoma. This differs from widely accepted classifications primarily in the subdivision into two types of what has generally been grouped under the heading, reticulum cell sarcoma: one in which the cells are highly undifferentiated and resemble lymphoid stem cells, for which we have proposed the name stem cell lymphoma; and a second in which the cells show recognizable features of differentiation in the direction of tissue phagocytes, which we have accordingly termed clasmatocytic lymphoma. It has also proved useful to divide the tumors showing clear evidence of belonging to the lymphocyte series of cells into lymphoblastic and lymphocytic types depending upon whether the immature or mature cells predominate. Hodgkin's disease, too, has appeared divisible into lymphomatous and sarcomatous types. Follicular lymphoma has been shown to be a form of malignant lymphoma and not, as has been claimed, merely an inflammatory process.

In Part II the value of this classification has been put to the test of

clinical correlation and, although considerable overlapping was observed as would be expected in so closely related a group of diseases, sufficiently constant differences were found in the age of onset, duration of the disease, maximal frequency of involvement of various organs and tissues, tendency to localization or generalization, the development of leukemia and the degree of radiosensitivity to delineate a series of recognizably different clinical syndromes.

The following conclusions appear justified on the basis of the recorded clinical and pathologic observations:

Prognostic implications may be guided to a surprising degree by the histologic character of the lesion. However, unexpectedly prolonged survival periods have been encountered, on the one hand, in cases in which the initial lesion appeared in the skin, bone or viscera and, on the other hand, in those in which the primary lesion was sufficiently circumscribed to be susceptible to surgical extirpation. Five-year survivals have been encountered in all groups but have ranged from 3 per cent of patients with lymphoblastic lymphoma to 53 per cent of those with follicular lymphoma.

As a general rule small doses of roentgen irradiation have a favorable effect upon patients with malignant lymphoma and there is evidence to show that such therapy does prolong life. Patients with clasmatocytic or stem cell lymphoma require somewhat higher dosages to produce beneficial effects and in a few instances, notably in lymphoblastic lymphoma and Hodgkin's sarcoma, irradiation fails to produce any improvement at all.

The presence or development of leukemia cannot be predicted on the basis of any constant morphologic criterion. In fact, very often the blood picture itself is inconstant and varies from time to time during the course of the disease. It seems more reasonable to consider lymphatic leukemia simply as a manifestation of an underlying lymphomatous process. Along the same lines, in the interests of clarity, it would seem judicious to discard such terms as "lymphosarcoma" (Kundrat) and "leukosarcoma" since these, too, appear merely to represent transient phases of malignant lymphoma and do not constitute disease entities.

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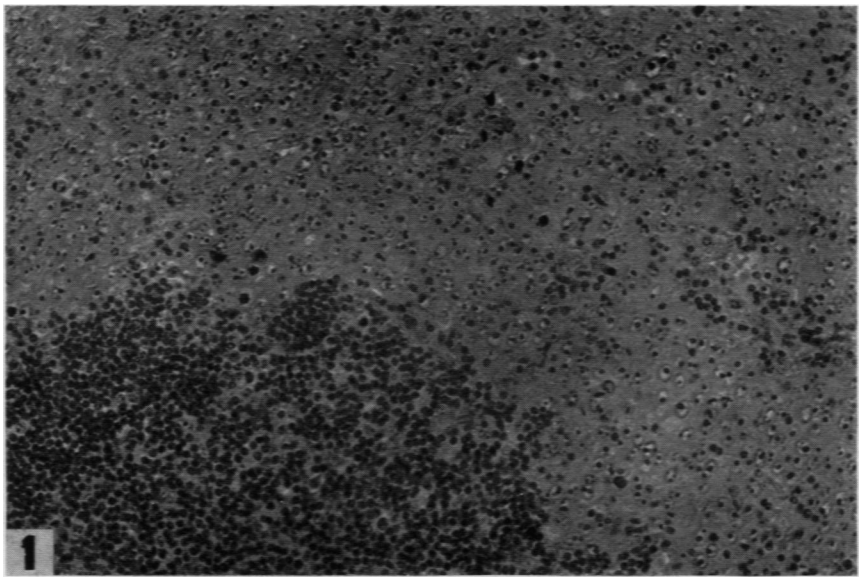
## DESCRIPTION OF PLATES

