

The Pathology and Nomenclature of Hodgkin's Disease

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Summary

The diverse morphologic expressions of Hodgkin's disease have been reviewed and compared to the numerous histologic terms in the literature and the author's recently proposed histologic types. The relationship of the histologic findings to the clinical stages and survival has also been analyzed. The histologic expressions of the Hodgkin's disease process appear to be separable into the following 6 groups: (a) lymphocytic and/or histiocytic (L & H),¹ nodular; (b) lymphocytic and/or histiocytic (L & H), diffuse; (c) nodular sclerosis; (d) mixed; (e) diffuse fibrosis; and (f) reticular. The L & H types represent essentially a predominant lymphocytic proliferation with histiocytes, while diffuse fibrosis and reticular are associated with lymphocytic depletion. Nodular sclerosis has a remarkably high incidence of mediastinal involvement when initially observed, exceeding all other types combined, and appears to represent a regional expression of Hodgkin's disease in the mediastinum. The mixed type appears to reflect a changing disease state. These histologic types, with the exception of nodular sclerosis, represent differences in the frequency of lymphocytes and Reed-Sternberg cells and serve to emphasize their inverse relationship. The histologic findings are regarded as reflections of differences in the state of the host responsiveness and are believed to be related to the recently described immunologic defect. The demonstrated relationship between these histologic types, and the clinical stages and survival, provides further support for the importance of host factors and also presents an effective basis for prognostication. In addition a new histologic type, nodular sclerosis, has emerged as the most important prognostic type when observed in clinical Stage I.

The majority of the terms proposed in the literature for the histologic types of Hodgkin's disease represent designations for the lesion with a predominantly lymphocytic proliferation of either nodular or diffuse type. This lesion is of prognostic significance, but it includes only a small proportion of the prolonged survivors. The classical histologic types of Jackson and Parker are of limited effectiveness in prognosis since the heterogeneous granuloma group includes 80-90% of reported series, contains 79% of the survivors at 15 years in our study, and yet has a relatively short median survival in our comparison study.

Introduction

The unique diversity of the morphologic features in Hodgkin's disease and the variable rates of progression of the disease have evoked an almost unparalleled variety of terms in an attempt to

relate the histologic features to survival and to depict the as yet unsettled nature of the basic process. Over 50 terms for the disease were collected from the literature by Wallhauser (35) from the 1st century after Thomas Hodgkin's description. This profusion of names for the disease primarily reflects the different concepts of the disease particularly in relationship to etiology. The noncommittal eponymic designation has gained general acceptance in the United States at the present time, even though the process is generally regarded as a neoplasm and included with the malignant lymphomas. In the past 4 decades numerous terms have been proposed for the histologic types of Hodgkin's disease as a result of the attempts to relate the histologic changes to the extremely variable rates of progression of the disease and to provide a prognostic basis for the recognition of potential prolonged survivors.

Interest in the importance of the histologic findings in prognosis was initiated by Rosenthal (31) when he demonstrated the relationship between lymphocytic proliferation and slowly progressive disease and stressed the importance of the frequency of lymphocytes in prognosis. Earlier Ewing (7) proposed the term *sarcoma* for a pleomorphic neoplastic proliferation of Reed-Sternberg cells. The classical histologic types of Jackson and Parker (11-15), namely paraganuloma, granuloma, and sarcoma, are related to many of the findings of Ewing (7) and Rosenthal (31). Subsequently the prognostic importance of the predominant lymphocytic lesions has been supported by the studies of Harrison (9), Lumb (22), Smetana and Cohen (33), Wright (37, 38), and Dawson and Harrison (6), although a variety of terms have been suggested for the association of lymphocytic proliferation with prolonged survival. The distinctive character of the predominant lymphocytic proliferation and its contrast to the granuloma type of Jackson and Parker stimulated Smetana and Cohen (33) to question its relationship to Hodgkin's disease. The term *reticular lymphoma* was proposed by Lumb (22) for this group to emphasize the distinctive histologic character, and in recognition of its neoplastic potentiality. The nodular character of the lymphocytic proliferation was initially recognized by Rappaport *et al.* (28), in their classical re-evaluation of follicular lymphoma. They included this nodular proliferation in follicular lymphoma as Type V (follicular lymphoma, Hodgkin's type), although it was acknowledged that this type more appropriately might be included with the paraganuloma group rather than with the general group of malignant lymphomas. Neither Croizat *et al.* (4) nor Winterhalter (36) found definite evidence of a relationship between the course of the disease and the histologic features.

The importance of clinical staging in Hodgkin's disease as initially defined by Peters (26) and later refined by Peters and Middlemiss (27) emphasized the prognostic importance of

¹ The groups designated lymphocytic and/or histiocytic will be referred to as "L & H" hereafter with the modification of the nodular or diffuse type.

localized manifestations in Hodgkin's disease and provided the basis for the recent proposal of the possibility of cure in Hodgkin's disease. The significance of the histologic features in untreated Hodgkin's disease in relationship to the clinical stages and survival was re-evaluated in the authors' recent study (R. J. Lukes, J. J. Butler, and E. Hicks, in preparation; Refs. 18, 20), of the World War II cases of Hodgkin's disease in a 15- to 18-year follow-up study. The results of this study reemphasized the importance of the lymphocyte in Hodgkin's disease and its inverse relationship to Reed-Sternberg cells, and demonstrated a definite relationship between the histologic features and the clinical stages existing at the time of biopsy. A new histologic type, nodular sclerosis, emerged as an important prognostic group and the regional expression of Hodgkin's disease in the anterior superior mediastinum. These observations on the nodular sclerosing type have been supported by Hanson (8). In the recent historic meeting on Hodgkin's disease in Paris (21), the re-evaluation by Lukes, Nezelof and Gompel (in preparation) of the pretherapy biopsies from the prolonged survival cases from many of the major radiotherapy groups provided evidence that the nodular sclerosing type was of major prognostic significance.

The purpose of this presentation will be to consider in detail the numerous histologic expressions of Hodgkin's disease grouped according to the histologic types reported by the authors (18-20) and relate them to the variety of histologic types that appear in the literature. The possible relationship of the histologic findings to the clinical stages, survival, and the recently described immunologic defect in Hodgkin's disease will be presented.

Morphology

The diversity of the morphologic findings in Hodgkin's disease is well known and the association of abnormal reticulum cell proliferation of the Reed-Sternberg cell type with a variable inflammatory type cellular proliferation represents a unique histologic process. The nature of this process has puzzled pathologists since the initial histologic description of Greenfield. Investigators in the past few decades have been primarily concerned with the evaluation of the histologic findings in prolonged survival cases for prognostic purposes, and little attention has been given to the study of the significance of the numerous variations in the histologic findings, although the process is generally regarded as neoplastic in the United States. In this consideration of the morphologic findings we will be concerned with the variation in the reticulum cell proliferation, particularly the Reed-Sternberg cell, the numerous histologic types, and the most appropriate terminology proposed for these variants. An attempt will be made to relate the variations in the histologic process to the gross findings, the clinical stages of the disease, the evolution of the histologic process, and the rate of progression of the disease in terms of median survival.

Classification of Hodgkin's disease as a neoplasm is based on the generally progressive character of the process, the occasional pleomorphic appearance of the Reed-Sternberg cell, and the tumor-like disseminated masses observed at autopsy that may exhibit infiltrative features. The indistinguishable appearance at times of the histologic findings of the fulminating terminal phase of Hodgkin's disease with those of histiocytic lymphoma (reticulum cell sarcoma) has been used as further support for the

neoplastic nature of the process. The critical point appears to revolve about the debatable issue whether the Reed-Sternberg cell is a neoplastic cell or simply a modified reticulum cell that at times may become pleomorphic—at which time it is definitely neoplastic. The common occurrence of numerous abnormal reticulum cells, without the distinctive features of classical Reed-Sternberg cells, that appear to represent intermediate or partially developed Reed-Sternberg cells provides support for the latter possibility. It has not been established whether the process, if neoplastic, involves all the cellular components and is a mixed lymphoma as proposed by Lumb (22), Berman (2), and others, or the Reed-Sternberg cell is the only neoplastic component—if indeed it is a neoplastic cell—and the associated histologic components are inflammatory reactions. Definite evidence of neoplasia is observed in a small proportion of cases at biopsy with fulminating disease and a limited number of cases at autopsy where Reed-Sternberg cells predominate and are distinctly pleomorphic. Biopsy specimens in the majority of cases exhibit morphologic expressions of an inflammatory process associated with an increase in the frequency of the Reed-Sternberg cells and a decrease in lymphocytes and other cellular elements with progressive disease. The change in character of the Reed-Sternberg cells with the development of distinctive pleomorphic features provides a basis for suggesting that the evolution of the Hodgkin's disease process may represent the induction of malignant neoplasia. In this situation the cellular and connective tissue components associated with the Reed-Sternberg cells would represent expressions of the host's attempt to counteract the induction of neoplasia. This consideration fits well with the associated variable cellular proliferation and the inverse relationship between lymphocytes and Reed-Sternberg cells. The possibility of neoplastic induction in Hodgkin's disease is unanswerable at the present time, but requires thorough consideration and investigation.

The reticulum cell proliferation in Hodgkin's disease involves not only the abnormal reticulum cell of the Reed-Sternberg cell type and its variants, but also a reactive histiocyte that is possibly related to the formation of fibrillar reticulum, the fibroblastic component and eventually fibrous connective tissue. A variety of Reed-Sternberg cells usually can be found in an individual biopsy or autopsy specimen. The frequency and character of Reed-Sternberg cells in our experience appears to be related in some degree to the type of associated cellular proliferation. Only a few variations of Reed-Sternberg cells, however, can be regarded as diagnostically reliable, since benign proliferation of reticulum cells in reactive processes, especially in viral infections, may exhibit large nucleoli and vesicular nuclei, 2 features often associated with Reed-Sternberg cells. Fortunately multinucleation does not appear to be a feature of the reticulum cell reaction in viral infections, and provides a basis for their differentiation. The 2 most distinctive and reliable features in the identification of Reed-Sternberg cells are the huge inclusion-like nucleolus and polyploidism, the occurrence of multiple divisions of the nuclei without cytoplasmic division. A few of the more common variations in Reed-Sternberg cells are presented in Fig. 1. Mononuclear forms are usually found in typical lesions of Hodgkin's disease (Fig. 1a) and also may exhibit the huge inclusion-like nucleolus and a vesicular nucleus. Although the mononuclear type appears to represent a form of the Reed-

Sternberg cell, it is not considered to be reliable diagnostically in our experience since it may be confused with the reticulum cells of viral reactions. Lobated and binucleated forms (Fig. 1b) represent manifestations of polyploidism, one of the important distinctive features of Reed-Sternberg cells. A peculiar clear zone about the huge nucleolus is another unusual feature of these cells and presents the nucleus with a vesicular appearance, but it is uncertain whether or not this feature is artifactual. The nuclear chromatin may be delicate and lacy, but it is usually observed to be compressed at the periphery, at times as a thickened nuclear membrane with a clear halo-like space about the nucleolus. The nucleolus typically is large, almost spherical in appearance, and resembles an inclusion body with a smooth margin. In staining character it varies from eosinophilic to amphophilic, but is of uniform intensity. The cytoplasm is rather inconsistent, both in quantity and staining, although it is most frequently observed to be abundant and lightly eosinophilic to amphophilic. The pleomorphic Reed-Sternberg cell that is regarded as sarcomatous (Fig. 18) is an unusually large cell with a tendency to extraordinary lobular nuclear variations and multinucleation that appear to represent an extreme degree of polyploidism.

