



## PATHOLOGICAL ASPECTS OF HODGKIN'S

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### 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 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 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 proposed the term "sarcoma" for a pleomorphic neoplastic proliferation of Reed-Sternberg cells. The classical histologic types of Jackson and Parker, namely paraganuloma, granuloma, and sarcoma, are related to many of the findings of Ewing and Rosenthal. Subsequently the prognostic importance of the predominant lymphocytic lesions has been supported by a number of observers, although a variety of terms have been suggested for the association of lymphocytic proliferation with prolonged survival. Neither Croizat et al. nor Winterhalter, however, 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 and later refined by Peters and Middlemiss emphasized the prognostic importance of localized manifestation 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 our recent study of the World War II cases of Hodgkin's disease in a 15 to 18 year follow-up study. The results of this study re-emphasized 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.

In this presentation I will attempt to define and demonstrate the histologic variations in Hodgkin's disease and relate our terminology for these variations to the wide variety of terms that have been employed in the past. An attempt also will be made to relate the histologic findings to the gross pathologic changes and the evolution of the disease process. In the next presentation the apparent relationship between the histologic findings and clinical stages and the significance in prognosis 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.

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 established whether the process, if neoplastic, involves all the cellular components and is a mixed lymphoma as proposed by Lumb, Berman and others, or (slide) 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 as a sarcomatous type 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 the **next slide**. Mononuclear forms are usually found in typical lesions of Hodgkin's disease 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 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 is an unusually large cell with a tendency to extraordinary lobular nuclear variations and multinucleation that appear to represent an extreme degree or polyploidism.

#### 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. In our recent study 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 have proposed the following terms (**slide**):

(a) lymphocytic and/or histiocytic (L & H), diffuse; (b) (**slide**) 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.

#### HISTOLOGIC FINDINGS

Variation in the major components within each histologic type is demonstrated schematically in Table 4 on the basis of 1 to 10 + with each plus representing approximately 10%. It should be emphasized that

the quantitation of Reed-Sternberg cells although only a small proportion of those included may exhibit classical diagnostic features. In addition, the components unquestionable at times may exhibit more variation than the degree indicated, particularly in the nodular sclerosis and mixed types. These general estimations of the histologic components in the various types illustrate several important basic features of the histologic process in Hodgkin's disease.

In general there is an inverse relationship between the frequency of lymphocytes and Reed-Sternberg cells, particularly the diagnostic cells. The lymphocytic proliferation of the L & H types is associated with a small proportion of Reed-Sternberg cells while in the diffuse fibrosis and reticular types, the depletion of lymphocytes is associated with numerous Reed-Sternberg cells. Connective tissue is observed in 2 distinctive forms: (a) orderly distributed interconnecting collagen bands in nodular sclerosis and (b) irregularly distributed finely fibrillar connective tissue or compact proteinaceous material that resembles pre-collagen in diffuse fibrosis. Diffuse fibrosis is associated with lymphocytic depletion.

#### 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 that are readily differentiated from the variants of the Reed-Sternberg cell. The histiocytic component varies widely from scattered individual histiocytes to a predominance 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 histio-

cytic (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.

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 nature neutrophils are uncommon or absent. There is essentially no fibrosis.

#### LYMPHOCYTIC AND/OR HISTIOCYTIC (L & H) TYPE, DIFFUSE

(Slide) In the diffuse L & H type the cellular proliferation extends uniformly throughout the lymph node with compression of sinusoids and absence of lymphatic follicles. In this example lymphocytes predominate and small clusters of pale histiocytes are seen irregularly distributed throughout the lymph node as a minor component. The capsule is uninvolved.

(Slide) In this higher magnification it is apparent that the lymphocytic proliferation is well differentiated, and the occasional histiocytes appear as large cells with abundant pale, lightly eosinophilic cytoplasm and small nuclei. Cells resembling Reed-Sternberg cells are not apparent in this area. When the lymphocytic component predominates in the diffuse type and histiocytes are infrequent or rare, the lesion may closely resemble a well differentiated lymphocytic lymphoma, the tissue counterpart of chronic lymphocytic leukemia. The two 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 to some degree and numerous abnormal reticulum cells related to Reed-Sternberg cells and occurs predo-

minantly in younger patients. The abnormal reticulum cell component that appears to be related to the Reed-Sternberg cells is often relatively prominent, as in this high magnification field, and may represent as much as 10% of the cell population. These peculiar large cells have folded, twisted, lobated pale nuclei, fine, lacy, delicate chromatin and small nucleoli. Characteristic Reed-Sternberg cells with large nucleoli are extremely infrequent in this lesion. It may be necessary to search a number of sections to find typical Reed-Sternberg cells on which to establish reliable diagnosis. In this field the distinctive reactive character of the large pale cytoplasmic reactive histiocytes can be readily differentiated from the partially modified polyploid reticulum cells that appear to be related to Reed-Sternberg cells.

(Slide) In this table, the numerous terms that have been proposed in literature for the predominantly lymphocytic proliferation observed in Hodgkin's disease, are listed in association with the author and year of publication.