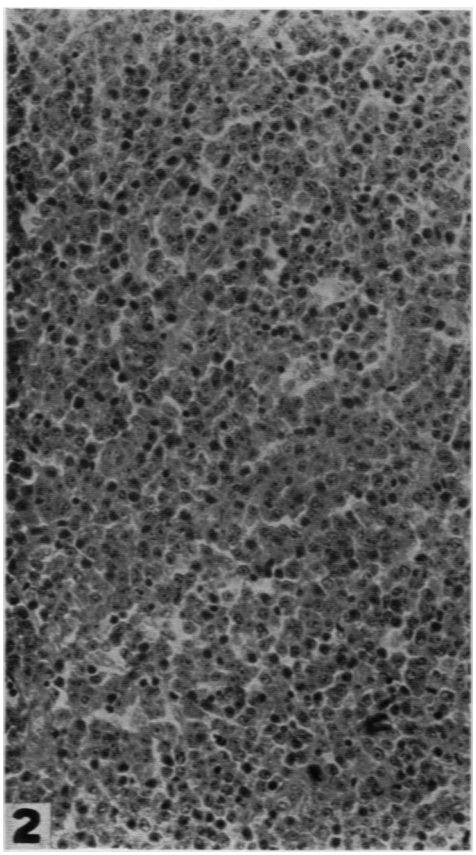
### PLATE 62

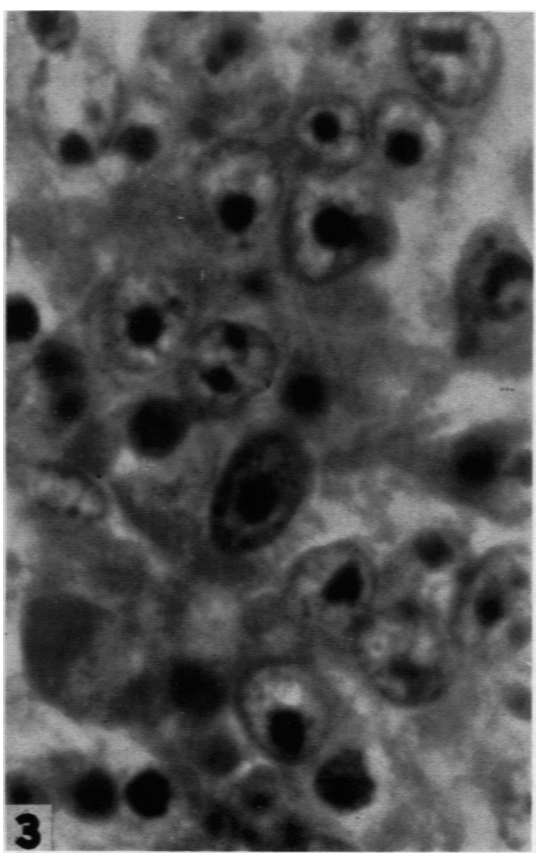
FIG. 1. (Lymph node). Stem cell lymphoma, syncytial type. The dark staining area in the left lower corner of the photomicrograph represents residual normal lymphocytes in the process of being displaced by invading tumor. The infiltrating syncytial mass produces the lighter staining region in which large, clear nuclei with prominent nucleoli may be seen. Cell boundaries cannot be distinguished. × 200.

FIG. 2. (Lymph node). Stem cell lymphoma in which the cells have become discrete and intercellular connections minimized. Nuclear characteristics are unchanged from those noted in the syncytial type. × 200.

FIG. 3. (Lymph node). Stem cell lymphoma, syncytial type. The nuclei are large, clear and contain prominent, densely staining nucleoli. All cytoplasmic substance is fused and there are no cell boundaries apparent. × 1000.