Several types of abnormal reticulum cells that are probably related to Reed-Sternberg cells are observed in association with 2 of the histologic types that will be described in a subsequent section. With lymphocytic proliferation where classical Reed-Sternberg cells are infrequent and difficult to find, numerous peculiar and abnormal reticulum cells are found with folded overlapping lobes, with delicate lacy chromatin and small nucleoli. This type appears to represent a partially modified reticulum cell, and possesses the polyploidism, but not the huge nucleoli, of Reed-Sternberg cells. In the nodular sclerosis type, an unusually large abnormal reticulum cell is found, often in great numbers. These cells have abundant pale eosinophilic cytoplasm, at times with an area of condensed deeply eosinophilic cytoplasm adjacent to the nucleus that has a tendency to be excessively multilobated with many small individual nuclei. Although these distinctive abnormal reticulum cells of nodular sclerosis (Fig. 13) are generally numerous and exhibit polyploidism, characteristic diagnostic Reed-Sternberg cells with huge nucleoli, vesicular nuclei, and amphophilic cytoplasm are often difficult to find.

In considering the variations of Reed-Sternberg cells and possibly related abnormal reticulum cells it seems that the number and type of Reed-Sternberg cells appear indirectly related to the intensity of lymphocytic proliferation. Where lymphocytic proliferation is prominent, the number of characteristic Reed-Sternberg cells is rare, although the peculiar polyploid reticulum cells with delicate, lacy chromatin may be numerous. Where lymphocytes appear to be depleted, typical Reed-Sternberg cells with characteristic polyploid vesicular nuclei and huge inclusion-like nucleoli are numerous, and at times the pleomorphic type may be evident. The distinctive abnormal reticulum cells associated with lymphocytic proliferation (L & H types) and nodular sclerosis appear to represent modified reticulum cells related to Reed-Sternberg cells, but they are not regarded, however, as diagnostically reliable Reed-Sternberg cells.

Histologic Types

Numerous histologic types have been described in the past 3 decades primarily in an attempt to account for the cases with slowly progressive disease or prolonged survival with asymptomatic disease. The terms commonly employed for the histologic types resulting from these studies are listed in Table 1 in relationship to the predominant histologic findings. In our recent study (18), in which the significance of the histologic features and clinical stages in Hodgkin's disease was evaluated, it was apparent that there were 6 predominant histologic expressions of untreated Hodgkin's disease for which we proposed the following terms: (a) lymphocytic and/or histiocytic (L & H), diffuse; (b) lymphocytic and/or histiocytic (L & H), nodular; (c) mixed; (d) nodular sclerosis; (e) diffuse fibrosis; (f) reticular. In the following discussion the more commonly employed types described in the literature will be analyzed in comparison with the 6 predominant histologic expressions of Hodgkin's disease.

Lymphocytic and/or Histiocytic Proliferation

There is general agreement on the existence of a histologic lesion composed predominantly of mature lymphocytes. Although the term *paragranuloma* is commonly used in the United States, numerous terms have been proposed. In addition, lymphocytic proliferation in Hodgkin's disease occurs usually in association with varying numbers of reactive histiocytes. These cells have abundant, pale, eosinophilic cytoplasm and medium size nuclei with uniformly distributed delicate chromatin (Fig. 7). They are readily differentiated from the variants of the Reed-Sternberg cell (Fig. 1). At times a small number of multinucleated histiocytes are found. The histiocytic component varies widely from scattered individual histiocytes to a predominance of histiocytes with only a small component of residual lymphocytes. The lesion composed predominantly of lymphocytes has been the subject of numerous reports, while the lesion where the histiocytic component is dominant has been overlooked and apparently included within the granuloma group. The term lymphocytic and/or histiocytic (L & H) was considered most appropriate because of the almost constant occurrence of histiocytes in lymphocytic proliferations, the frequency of lesions with a predominance of histiocytes, and the wide spectrum of lymphocytic or histiocytic proliferation observed in this group. The term lymphocytic and/or histiocytic (L & H), although somewhat cumbersome, serves to emphasize the frequent, prominent histiocytic component and avoids classification of the predominantly histiocytic lesions as the granuloma type according to the criteria of Jackson and Parker (11). It is interesting to note that, in a comparison evaluation, over 50% of the L & H cases of our study (18, 20) fulfilled the criteria for the granuloma type on the basis of the frequency of histiocytes when classified according to the criteria of Jackson and Parker (11). With this spectrum of lymphocytic and histiocytic proliferation, characteristic Reed-Sternberg cells are rare, although the peculiar abnormal polyploid reticulum cells previously discussed with Reed-Sternberg cells may be relatively numerous. Eosinophils, plasma cells, and mature neutrophils are uncommon or absent. There is essentially no fibrosis.

TABLE 1
RELATIONSHIP OF PREDOMINANT HISTOLOGIC FEATURES TO HISTOLOGIC TYPES IN THE LITERATURE

Histologic types by predominant histologic features (Refs. 18, 20)	Histologic types in literature	Author and year
Lymphocytic and/or histiocytic (L & H) (lymphocytes predominating)		
a. Diffuse	L & R Early Hodgkin's Paragranuloma Lymphoreticular medullary reticulosis Benign Hodgkin's Reticular lymphoma Indolent Hodgkin's Follicular lymphoma, Hodgkin's type	Rosenthal, 1936 (31) Jackson, 1937 (14) Jackson and Parker, 1944 (11) Robb-Smith, 1947 (30) Harrison, 1952 (9) Lumb, 1954 (22) Symmers, 1958 (34) Rappaport <i>et al.</i> , 1956 (28)
b. Nodular		
Lymphocytic and/or histiocytic (L & H) (histiocytes predominating)		
Nodular or diffuse	Granuloma	Jackson and Parker, 1944 (11)
Mixed	Granuloma Fibromyeloid medullary reticulosis	Jackson and Parker, 1944 (11) Robb-Smith, 1947 (30)
Nodular sclerosis (collagen formation)		
Diffuse fibrosis (disorderly reticulum)	F & R Granuloma Granuloma with sclerosis	Rosenthal, 1936 (31) Jackson and Parker, 1944 (11) Smetana and Cohen, 1956 (33)
Reticular		
a. Reed-Sternberg cells (predominating)	R & L Granuloma Reticulo-Hodgkin's	Rosenthal, 1936 (31) Jackson and Parker, 1947 (11) Lennert, 1957 ^a
b. Reed-Sternberg cells (pleomorphic)	Sarcoma Sarcoma	Ewing, 1928 (7) Jackson, 1937 (14)

^a As quoted by Offerhaus (25).

Lymphocytic and/or Histiocytic (L & H) Type, Diffuse

A lymph node exhibiting lymphocytic and histiocytic proliferation is usually a single, enlarged node that may reach considerable size and range from 3 to 5 cm in diameter upon biopsy. In the diffuse L & H type the cellular proliferation extends uniformly throughout the lymph node, with compression of the sinusoids and absence of lymphatic follicles (Fig. 2). Occasionally, a small portion of compressed, distorted, uninvolved lymph node cortex remains in the periphery. The diffuse type frequently exhibits a prominent histiocytic component (Fig. 6), while the nodular type is generally predominantly lymphocytic. When the lymphocytic component predominates in the diffuse type (Fig. 5), the cellular proliferation is composed of mature lymphocytes and closely resembles a well-differentiated lymphocytic lymphoma, the tissue counterpart of chronic lymphocytic leukemia. The 2 processes are differentiated histologically on the basis of an essentially single cell type of proliferation, the small lymphocyte, in lymphocytic lymphoma, with only a rare reticulum cell or other cellular elements. In addition this lymphoma occurs predominantly in patients over 55 years of age and rarely under 45 years. The diffuse L & H type by contrast usually has a histiocytic component and numerous abnormal reticulum cells related to Reed-Sternberg cells and usually occurs in younger patients. The abnormal reticulum cell component that appears to be related to Reed-Sternberg cells is often relatively prominent

and may represent as much as 10% of the cell population. It is composed primarily of peculiar large cells with folded, twisted, lobated pale nuclei that have fine, lacy, delicate chromatin and small nucleoli. Characteristic Reed-Sternberg cells with large nucleoli, however, are extremely infrequent, or rare, and it may be necessary to search a number of sections to find typical Reed-Sternberg cells on which to establish a reliable diagnosis. Inspection of Table 1 indicates that this group has aroused most of the attention of pathologists as a result of its distinctive histologic character and the association of lymphocyte proliferation with prolonged survival. It should be emphasized that the terms listed refer to a predominant lymphocytic proliferation with a small component of histiocytes. Eosinophils and plasma cells were infrequent or absent. There was little or no fibrosis and necrosis was absent. Almost 30 years ago, Rosenthal recognized the prognostic significance of the predominant lymphocytic proliferation and the associated relative infrequency of Reed-Sternberg cells, for which the term L & R (lymphocytic and reticulum cell) was proposed. Subsequently, Jackson (14) suggested that this lesion might represent early Hodgkin's disease, but later Jackson and Parker (11) indicated that this was an unfortunate choice of terms and recommended *paragranuloma* as a more appropriate designation to indicate a close relationship to Hodgkin's granuloma. The term *lymphoreticular medullary reticulosis* was proposed several years later by Robb-Smith (30),

apparently for the same lesion. The high incidence of survivors at 5 and 10 years and good prognosis of this lesion prompted the proposal of the term *benign Hodgkin's* by Harrison (9) in 1951, in preference to the term *paragranuloma*. It evolved from a retrospective study of cases with prolonged survival in their group. Histologically the lesion was composed predominantly of small lymphocytes with a prominent component of abnormal reticulum cells. Subdivision of the cellular proliferation by either collagen bands or reticulum fibers into cellular nodules was a common feature. It appears from their photomicrographs and description that the majority of their cases may represent the cellular phase of the nodular sclerosing type with limited collagen formation. This lesion will be considered in a subsequent section. The study was subsequently enlarged, again under the term *benign Hodgkin's disease* by Dawson and Harrison (6). A similar cellular proliferation was observed also in nodular distribution in this series, in approximately $\frac{2}{3}$ of their cases in association with compression of the reticulum fibers about the periphery of the nodules. The resemblance of the nodular proliferation to the type of follicular lymphoma described by Rappaport *et al.* (28) was noted. The term *reticular lymphoma* was urged by Lumb (22) for the lesion he regarded as identical to paragranuloma in an attempt to emphasize its distinctive character and definite relationship to Hodgkin's disease. Definite doubt over the relationship of paragranuloma to Hodgkin's disease was expressed by Smetana and Cohen (33), although the usual predominant lymphocytic lesion with Reed-Sternberg cells was described in their cases of paragranuloma. Evidence that Hodgkin's disease with a predominance of lymphocytes has progressed to the disseminated form of Hodgkin's disease recently has been presented by a number of authors, including Wright (37, 38), Lumb (22, 23) and Dawson and Harrison (6). Symmers (34) prefers the term *indolent* to emphasize the need for caution in prognosis, although he acknowledges its identity with paragranuloma.