Gall and Mallory

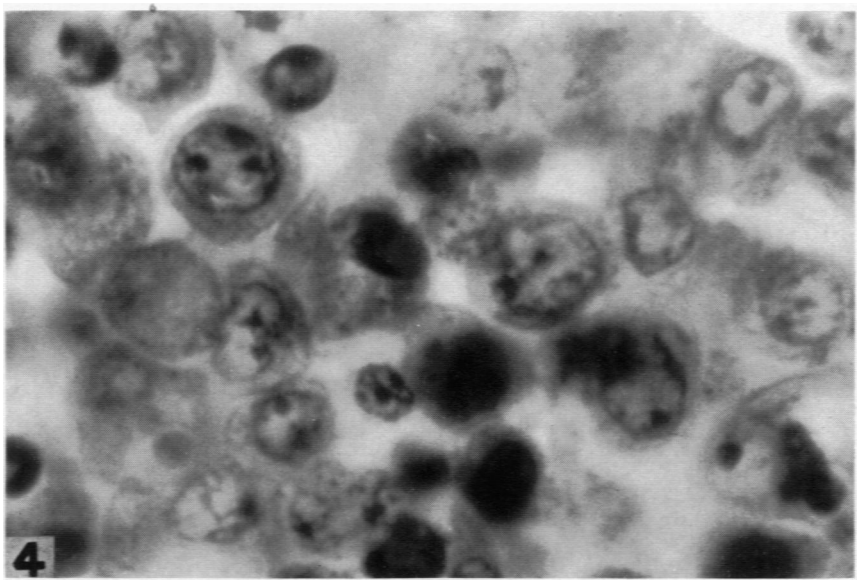
Malignant Lymphoma

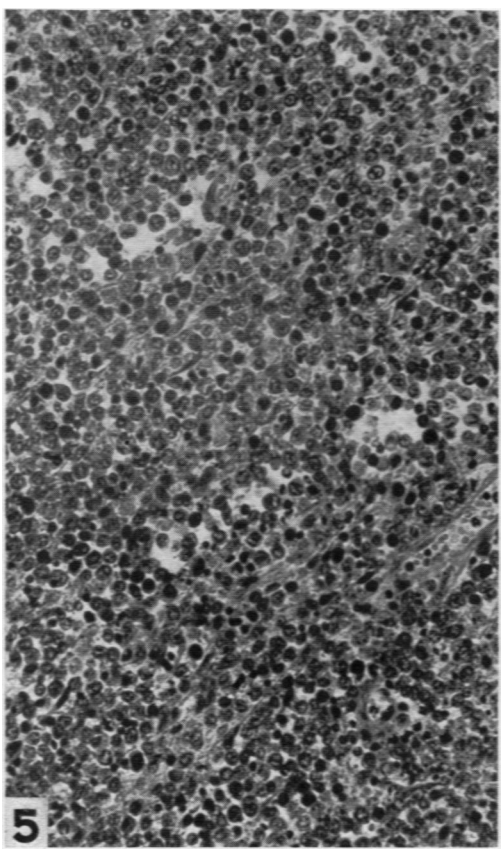
PLATE 63

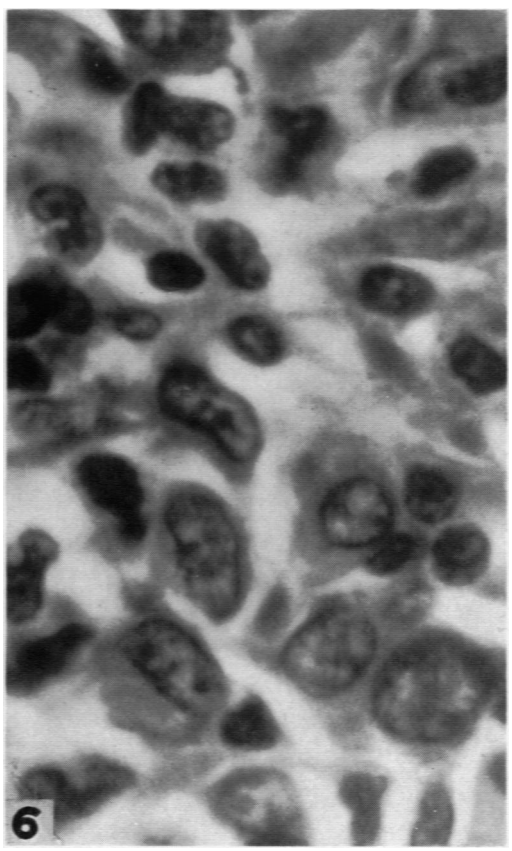
FIG. 4. (Lymph node). Stem cell lymphoma. Nuclear characteristics are essentially similar to those noted in Figure 3. Although intercellular connections may be seen, cellular identity is now evident. There are a few dark staining lymphocytes present in this section. × 1000.

FIG. 5. (Lymph node). Clasmatocytic lymphoma. Cells similar in size to those noted in stem cell lymphoma comprise this lesion. Cytoplasm is abundant, distinctly outlined, and nuclei exhibit a marked degree of variation in configuration. × 200.

FIG. 6. (Lymph node). Clasmatocytic lymphoma. Characteristic cells show an abundant, clearly delimited cytoplasm which occasionally contains small vacuoles. Nuclei are eccentric, contain a reticulated chromatin and are reniform in shape. A stem cell is present in the right lower corner and there are several lymphocytes scattered throughout the field. × 1000.