Lymphocytic and/or Histiocytic (L & H), Nodular

In this process the cellular proliferation is aggregated in a vaguely nodular fashion (Fig. 3) and the abnormal polyploid reticulum cells and histiocytes are often concentrated in the central portion of the nodules, though usually not in cohesive clusters. The proliferation is usually overwhelmingly lymphocytic, involving both nodules and internodular tissue. Histiocytes have predominated in the nodular type on only a few occasions in our series. The nodules are generally large, closely situated, and often involve only a portion of the lymph node. The remainder of the node in these instances is involved diffusely by a cellular proliferation similar to that within the nodules. The nodular character of the lesion is clearly demonstrated in reticulum stained sections where the reticulum fibers are compressed to the periphery about the nodules (Fig. 4). Typical Reed-Sternberg cells are rare, although abnormal polyploid reticulum cells with small nucleoli may be numerous. The nodular character of this type of Hodgkin's disease was initially demonstrated by Rappaport *et al.* (28) under the term *follicular lymphoma, Type V (Hodgkin's type)*, in their classical study on the re-evaluation of follicular lymphoma. It was indicated that the lesion would have been regarded as a paragranuloma if it had lacked nodularity. It was suggested furthermore that paragranuloma might

TABLE 2
COMPARISON OF HISTOLOGIC CLASSIFICATIONS

Jackson and Parker (11)	Lukes <i>et al.</i> (18, 20)
Paragranuloma	Lymphocytic and/or histiocytic ^a a. Diffuse b. Nodular
	Nodular
	Mixed
Granuloma	Diffuse fibrosis
Sarcoma	Reticular

^a L & H types may have predominance of either lymphocytes or histiocytes.

be a more ideal designation than to include the lesion with the general group of lymphomas. Dawson and Harrison (6) and Wright (38) have emphasized the resemblance of many of their cases under the term *benign Hodgkin's* to the group described by Rappaport *et al.* (28).

Mixed Type

This histologic type is of heterogeneous composition and occupies a somewhat intermediate position between the predominantly lymphocytic proliferation at 1 extreme and lymphocytic depletion with diffuse fibrosis and reticular types at the other. It is composed of histiocytes, mature neutrophils, eosinophils, plasma cells, histiocytes, and lymphocytes in varying proportions, usually with a slight to moderate degree of disorderly fibrosis, but without collagen formation (Fig. 8). Reed-Sternberg cells and related abnormal reticulum cells are often rather numerous and prominent. Focal necrosis may be present, but is usually not marked. The process generally extends throughout the entire lymph node and is associated with obliteration of the lymphatic sinusoids and follicles. Focal involvement by a similar process may extend through portions of a lymph node or be limited to small interfollicular areas, apparently as evidence of early involvement of the node. Delineation of this type from the L & H types at 1 extreme and the lymphocytic depletion types at the other may be somewhat difficult at times. Differentiation from nodular sclerosis is readily accomplished and appears to depend primarily on the frequency and character of the Reed-Sternberg cells and the degree and character of fibrosis. The mixed type most closely approximates the classical concept of granuloma as presented by Jackson and Parker (11). Granuloma, however, unfortunately incorporates a variety of histologic expressions, including the prominent histiocytic proliferation, the advanced fibrosis types, and the lesions composed predominantly of Reed-Sternberg cells where pleomorphism is absent. The granuloma group includes almost the whole spectrum of cellular proliferations (Table 2) with the exception of the extremes where either lymphocytes predominate or Reed-Sternberg cells are numerous and pleomorphic. Fibromyeloid medullary reticulosis, the term of Robb-Smith (30), apparently represents a group comparable to the granuloma of Jackson and Parker (11).

Advanced Fibrosis

Advanced fibrosis in Hodgkin's disease appears to involve 2 distinctive types. The 1st, nodular sclerosis, exhibits orderly bands of dense collagenous connective tissue that has a definite tendency to subdivide lymphoid tissue into isolated cellular nodules. The 2nd, diffuse fibrosis, is characterized by a disorganized type of fibrosis of variable character which may be composed of cellular fibroblastic connective tissue or compact hypocellular fibrillar connective tissue associated with cellular depletion, particularly of lymphocytes. Both types are generally included together in the granuloma group. Smetana and Cohen (33) referred to the lesions that exhibited an advanced degree of fibrosis as granuloma with sclerosis, but did not distinguish between the lesions of nodular sclerosis and diffuse fibrosis.

Nodular Sclerosis

This histologic type is characterized by orderly bands of interconnecting collagenous connective tissue that subdivides distinctively abnormal lymphoid tissue, partially or entirely, into isolated cellular nodules (Fig. 9). The degree of collagen formation and the character of the cellular proliferation vary widely, at times even within the same specimen. The entire lymph node or mass on occasion may undergo spontaneous sclerosis with residual evidence of nodularity still apparent. The birefringent character of the connective tissue readily permits its identification as collagen (Fig. 10). The process at times may be predominantly cellular, apparently representing a cellular phase, and the formation of collagen bands and isolation of cellular nodules may be limited to a small portion of the specimen. The cellular proliferation in nodular sclerosis, although varying widely, is distinctive and exhibits similar variations both in the nodules and the abnormal lymphoid tissue not subdivided by collagen (Fig. 11, 12). The distinctive feature of the cellular proliferation in nodular sclerosis is the unusually large variant of the Reed-Sternberg cell which has abundant pale eosinophilic cytoplasm with well-defined cellular borders that present the appearance of a Reed-Sternberg cell situated in a lacuna-like space (Fig. 13). These cells have prominently lobated nuclei, often with numerous lobes, delicate lacy nuclear chromatin and small to medium size nucleoli. Huge nucleoli, characteristic of diagnostic Reed-Sternberg cells are infrequent and often difficult to find. The distinctive features of the Reed-Sternberg cells of nodular sclerosis are the abundant pale eosinophilic cytoplasm, the well-defined cellular borders that present a lacuna-like appearance, the unusually delicate nuclear chromatin with small nucleoli and the unusual degree of hyperlobation. For a diagnosis of Hodgkin's disease, nodular sclerosing type, binucleated or multinucleated cells with large or huge nucleoli (Fig. 1) are still required. The cellular proliferation accompanying the unusual Reed-Sternberg cells, both within the nodules and in the nonnodular tissue may be predominantly lymphocytic, or of mixed composition with numerous eosinophils or mature granulocytes or both. At times Reed-Sternberg cells dominate the proliferation and often in association with focal necrosis. There is an apparent tendency of the isolated cellular nodules to undergo obliterative fibrosis. The initial phase of this process is the appearance of numerous mature granulocytes associated with the loss of lymphocytes. Next, numerous small vessels extend from the periphery of the

nodule from the circumscribing collagen bands followed by the formation of cellular connective tissue and finally collagen.

Diffuse Fibrosis

This type appears to represent primarily a histologic manifestation of cellular depletion in Hodgkin's disease involving all cell types with the exception of the Reed-Sternberg cell and specifically involves the lymphocytes. Diffuse fibrosis is the common terminal histologic expression of untreated Hodgkin's disease and is associated with variable numbers of Reed-Sternberg cells and focal necrosis. It constitutes the typical findings noted at autopsy. Although therapy undoubtedly contributes to the cellular depletion and the fibrosis observed at autopsy, a similar lesion frequently is observed in biopsies, particularly from patients in untreated, febrile, toxic Stage III disease. The fibrosis is somewhat variable in appearance, disorderly in reticulum fiber distribution, and nonbirefringent in character. It is generally composed of compact, amorphous, proteinaceous-appearing, hypocellular material that has a fibrillar character at times and in general bears a resemblance to precollagen (Fig. 15). On occasions the fibrosis may be partially or prominently fibroblastic (Fig. 16). No bands of collagen appear to be formed. The process involves lymph nodes irregularly, and small loosely cellular portions may remain (Fig. 14) that are usually composed predominantly of Reed-Sternberg cells. Differentiation from the nodular sclerosing type is readily accomplished on the basis of the birefringent, orderly, collagen bands usually surrounding cellular nodules and of the distinctive, large, cytoplasmic Reed-Sternberg cells in the nodular sclerosing type. Diffuse fibrosis by contrast has disorderly nonbirefringent connective tissue with cellular depletion.

Reticular

This term is employed to refer to the type of lesion in Hodgkin's disease that has a predominant component of Reed-Sternberg cells associated with a mixture of cell types and usually a small amount of disorderly fibrosis. It includes lesions in which the Reed-Sternberg cells may be either pleomorphic and sarcomatous (Fig. 18) according to the criteria of Jackson and Parker (11), or exhibit a simple numerical predominance of characteristic Reed-Sternberg cells (Fig. 17). The entire lymph node may be loosely cellular and composed predominantly of Reed-Sternberg cells with depletion of other cellular elements. Frequently areas of necrosis are found and at times a portion of the lymph node may exhibit features of diffuse fibrosis. The 2 types, diffuse fibrosis and reticular, appear to be closely related, although at times 1 may predominate to the exclusion of the other. The reticular type is most commonly observed in autopsy material of post-therapy cases or in lymph node biopsies from Stage III disease with systemic symptoms. The pleomorphic Reed-Sternberg cell proliferation that fulfills the definition of Hodgkin's sarcoma is very uncommon in our experience in untreated cases, and only 1% of the cases of our series exhibited this manifestation.

Lennert used the term *reticulo-Hodgkin's*, according to Offerhouse (25), for a somewhat similar lesion which is intermediate between granuloma and sarcoma. The predominance of the

nonpleomorphic portion of the reticular group in our series (18, 19) over the sarcoma type justifies its separation from the granuloma group, but its prognostic similarity to sarcoma provides evidence of their close relationship.

Gross Pathology

A few brief comments on the gross pathology of lymph nodes and the distribution of lymph node and organ involvement in Hodgkin's disease are believed indicated, particularly where a relationship to the histologic findings appears to exist. In the lymph node exhibiting lymphocytic and histiocytic proliferation (L & H types) evidence of lymph node involvement is generally confined to a single large node or a cluster of enlarged nodes, most commonly in the cervical region. The individual nodes may vary 3-5 cm in diameter, but excision biopsy appears to be the limiting factor for the size of the nodes. The lymph nodes are well defined, nonadherent, soft to moderately firm, and have bulging moist tan to grayish-white cut surfaces. In the nodular sclerosing type, lymph node involvement appears to be limited primarily to an inverted triangular region that includes the anterior superior mediastinum, the scalene, supraclavicular and lower cervical regions. In our series, the nodular sclerosing type at the time of initial involvement was associated with an incidence of mediastinal involvement 15 times as great in Stage I as in all other types combined and more than twice as frequently when all stages are combined. The nodes may vary extensively, depending upon the degree of collagen formation and, apparently, on the occasional infiltrative character of the cellular proliferation. The lesion usually consists of a well-defined firm to hard individual lymph node or densely clustered matted nodes forming a single well-defined large mass. In the mediastinum it may resemble a thymoma radiologically except that it is usually located high in the anterior superior mediastinum. The cut surface typically exhibits a distinctly nodular character, with firm dense retracted grayish-white interconnecting bands, circumscribing slightly bulging yellowish-tan areas that may exceed 1.0 cm in diameter (Fig. 19). On a few occasions in our experience the mediastinal masses removed surgically have involved the thymus partially, even though Marshall (24) has shown that thymic involvement in Hodgkin's disease is distinctly unusual in autopsy material. At times in the nodular sclerosing type the lesion may be ill defined, with infiltration of adjacent tissue and organs, and absence of discernible lymph nodal demarcation. The cut surface of these lesions may contain areas of dense, retracted, grayish-white tissue, intermingled with firm grayish-white, so-called "fish flesh"-appearing, tissue. The classical gross appearance of the lymph nodes in Hodgkin's disease is found in the remaining histologic types, the mixed, diffuse fibrosis, and reticular. When observed at autopsy they may form continuous, adherent, irregularly nodular masses that follow the major vessels in the abdomen, encompass the aorta and vena cava and even the adjacent ureters, and extend from the inguinal ligament to the diaphragm (Fig. 20). This involvement provides the morphologic counterpart of the remarkable process recently observed by lymphangiography. Similar massive contiguous involvement may be observed in the thorax extending from the diaphragm to and above the clavicles, about the great vessels, into the hilus of the lungs, over and through the pericardium.

TABLE 3
RELATIONSHIP OF HISTOLOGIC TYPES TO CLINICAL STAGES

HISTOLOGIC GROUPS	NO. OF CASES	DISTRIBUTION OF CASES BY CLINICAL STAGE (%)		
		I	II	III
L & H ^a				
Nodular	23	78	9 ^b	13 ^c
Diffuse	40	65	27	8 ^c
Nodular sclerosis	149	36	36	28
Mixed	97	37	40	23
Diffuse fibrosis	47	11	27	62
Reticular	21	19	38	43
Total	377	38	34	28

^a Lymphocytic and/or histiocytic proliferation.

^b This group contains only 2 cases.

^c This group consists of 3 cases.

Pathologic evidence of the extent of lymph node involvement is available essentially only in autopsy material in which there usually has been extensive modification by a variety of therapeutic agents. The occurrence of continuous masses of lymph nodes at this time does provide support for the belief that Hodgkin's disease may disseminate by direct extension. This evidence, however, is of limited reliability since it is derived from extensively modified advanced disease. The nodular character of the involvement of the spleen (Fig. 21), liver, and bone marrow, represents a type of involvement that is similar to that observed with metastatic tumors or disseminated granulomas. Isolated nodules of varying frequency are irregularly distributed throughout these tissues. The predominant histologic character of these disseminated nodules is of the diffuse fibrosis or reticular type with the former usually predominating.

Extensive infiltration of organs and extra lymph node tissue, such as the adrenals in retroperitoneal infiltration, may occur, with obliteration of architectural features of the involved organ. Histologically they are usually either the diffuse fibrosis or reticular types, and at times both may be seen in different portions of the process in association with varying degrees of pleomorphic changes in the reticulum cells. This infiltrative aggressive form of Hodgkin's disease has been used as evidence for the neoplastic character of Hodgkin's disease.

The Relationship of Histologic Features to Clinical Stages and Survival

A brief consideration of the relationship of the morphologic features to clinical stages and survival may shed light on the significance of the morphologic changes. To accomplish this some of the data from our recent report (18, 19) on a 15- to 18-year follow-up study of 377 U. S. Army cases from World War II will be briefly reviewed. The relationship of the histologic types to clinical stages along with the distribution of the cases is recorded in Table 3. In this population of predominantly young adult American males of military age, nodular sclerosis represents the most common histologic type (40%) and the remaining cases are irregularly distributed in the other groups. Consideration of the

TABLE 4
RELATIONSHIP OF HISTOLOGIC TYPES AND
CLINICAL STAGES TO SURVIVAL

HISTOLOGIC GROUPS	NO. OF CASES	NO. OF SURVIVORS	MEDIAN SURVIVAL (yr)			
			All stages	I	II	III
L ^a & H ^a						
Nodular	23	10	12.4	16.0	12.0 ^b	4.3 ^c
Diffuse	40	11	7.4	9.5	4.8	5.5 ^c
Nodular sclerosis	149	23	4.2	11.0	3.2	1.8
Mixed	97	10	2.5	4.8	2.5	1.2
Diffuse fibrosis	47	1	0.9	1.1	3.2	0.4
Reticular	21	1	2.3	5.7	2.7	0.6
All cases	377	56	4.0	9.1	3.2	1.3

^a Lymphocytic and/or histiocytic proliferation.

^b Only 2 cases were in this group; therefore the average was used as more representative.

^c Only 3 cases were in these groups; therefore an average was used.

clinical stages existing at the time of biopsy indicates a definite relationship between the histologic types and clinical stages. The majority of the L & H types were initially observed in Stage I, while diffuse fibrosis and reticular types where lymphocytes are depleted are most commonly in Stage III and in over 80% of the cases in Stages II and III. Nodular sclerosis, which appears to be a regional expression of Hodgkin's disease in the anterior superior mediastinum and adjacent cervical region, apparently may be seen in any clinical stage as the process evolves and yet retains the distinctive histologic features of this type. The mixed type appears to represent a histologic expression of changing disease, with equal distribution clinically in the 3 stages, in an intermediate histologic position between the lymphocytic proliferation of the L & H types and the lymphocytic depletion of the diffuse fibrosis and reticular types.

The relationship of histologic types to clinical stages along with the number of survivals is recorded in Table 4. There is a definite relationship between histologic types and survival. In addition, the majority of survivors at 15 years, 44 cases (79%), were observed in the prognostically favorable groups, the L & H and nodular sclerosing types.

The survival period for the L & H types, both nodular and diffuse, is significantly longer than for the remaining types and for the nodular type, is significantly longer than for the diffuse type. The large group of patients composing the nodular sclerosing group also have a significantly longer survival than those with the mixed, diffuse fibrosis and reticular types. Diffuse fibrosis, the type associated with lymphocytic depletion, has a remarkably brief median survival of only 0.9 year.

A brief consideration of the median survivals when the histologic types are combined with the clinical stages in Table 5, keeping in mind the distribution of histologic types and stages, demonstrates several very significant features. The L & H types which occur predominantly in Stage I have prolonged median survivals of 16 and 9.5 years for nodular and diffuse types respectively. This is in marked contrast to the diffuse fibrosis and reticular groups which are usually found in Stage III with

prominent lymphocytic depletion and have median survivals of 0.4 to 0.6 year, respectively. Nodular sclerosis, which has the largest single group of cases initially observed in Stage I, has a median survival of 11 years in Stage I which is similar to the median survival often recorded for the paraganuloma type.

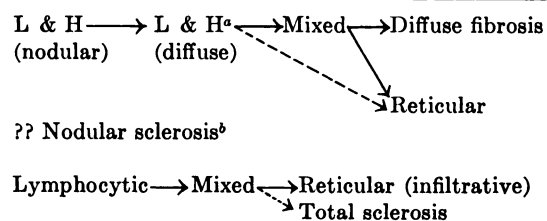
Several definite conclusions appear to be indicated from the data that was derived from our re-evaluation study (18, 19) of the significance of the histologic features and clinical stages in Hodgkin's disease. Lymphocytic and histiocytic proliferation is associated predominantly with Stage I disease and is associated with prolonged median survivals. The lymphocytic depletion types manifested histologically by diffuse fibrosis and the predominant Reed-Sternberg cell proliferation in the reticular type are usually observed in Stage III disease with rapidly progressive disease of brief duration. Nodular sclerosis is of major prognostic significance in Stage I since it is the most common histologic type and has a prolonged median survival. Comparison classifications of the same case population using the histologic types of Jackson and Parker (12) indicates that this classification is generally ineffective prognostically in recognizing the majority of prolonged survivals. Since over 90% of the case population were classified as the heterogeneous granuloma type, correlation of the histologic type and clinical stages was impossible with histologic types of Jackson and Parker. It is believed that results of this study re-emphasize the importance of the lymphocyte in Hodgkin's disease initially demonstrated by Rosenthal (31).

Evolution of the Morphologic Process

The results of the evaluation of the significance of the histologic features and clinical stages provide insight into the evolution of the histologic process of Hodgkin's disease. Somewhat similar observations have previously been reported by Custer and Bernhard (5) and others although different terminology was employed. Reconstruction of the histologic evolution of the process from our observations appears possible in all except the nodular sclerosing type, where the spontaneous tendency to undergo sclerosis and the significance of the frequently prominent Reed-Sternberg cell proliferation has been a difficult problem to unravel. The apparent histologic evolution of the Hodgkin's disease process is summarized in Table 5; the nodular sclerosing type is set aside in a questionable state.