Gall and Mallory

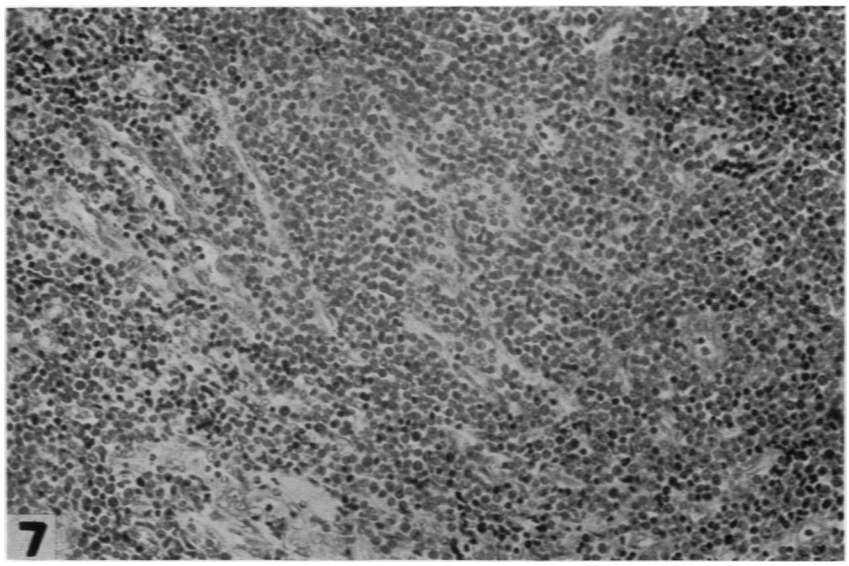
Malignant Lymphoma

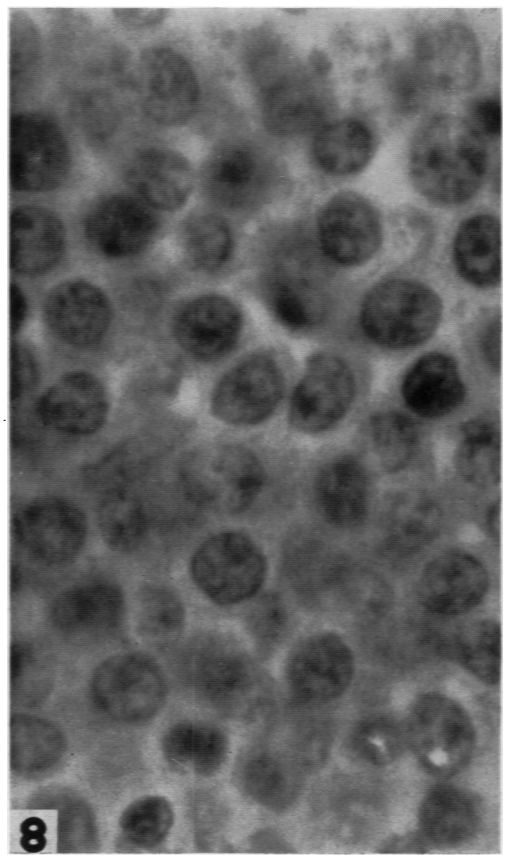
PLATE 64

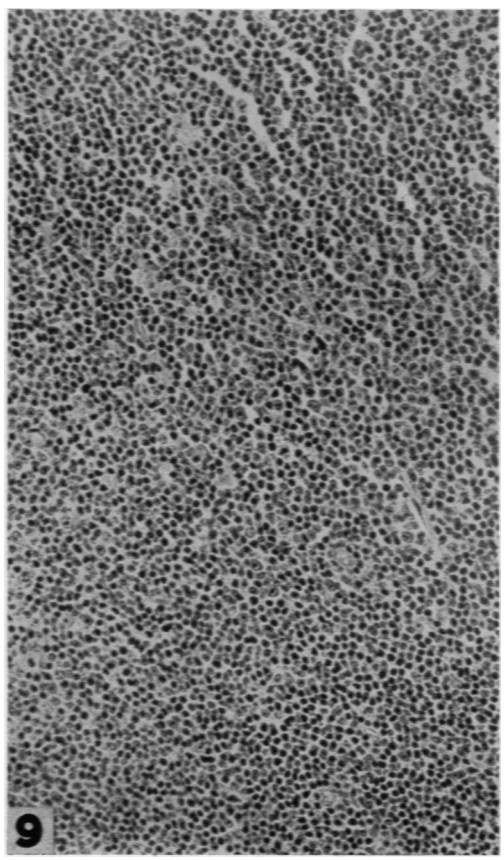
FIG. 7. (Lymph node). Lymphoblastic lymphoma with revision of nodal architecture by closely packed lymphoblasts. × 200.

FIG. 8. (Lymph node). Lymphoblastic lymphoma; predominant cells exhibit scanty cytoplasm with larger and paler nuclei than those observed in the lymphocytic type. Chromatin is less prominent and more diffusely distributed. × 1000.

FIG. 9. (Lymph node). Lymphocytic lymphoma with replacement of normal nodal structure by uniformly distributed, small lymphocytes. × 200.




Gall and Mallory

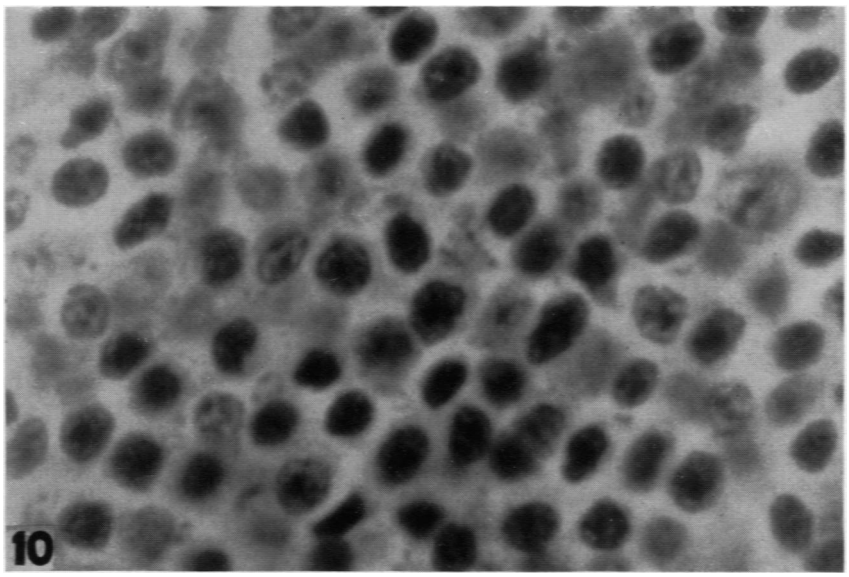
Malignant Lymphoma

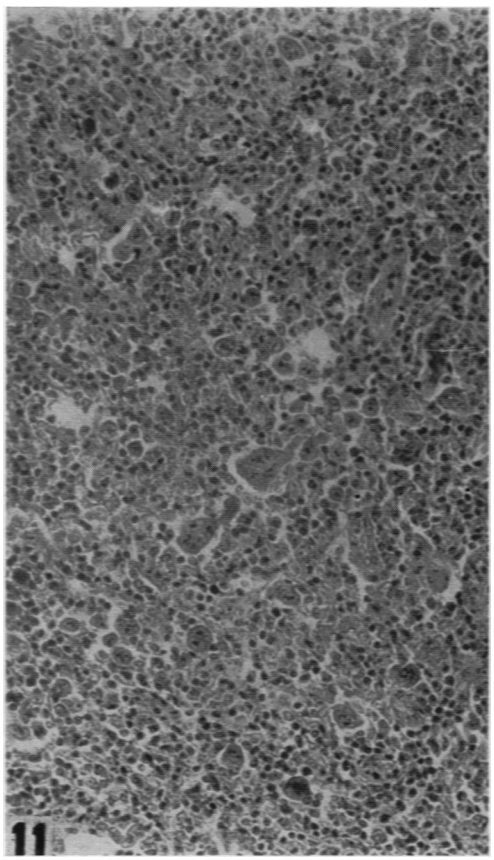
## PLATE 65

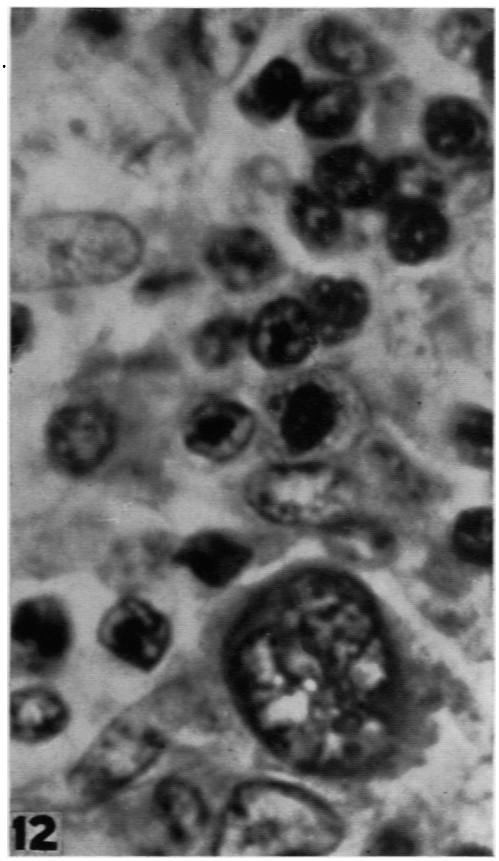
FIG. 10. (Lymph node). Lymphocytic lymphoma showing predominance of small lymphocytes with dark staining, heavily chromatinized nuclei. An occasional, large, pale nucleus of a less mature cell may be seen. × 1000.