It appears that a lymphocytic proliferation, associated with

TABLE 5
EVOLUTION OF HISTOLOGIC PROCESS IN HODGKIN'S DISEASE



^a L & H, lymphocytic and/or histiocytic proliferation.

^b Evolution of process with nodular sclerosis is uncertain, although a general parallel appears to exist.

small numbers of histiocytes and Reed-Sternberg cells, may be the initial manifestation of Hodgkin's disease as Stage I disease. It may persist for a variable period of time, possibly depending upon the effectiveness of the lymphocytic proliferation. When it occurs in nodular fashion it is more likely to present clinically as localized Stage I disease, persist for considerable periods, and possibly remain unchanged. When the proliferation is diffuse, histiocytes are often more numerous and extension may occur with the appearance of Stage II disease. The appearance of eosinophils, noncollagenous connective tissue, and increased numbers of Reed-Sternberg cells presents the features of the lesion designated the mixed type, which appears to herald the onset of a changing host response and the beginning of disseminated disease. The mixed type is regarded as a histologic expression of changing disease since it is encountered with equal frequency in each stage. The next phase in the evolution of the histologic process appears to be the depletion of lymphocytes, which may occur at varying rates and is associated with either the appearance of diffuse fibrosis or a marked increase in the number of Reed-Sternberg cells. Although this change occurs without therapy, cellular depletion and diffuse fibrosis also result from local and systemic therapeutic measures. Reed-Sternberg cells, when predominant, may be pleomorphic and may participate in an infiltrative process and fulfill the criteria for the sarcoma type.

The evolution of the process in the nodular sclerosing type is uncertain at the present time, although the natural tendency of the nodules to undergo sclerosis is readily apparent. It appears, however, that there is an association of predominantly lymphocytic lesions with a well-defined nodular sclerosing process. The appearance of fibrosis within the nodules, with loss of lymphocytes, however, does not seem to have the same significance as diffuse fibrosis elsewhere, but represents part of the sclerosing process. An aggressive infiltrative form of nodular sclerosis has been observed on occasions in which the process is ill defined, locally infiltrative, and composed predominantly of abnormal reticulum cells of the Reed-Sternberg type, with residual collagen bands or isolated nodules still in evidence in part of the specimen. Further study of this lesion is necessary to clarify the variations of this process and the phases in the evolution of the process. The individual nodules appear to evolve from a predominantly lymphocytic proliferation with distinctive abnormal reticulum cells scattered through the central portion of the nodules to total sclerosis that is almost completely devoid of cellularity. The initial modification of the cellular nodule begins with the occurrence of proliferating vessels from the periphery of the nodules, associated with gradual loss of lymphocytes, often in association with infiltration of numerous mature granulocytes and marked increase in abnormal reticulum cells. At this point it seems that the nodule may either progress to total sclerosis or undergo central necrosis.

The disseminated foci of Hodgkin's disease, particularly in reticuloendothelial organs, have a fairly consistent histologic appearance and distribution. They are characterized by diffuse fibrosis, associated with a variable number of abnormal reticulum cells of the Reed-Sternberg type. Other cell types are uncommon. At times either Reed-Sternberg cells or diffuse fibrosis may predominate. The lesions in the spleen, bone marrow, and liver are distributed in a fashion similar to disseminated granulomas and

are found primarily in the Malpighian corpuscles in the spleen, as isolated nodules in the hematopoietic marrow, and usually in portal areas in the liver. In other organs disseminated foci also appear to occur initially in preexisting lymphoid tissue sites, such as the peribronchial lymphoid tissue in the lungs, and the lamina propria of the gastrointestinal tract. These observations on the generalized sites of Hodgkin's disease suggest that it disseminates in a fashion similar to granulomas of infectious disease as lymphocytic depletion develops.

Comparison of Histologic Classifications

The classifications of Jackson and Parker (11) and the authors are related schematically in Table 2 and were analyzed in a comparative study (18-20) of our cases. It is apparent that the granuloma type of Jackson and Parker incorporates most of the histologic expressions of Hodgkin's disease and includes nodular sclerosis, mixed, and diffuse fibrosis types, part of the L & H types, and almost all of the reticular type. Classification of the 377 cases in our recent study according to the criteria of Jackson and Parker (11) resulted in 30 cases (8%) being classified as paraganuloma, 344 cases (91%) as granuloma, and 3 cases (1%) as sarcoma. This represents a distribution similar to that reported in the majority of studies (1). It is apparent that the granulomatous type is a heterogeneous group that encompasses a variety of histologic expressions and includes the overwhelming majority of the cases of all reported series. The distribution of the same group of cases into the 6 histologic types of the authors is listed in Table 4 with the median survival and number of survivors at 15 years. The prognostic value of the classification of Jackson and Parker (11) is limited to the paraganuloma group, which included only 12 (21%) of the 56 survivors in our study, while the remaining 44 survivors (79%) at 15 years exhibited features of granuloma. This finding represents dramatic evidence of the limitations of the classification of Jackson and Parker in prognosis. The prolonged median survivals of 11.2 years with paraganuloma and 0.6 year with sarcoma are significant, but the groups are small.

Discussion

The numerous histologic expressions found in Hodgkin's disease appear to represent manifestations of differences in the host's response rather than a mixed lymphoma as suggested by Lumb (22) and Berman (2). Evidence of the importance of the lymphocyte in the response of the host is provided by the association of lymphocytic proliferation of the L & H types with clinical Stage I and prolonged median survival, and of the lymphocytic depletion types, diffuse fibrosis and reticular, with Stage III and rapidly progressive disease. The role of the lymphocyte in Hodgkin's disease appears to be related to the recently observed immunologic defect that is manifested by an inability to develop delayed hypersensitivity (17, 32), delay in homograft rejection (16), and the depletion in lymphocytes in the inflammatory reactions in the skin window of Rebuck (29). Support for a lymphocyte defect is becoming apparent also in the form of defective lymphocyte transformation with phytohemagglutinin in the studies of Hirschhorn *et al.* (10), Aisenberg (1), and R. J. Lukes, J. W. Parker, and H. Wakasa (in prepara-

tion). The inverse relationship of lymphocytes and Reed-Sternberg cells observed by Rosenthal (31) and the authors (18-20) is a dramatic demonstration of the interplay of the host factors and the basic alteration of the disease as manifested by the Reed-Sternberg cell. From the authors' experience with histologic material from over 3000 cases, the basic process seems to involve the Reed-Sternberg cell, while the associated cellular and connective tissue features represent expressions of the attempted response of the host.

The association of a variety of inflammatory type cellular proliferations with Reed-Sternberg cells raises a serious question about the neoplastic nature of the process. The variation in the character and frequency of Reed-Sternberg cells in the various histologic types provides the basis for the proposal that the Hodgkin's disease process may represent the gradual induction and development of malignant neoplasia and that the numerous histologic types reflect differences in the effectiveness of the host's ability to prevent the neoplastic induction. If this proposal is correct, fully developed neoplasia may be limited to the small proportion of cases in the reticular group with definite pleomorphism.

The majority of the terms in the literature for the histologic manifestations of Hodgkin's disease have been proposed primarily for a predominant lymphocyte proliferation that may be either nodular or diffuse. This group includes the L & R type of Rosenthal (31), paraganuloma of Jackson and Parker (11), lymphoreticular medullary reticulosis of Robb-Smith (30), indolent Hodgkin's disease of Symmers (34), and follicular lymphoma, Hodgkin's type, of Rappaport *et al.* (28). These terms with the exception of that of Rosenthal (31), of Robb-Smith (30), and Rappaport *et al.* (28), have resulted from retrospective studies that attempted to evaluate the significance of this distinctive histologic lesion and relate it to the prolonged survivals for prognostic purposes. The opportunity for systematic evaluation of the significance of the histologic features in a large group of cases of Hodgkin's disease with long term follow-up has been limited, particularly in relationship to the clinical stages and in light of the recent immunologic developments. In our recent study (18-20) in which this systematic approach was used, the histologic findings appeared to fall into 6 histologic groups based on the predominant histologic feature. Undoubtedly greater separation could have been accomplished, but it is questionable whether it would have served a useful purpose. The groupings selected were the result of several basic considerations: (a) the importance of the lymphocyte and the inverse relationship of the frequency of lymphocytes to Reed-Sternberg cells; (b) the occurrence of 2 distinctive types of fibrosis in Hodgkin's disease—the formation of collagen in nodular sclerosis, and a disorderly fibrosis associated with lymphocytic depletion in diffuse fibrosis; (c) the realization that a number of types of reticulum cells are found in Hodgkin's disease, including a variety of abnormal reticulum cells apparently related to the Reed-Sternberg cell, that appear to be distinctive for several of the histologic types; and (d) the consistent occurrence of reactive histiocytes with lymphocytic proliferations and often as a major component.

Establishment of the L & H types permitted the recognition of the prognostic importance of the histiocytic component, which more than doubled the size of this favorable prognostic group with lymphocytic proliferation in our series of cases. The signifi-

cance of the relationship of lymphocytes and histiocytes is unclear, although the presence of a prominent number of histiocytes seems to indicate a less effective host response. The proposal that lymphocytic and histiocytic proliferations should be considered jointly appears justified to the authors. This belief is based on the following observations: (a) lymphocytes and histiocytes occur consistently together in varying degrees and are difficult to separate; (b) the proliferation of lymphocytes or histiocytes when either predominates may be nodular or diffuse; and (c) the L & H lesion is associated with Stage I disease. Recognition of the diffuse and nodular types of L & H seems clearly indicated from the striking difference in the median survival recorded in Table 4, with 7.4 years for diffuse and 12.4 years for nodular. The nodular character of the predominantly lymphocytic proliferation was demonstrated originally by Rappaport, Winter, and Hicks (28) as a Hodgkin's type of follicular lymphoma. These authors, however, acknowledged that the process might be more appropriately incorporated with the predominantly lymphocytic proliferations of Hodgkin's disease, a view with which we definitely agree. The nodular character of the proliferation is vague and not striking, and may be easily overlooked. It is readily recognizable, however, on reticulum stains as demonstrated by Wright (38) and Dawson and Harrison (6). The descriptive term, "lymphocytic and/or histiocytic (L & H) with nodular and diffuse types," is believed to be more appropriate than those previously reported since it characterizes the histologic appearance, emphasizes the important histiocytic component, and permits the identification of twice the number of prolonged survivors in our study (18, 20). The desirability of a histologic descriptive term has been stressed previously by Bonefant (3) and others, to avoid the various prognostic and conceptual terms prevalent in the literature. The term "paraganuloma" is therefore undesirable since it is not a histologic term and does not recognize the nodular or diffuse variations or the histiocytic component found in the L & H types.