FIG. 11. (Lymph node). Hodgkin's lymphoma. Characteristic multinucleated giant cells are obvious. There is also a marked degree of polycellularity. × 200.

FIG. 12. (Lymph node). Hodgkin's lymphoma. In the lower portion of the photomicrograph there is a Sternberg-Reed giant cell. Scattered throughout the area may be seen lymphocytes, monocytes, fibroblasts and an occasional granulocyte. × 1000.




Gall and Mallory

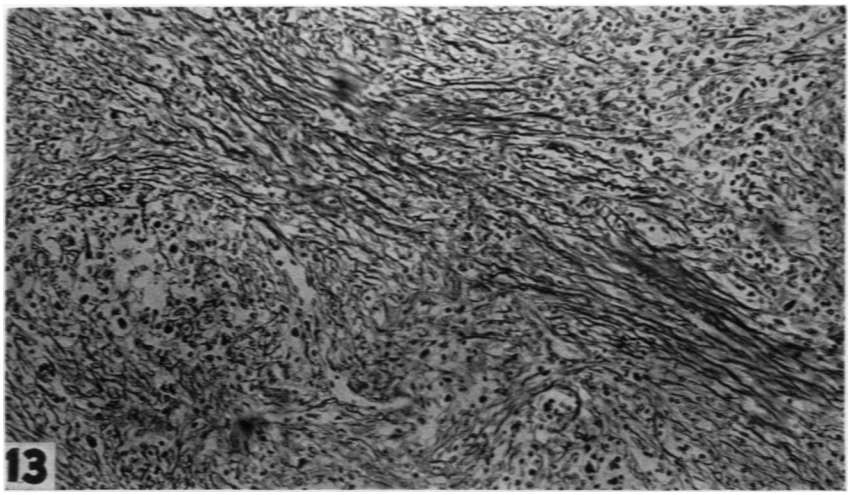
Malignant Lymphoma

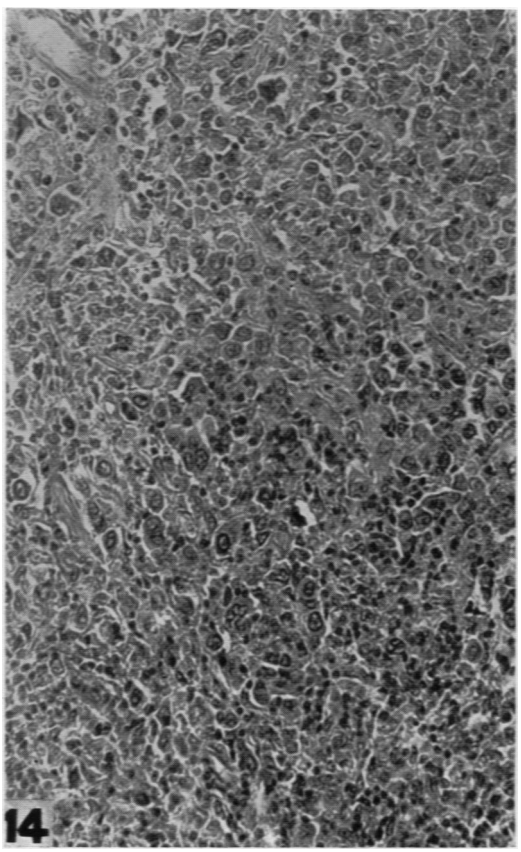
## PLATE 66

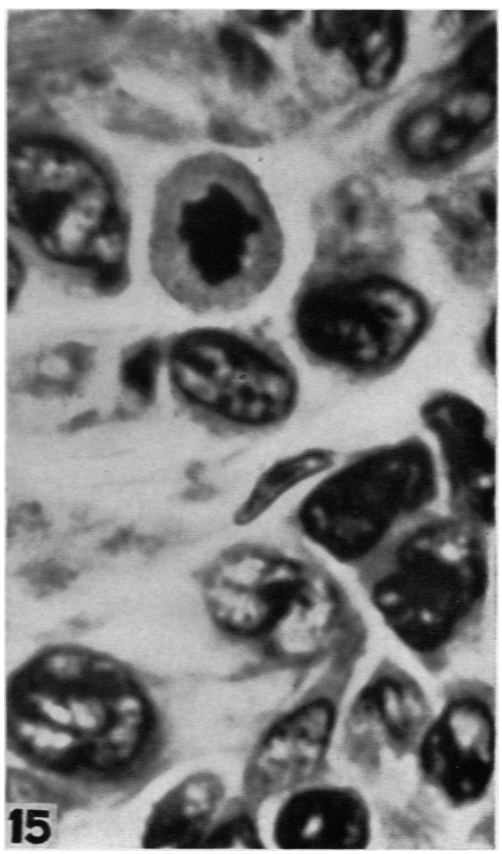
FIG. 13. (Lymph node). Hodgkin's lymphoma, scirrhous type. Broad strands of fibrous tissue infiltrate among the tumor cells, producing islet arrangement. × 150.