Advanced degrees of fibrosis in Hodgkin's disease have been included in the past under the old term, "classical Hodgkin's disease" or in the "granuloma type" of Jackson and Parker (11, 12). It was emphasized as somewhat distinctive by Smetana and Cohen (33) by the term "granuloma with sclerosis," but this term included the 2 distinctive types of advanced fibrosis identified by the authors (18-20), nodular sclerosis and diffuse fibrosis. Through the years the prognostically favorable nodular sclerosis has been combined with the rapidly progressive diffuse fibrosis as a single group of advanced fibrosis and more recently have been included within the granuloma type. The failure to separate these lesions undoubtedly accounts for the debated significance in the past of advanced fibrosis in Hodgkin's disease. Rosenthal (31) many years ago, however, emphasized the unfavorable nature of fibrosis in his F & R type, which was never accepted but now appears to be related to diffuse fibrosis. Nodular sclerosis and diffuse fibrosis are readily separable histologically. Nodular sclerosis is identified by the occurrence of birefringent collagen band formation with a tendency to nodule formation and the presence of distinctive large cytoplasmic Reed-Sternberg cells. Diffuse fibrosis exhibits cellular depletion and disorderly non-birefringent loose hypocellular connective tissue. The distinctive histologic character and prognostic significance of nodular sclerosis has been supported by Hanson (8). At the recent Paris

meeting on Hodgkin's disease, nodular sclerosis emerged as the most significant prognostically of the histologic types in the review (R. J. Lukes, C. Nezelof, and C. Gompel, in preparation) of the pretherapy lymph node biopsy material from the prolonged survival cases collected from many of the major radiotherapy series of cases of Hodgkin's disease.

The mixed type appears to be useful to identify the histologic type intermediate between the lymphocytic and histiocytic proliferations at 1 extreme and the lymphocytic depletion types, diffuse fibrosis and reticular types, at the other extreme. The sarcoma type of Jackson and Parker (11) is histologically distinctive, and a separate designation may be justified on this basis. However, the infrequency of this type in biopsy specimens—1% in our series—and in autopsy material where there is extensive therapeutic modification, provided sufficient evidence for the authors to include the lesion in the reticular group. Furthermore, the remaining cases of the reticular group appear in general to present a relatively similar rate of progression, particularly in Stage III disease.

The effectiveness of the histologic classification proposed by the authors will ultimately be determined by the ease of application and the prognostic usefulness for other workers. These histologic classification have proven even more effective as a basis for evaluating the state of the disease and in estimating prognosis during the past few years in the authors' experience than in our reported study because of more ideal control over the quality and selection of biopsies. The commonly emphasized variability of the histologic findings in different sites in Hodgkin's disease that has caused considerable debate now can be answered on the basis of the histologic observations of the authors when considered in relationship to the clinical states. Differences in the histologic findings in 2 sites are believed to reflect changing disease which is related to the existence of lymphadenopathy in more than 1 area, e.g., Stage II or III disease. Differences in the findings in a single lymph node in Stage I also may indicate that the rate of progression and the state of the host are changing. Our experience with biopsies of recurrent lymphadenopathy in a single region in patients with prolonged survival, however, demonstrates a maintenance of histologic type, 1 case exhibiting the same L & H nodular process in 5 biopsies over a period of 10 years.

The relationship of the histologic findings to the clinical stages reemphasizes the importance of staging and provides evidence that the clinical stages are dependent on the state of the host, which is reflected by the histologic findings. A question has been raised whether the correlation in our case material between the histologic type and prognosis is not attributable to the correlation of the histologic type and anatomic extent and that therefore, the prognosis is related to the anatomic extent. This consideration, in fact, is the crux of our proposal, but with an important basic difference in the interpretation. The histologic changes do appear to be related to the anatomic extent of the disease. It seems to the authors, however, that the anatomic

TABLE 6
RELATIONSHIP OF RATE OF PROGRESSION TO THE CLINICAL AND HISTOLOGIC FACTORS IN HODGKIN'S DISEASE

Type	Median survival (yr)	Clinical stage (distribution)	Systemic symptoms	Histologic manifestations
Quiescent	9-15	I	0	L & H nodular L & H diffuse Nodular sclerosis
Changing	3-6	II and III	0	Nodular sclerosis Mixed
Progressive	0.5-1.5	II and III	+	Nodular sclerosis Mixed Diffuse fibrosis Reticular

extent and the rate of progression are related to the state of the host, which is reflected by the histologic type. It therefore appears that the anatomic extent or clinical stage is the result of the state of the host and the histologic type rather than the reverse.

Together the histologic types and the clinical stages provide an effective basis for prognosis as demonstrated in the prognostic schema, Table 6, from the authors' study, particularly when systemic symptoms are used as criteria to modify staging. From this summary in Table 6 it appears that Hodgkin's disease occurs essentially in 2 forms, quiescent and progressive, with intermediate changing disease. Quiescent disease is associated with the histologic expressions of the L & H and nodular sclerosis types and with clinical Stage I. Progressive disease is associated with the lymphocytic depletion types, diffuse fibrosis and reticular, and with Stages II and III and systemic symptoms. Nodular sclerosis may be found in any form as a regional expression of Hodgkin's disease, but it has emerged as a lesion of major prognostic importance in Stage I, where it is the most frequent histologic type and has a median survival similar to the L & H types. Consideration of the histologic types as expression of the state of the host and their relationship to the clinical stages provides a basis for suggesting that the effectiveness of therapy and the possibility of cure, therapeutic or spontaneous, may be largely dependent on the state of the host. Undoubtedly the accuracy of prognosis and the evaluation of the status of individual patients will be greatly enhanced by the addition of immunologic studies as another parameter of the prognostic schema in Table 6. The importance of the lymphocyte in the histologic process of Hodgkin's disease, the recently demonstrated immunologic defect involving the lymphocyte, and the initial observations of defective lymphocyte transformation with phytohemagglutinin emphasize the key role of the lymphocyte in the Hodgkin's disease process and the need for intensive investigation to elucidate the precise nature of the lymphocyte abnormality.

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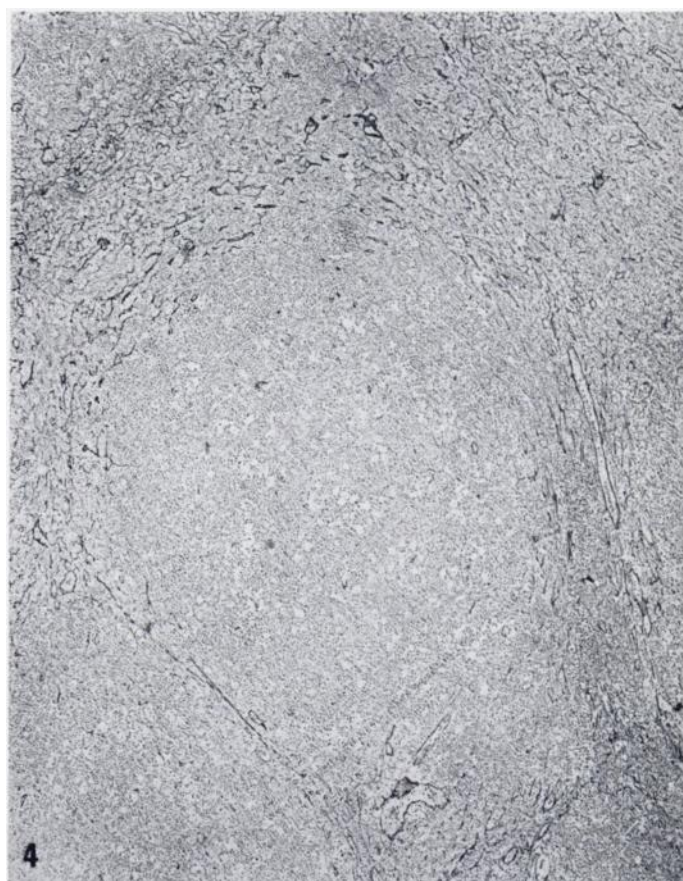
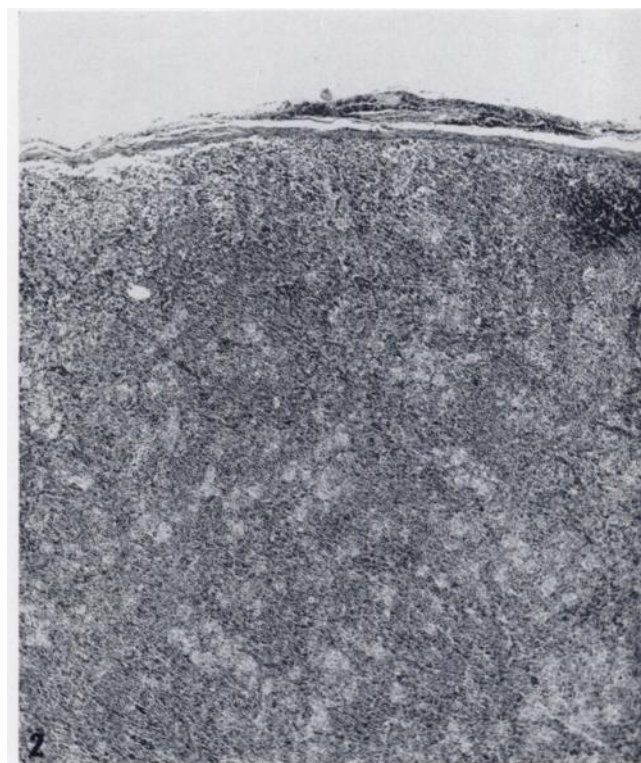
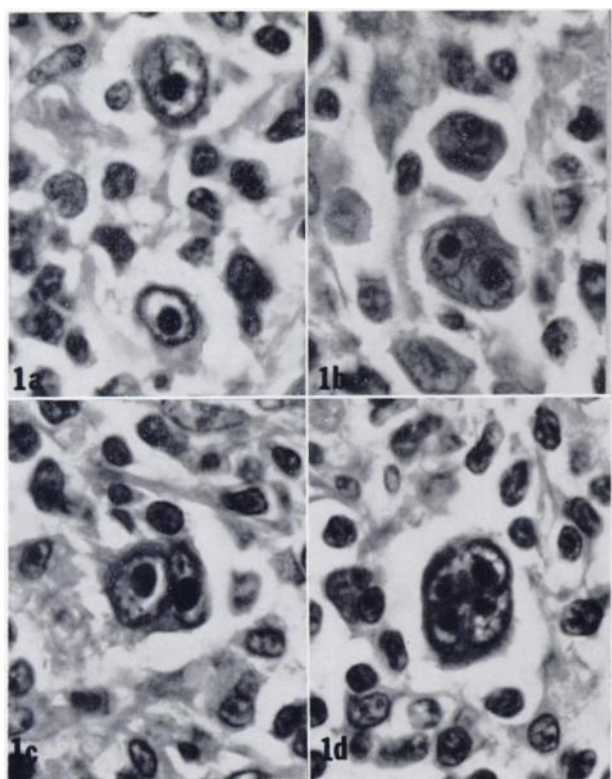
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FIG. 1. Variants of Reed-Sternberg cells with large inclusion-like nucleoli, vesicular nuclei, thick nuclear membranes. *a*, Mononuclear; *b*, bilobed and lobating; *c*, so-called "mirror image" bilobed type; and *d*, multinucleated type. The mononuclear type is not regarded as diagnostically reliable. LACH S-65-13924. H & E, $\times 850$.