FIG. 14. (Lymph node). Hodgkin's sarcoma. The lesion consists almost wholly of Sternberg-Reed cells with a background of fibrous tissue. Relatively few mature cells are present. × 200.

FIG. 15. (Lymph node). Hodgkin's sarcoma. Giant cells with bizarre, irregular and multiple nuclei are apparent. The only other recognizable elements are fibroblasts. × 1000.




Gall and Mallory

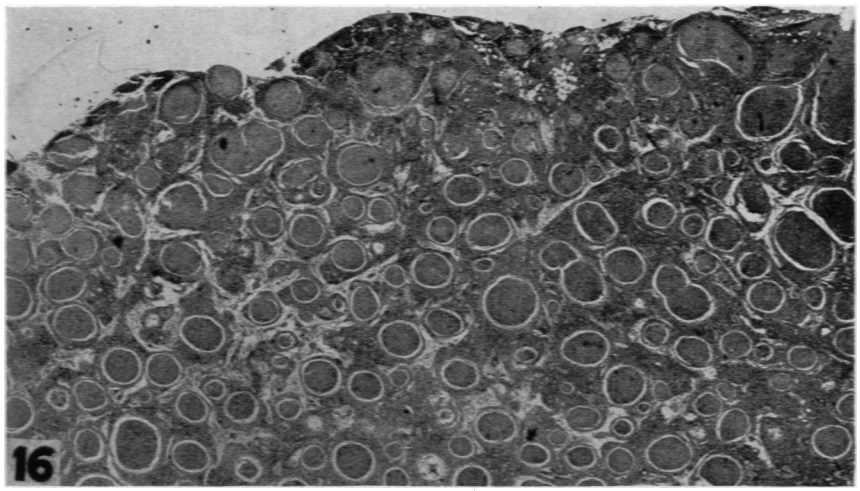
Malignant Lymphoma

PLATE 67

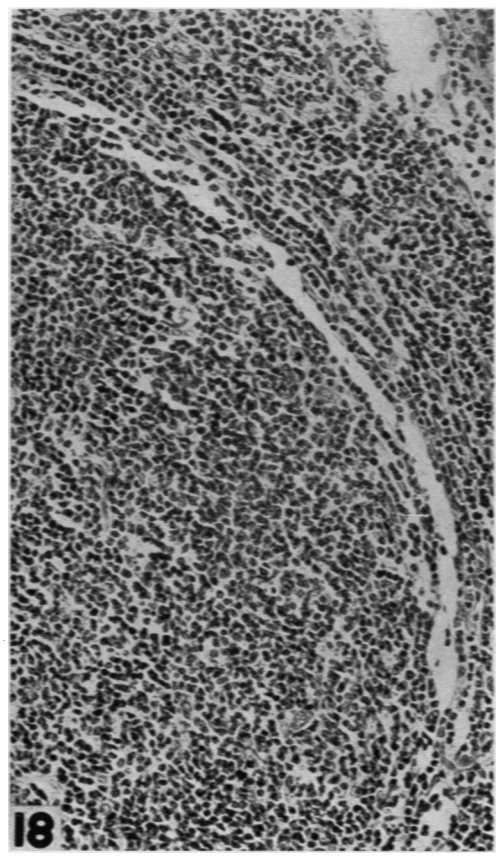
FIG. 16. (Lymph node). Follicular lymphoma. Normal architecture is revised by considerably increased numbers of follicles which vary considerably in size. Clear spaces surrounding each one represent the "cracking off" phenomenon described in the text. × 50.

FIG. 17. (Spleen). Follicular lymphoma. Follicles are enormous and extremely irregular in configuration. Fusion of adjacent follicles may be seen. × 50.

FIG. 18. (Lymph node). Follicular lymphoma. Similarity of cells (small lymphocytes) in the pulp and follicles may be seen. The "cracking off" phenomenon is evident. × 300.