FIG. 2. L & H diffuse: numerous histiocytes are scattered individually and in small clusters throughout a predominantly lymphocytic proliferation. AFIP Neg. 57-4423. H & E, $\times 40$.

FIG. 3. L & H nodular: the predominantly lymphocytic proliferation is aggregated in a vaguely nodular pattern. AFIP access. 1024731. H & E, $\times 20$.

FIG. 4. L & H nodular: the nodular character of the cellular proliferation is clearly evident in reticulum-stained sections, with compressed reticulum fibers in the periphery of the nodules. Gomori reticulum stain. AFIP Access. No. 1024731. $\times 55$.



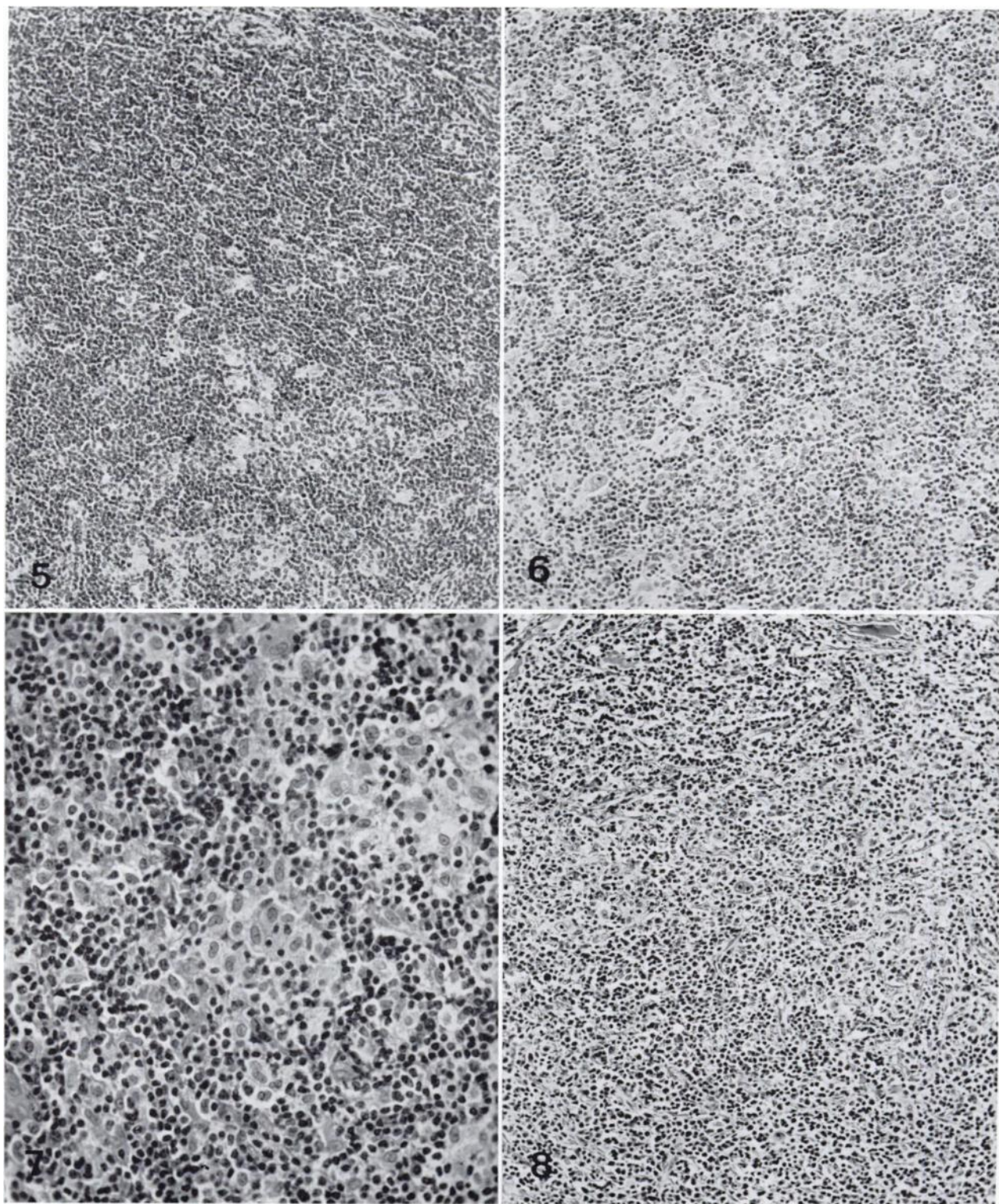


FIG. 5. L & H diffuse: large histiocytes are scattered throughout this predominantly well-differentiated lymphocytic proliferation. AFIP Neg. 57-16885. H & E, $\times 150$.

FIG. 6. L & H diffuse: histiocytes are present in almost equal proportions with lymphocytes. AFIP neg. 57-16780. H & E, $\times 150$.

FIG. 7. Reactive histiocytes of the L & H types with a variable amount of cytoplasm, medium size nuclei with delicate chromatin and small nucleoli. AFIP Neg. 63-5613. H & E, $\times 400$.

FIG. 8. Mixed type: a variety of cellular components and disorderly distributed fine fibrillar connective tissue is found in the mixed type. AFIP Neg. 57-16819. H & E, $\times 150$.



FIG. 9. Nodular sclerosis: the sclerosing and nodular character of the process is evident. AFIP Neg. 61-1658. H & E, $\times 8$.

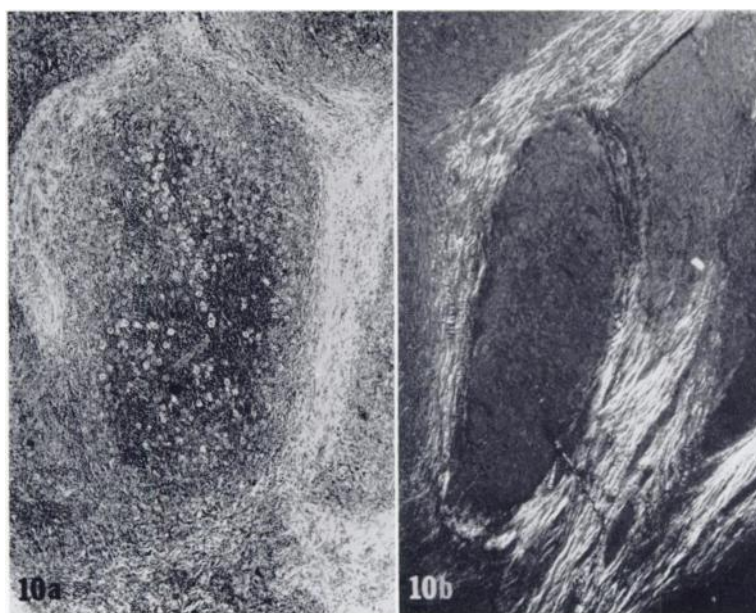


FIG. 10. Typical nodule of nodular sclerosing type: *a*, Collagen bands partially circumscribe the typical cellular nodule in which large pale reticulum cells are situated in lacuna-like spaces. LACH S65-4895. H & E, $\times 35$. *b*, The birefringent character of the collagen is demonstrated by polarized light. LACH S65-4895. $\times 35$.