Gall and Mallory

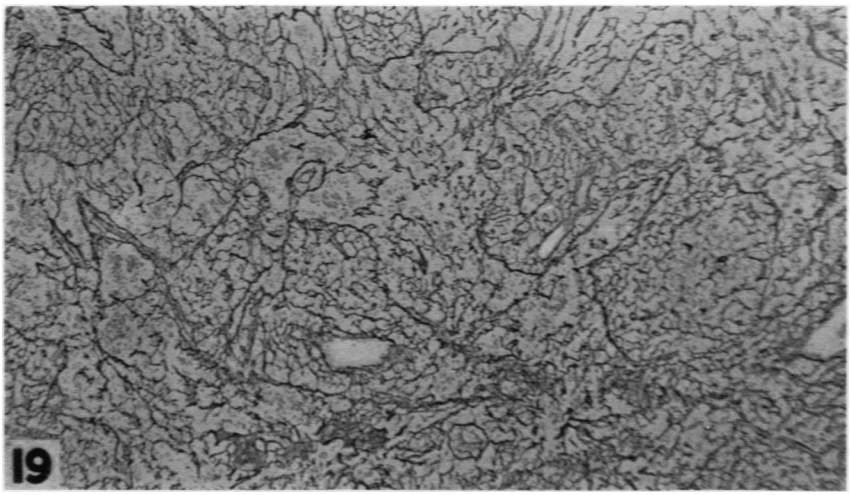
Malignant Lymphoma

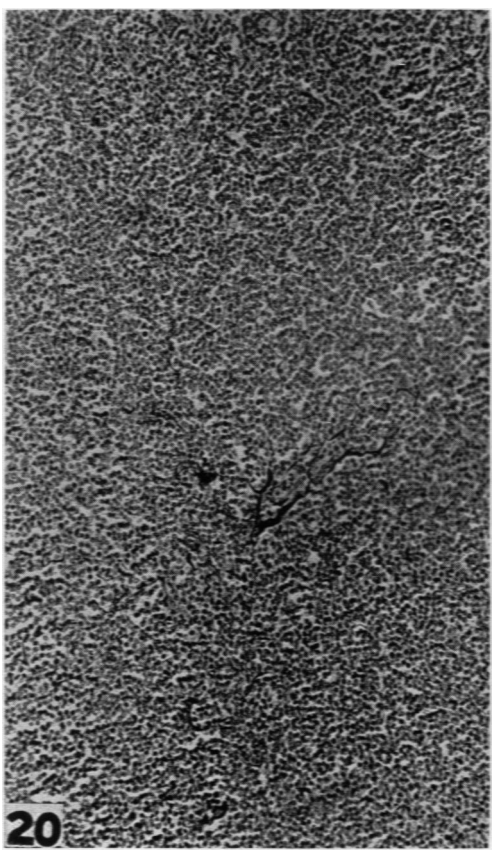
## PLATE 68

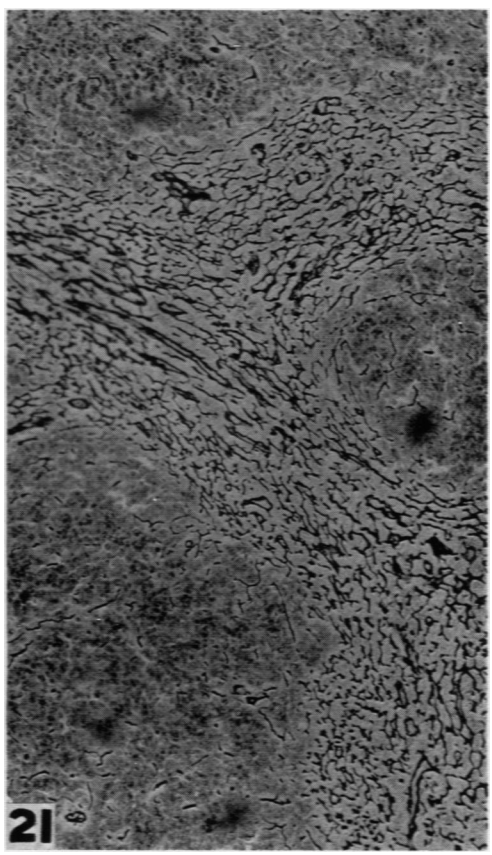
FIG. 19. Normal lymph node (Perdrau silver stain). The fine fibrillar framework is well shown and there is condensation at the edge of the sinuses. Although present in both follicles and sinuses, reticulum is scanty in these regions. × 200.

FIG. 20. Lymphocytic lymphoma (Perdrau silver stain). The normal meshwork has been replaced and only a few, fine argentophilic fibrils are seen. × 200.

FIG. 21. Follicular lymphoma (Perdrau silver stain). Stromal reticulum is obviously compressed and interfibrillar spaces narrowed and elongated. Sinuses are not seen. Reticulum content of follicles is remarkably scanty. × 200.




Gall and Mallory

Malignant Lymphoma