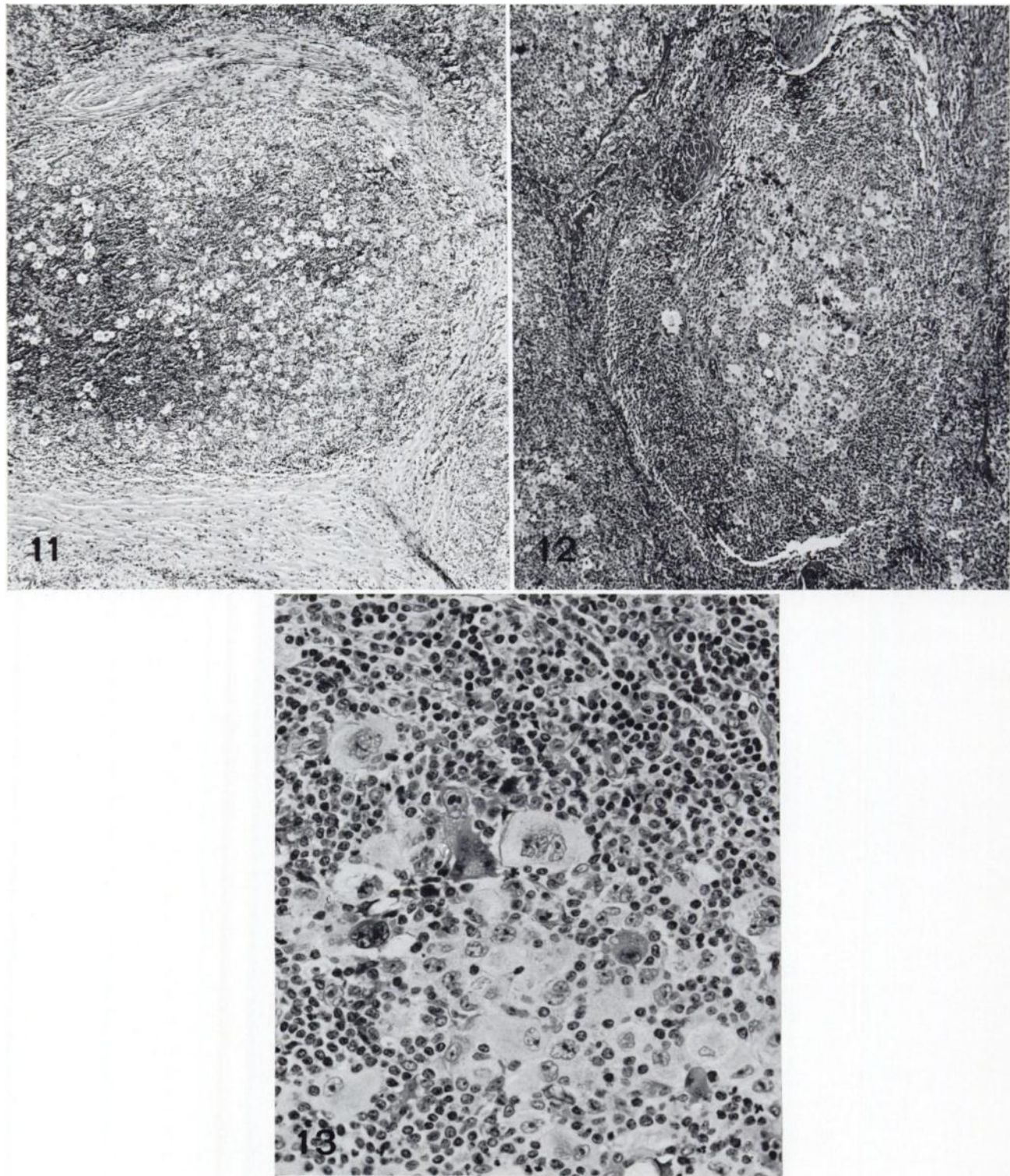


FIG. 11. Nodular sclerositis: the large Reed-Sternberg cells are situated in lacuna-like spaces in a typical partially circumscribed cellular nodule. LACH S 65-4895. H & E, $\times 55$.

FIG. 12. Nodular sclerositis: a typical nodule formation without circumscription by collagen bands. AFIP access. 940771. H & E, $\times 100$.

FIG. 13. Nodular sclerositis: the distinctive large variant of Reed-Sternberg cells with abundant pale cytoplasm, prominent lobation, and sharp cellular borders characteristically found in this type. AFIP access. 940771. H & E, $\times 350$.

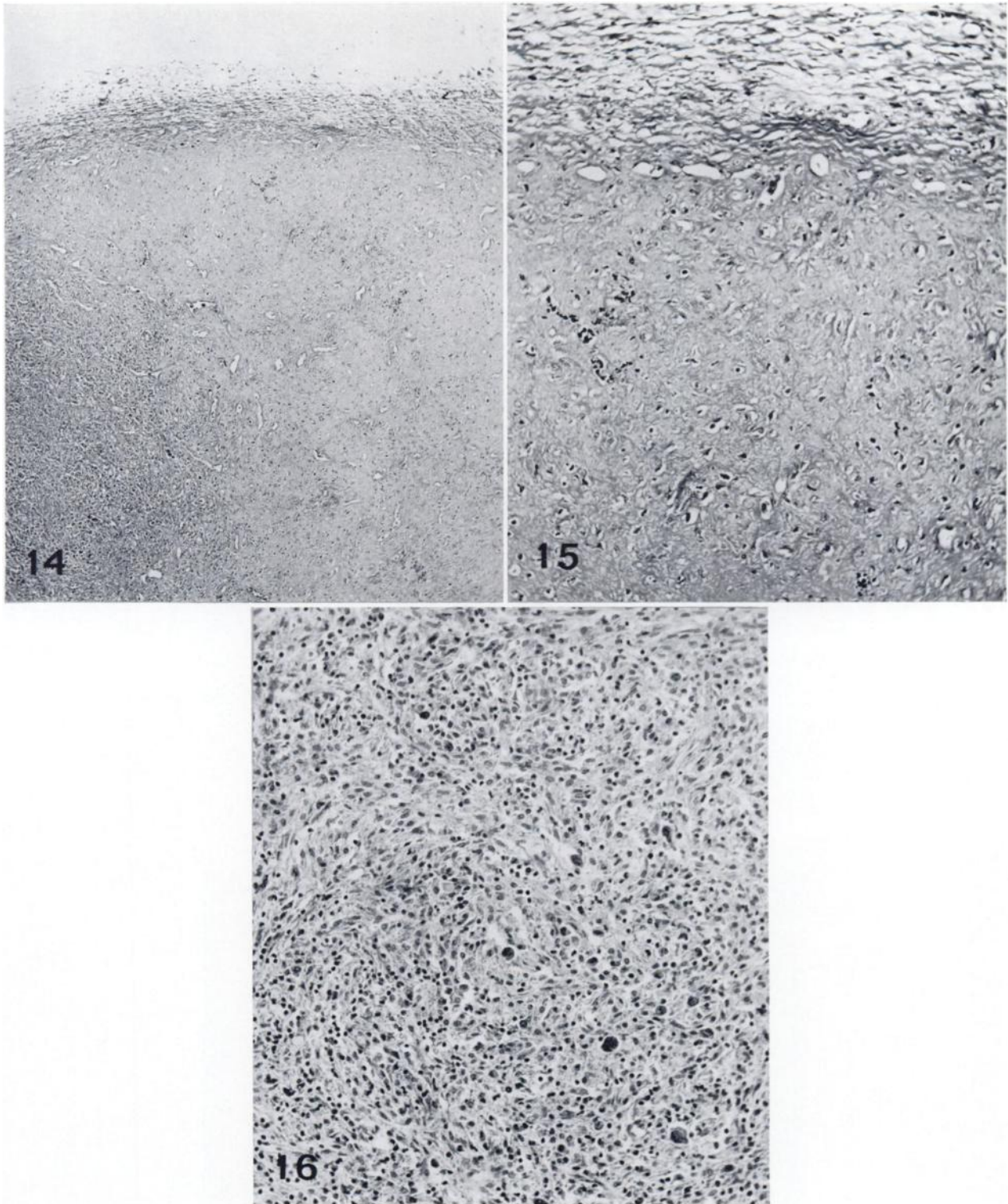


FIG. 14. Diffuse fibrosis: the typical hypocellular connective tissue with residual sinusoids is associated with a residual small, moderately cellular, partially fibrotic area. AFIP Neg. 57-16817. H & E, $\times 40$.

FIG. 15. Diffuse fibrosis: compact hypocellular, partially hyalinized, connective tissue has a precollagen-like appearance. AFIP Neg. 57-16817. H & E, $\times 150$.

FIG. 16. Diffuse fibrosis: cellular fibroblastic connective tissue occurs at times in this type. LACH 70601. H & E, $\times 150$.

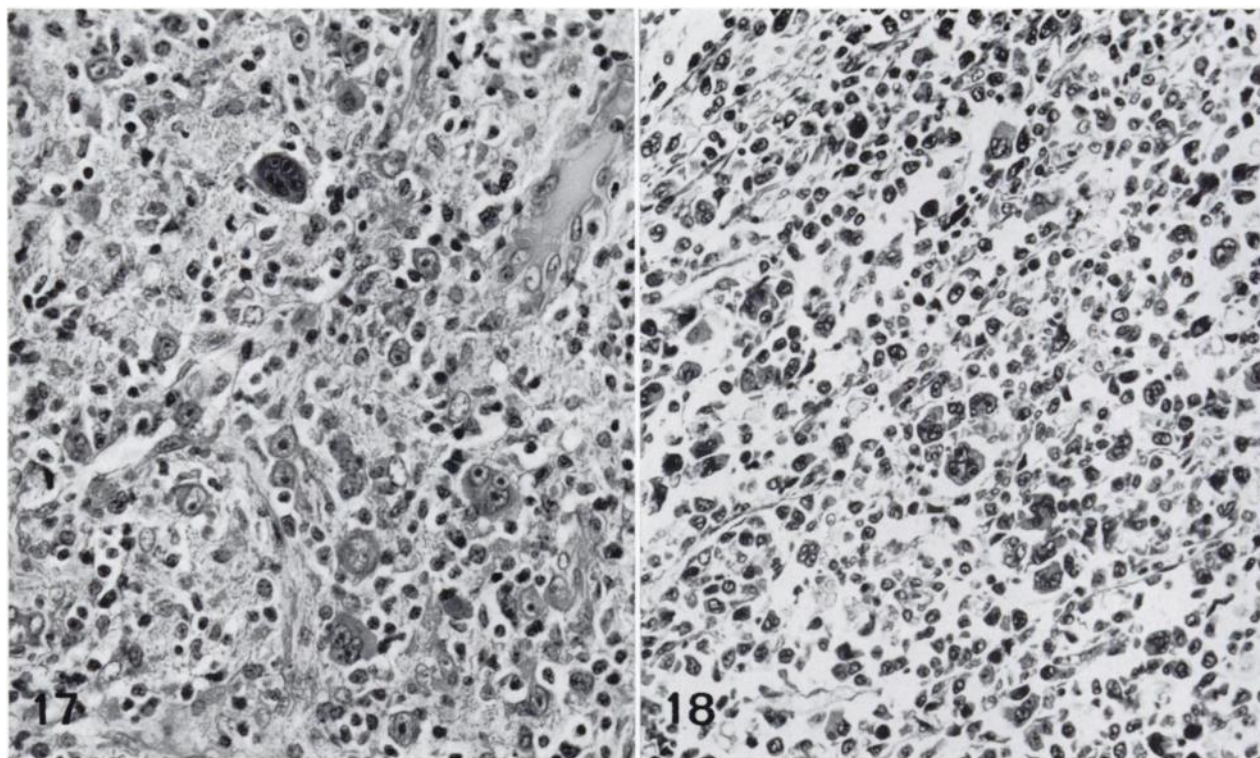


FIG. 17. Reticular: a variety of Reed-Sternberg cells represent the prominent component of this lesion. AFIP access. 854521. H & E, $\times 150$.

FIG. 18. Reticular, pleomorphic: numerous pleomorphic Reed-Sternberg cells represent the predominant component. AFIP access. 96106. $\times 150$.



FIG. 19. Nodular sclerosis: the bulging nodular character with retracted bands is evident in the cut surface of this mediastinal mass. AFIP Neg. 56-1652.



FIG. 20. Massive retroperitoneal nodes represent the gross pathologic counterpart to positive lymphangiographic studies in this partially eviscerated abdomen. The costal margin is visible at the *upper left* and the pleural space at *upper right*. AFIP Access. 165616.



FIG. 21. Multiple irregularly distributed nodules in the spleen characterize organ involvement. AFIP Neg. 61-1504.