It is readily apparent that this group has aroused most of the attention of pathologists as a result of its distinctive histologic character and the association of lymphocytic proliferation with prolonged survival. It should be emphasized that the terms listed refer to a predominant lymphocytic proliferation with a small component of histiocytes where eosinophils and plasma cells were infrequent or absent, and there was little or no fibrosis and necrosis was absent. Almost thirty years ago Rosenfeld 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 suggested that this lesion might represent early Hodgkin's disease. Later Jackson and Parker indicated that this was an unfortunate choice of terms and recommended paraganuloma as a more appropriate definition to indicate a close relationship to Hodgkin's granuloma. The term "lymphoreticular medullary reticulosis" was proposed several years later by Robb-Smith 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 in 1951 in preference to the term "paraganuloma." It evolved from a retrospective study of cases with prolonged survival in this 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. A similar cellular proliferation was observed in nodular distribution in this series in approximately 2/3 of their cases in association with compression of 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 was noted. The term "reticular lymphoma" was urged by Lumb to emphasize its distinctive character and definite relation to Hodgkin's disease. Symmers prefers the term "indolent" to emphasize the need for caution in prognosis. Although he acknowledges its identity with paraganuloma.

#### LYMPHOCYTIC AND HISTIOCYTIC (L & H), NODULAR

(Slide) In this process the cellular proliferation is aggregated in a vaguely nodular fashion. The proliferation is usually overwhelmingly lymphocytic, involving both nodules and internodular tissue as in this lesion.

Histiocytes have predominated in the nodular type on only a few occasions in our experience.

The nodules are generally large, closely situated, and often involve only a portion of the lymph node. The individual nodules are vaguely outlined, but clearly demonstrated in a reticulum stain with compres-

sion of the reticulum fibers about the periphery of the nodules. Typical Reed-Sternberg cells are rare, although abnormal polyploid reticulum cells with small nucleoli may be numerous and tend to be concentrated in the central portion of the nodules.

(Slide) The nodular character of this type of Hodgkin's disease was initially demonstrated quite recently by Rappaport, et al under the term "follicular lymphoma, type V" Hodgkin's type in their classical study on the re-evaluation of follicular lymphoma. These authors indicated the lesion would be regarded as a paraganuloma if it had lacked nodularity. They also suggested that paraganuloma might be a more ideal designation rather than to include the lesion within the general group of lymphomas. Subsequently Dawson and Harrison and also Wright have emphasized the resemblance of many of their cases under the term "benign Hodgkin's" to the group described by Rappaport, et al.

#### LYMPHOCYTIC AND HISTIOCYTIC (L & H), DIFFUSE, HISTIOCYTES PREDOMINATING

(Slide) In this magnification of photomicrograph the diffuse L & H type of Hodgkin's disease where histiocytes predominate is demonstrated.

There is little or no fibrosis, essentially no admixture of eosinophils, plasma cells and no necrosis.

(Slide) The lesion is composed predominantly of histiocytes with a number of residual lymphocytes. Diagnostic Reed-Sternberg cells are usually infrequent and difficult to find as in the predominantly lymphocytic lesions.

(Slide) In the past this predominantly histiocytic lesion appears to have been included within the granuloma group of Jackson and Parker. Its importance appears to be dependent upon its relationship to the predominantly lymphocytic type and both in type of clinical disease and slow progression.

#### MIXED TYPE

(Next Slide) This histologic type is of heterogeneous composition and occupies a somewhat intermediate position between

the predominantly lymphocytic proliferation at one extreme and lymphocytic depletion with diffuse fibrosis and reticular types at the other. As the name implies it is composed of a variety of histologic components, including 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. The Reed-Sternberg cells and related abnormal reticulum cells are often rather numerous and prominent. Focal necrosis may be seen, but is usually not marked. The process generally extends throughout the entire lymph node and is associated with obliteration of lymphatic sinusoids and follicles. Focal involvement by a similar process, however, may extend throughout 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 one extreme and the lymphocytic depletion types at the other at times may be difficult. It appears to depend primarily on the frequency and character of the Reed-Sternberg cells and the degree and character of fibrosis.

(Next Slide) The mixed type most closely approximates the classical concept of granuloma as presented by Jackson and Parker.

(Next Slide) Granuloma, unfortunately incorporates a variety of histologic expressions, including the prominent histiocytic proliferation and the advanced fibrosis types, and those where Reed-Sternberg cells predominate but are not sarcomatous. Thus, the granuloma group includes almost the whole spectrum of cellular proliferation. Fibromedullary reticulosis, the term of Robb-Smith, apparently represents a group comparable to the granuloma.

#### ADVANCED FIBROSIS

(Next Slide) The advanced degree of fibrosis in Hodgkin's disease through the years have been generally considered together although they appear from our study to represent two distinct types.

The first, nodular sclerosis, exhibits orderly bands of dense collagenous connec-

tive tissue that has a definite tendency to subdivide lymphoid tissue into isolated cellular nodules. The second, diffuse fibrosis, is characterized by disorganized type of fibrosis of variable character which may be composed of cellular fibroblastic connective tissue or hypocellular fibrillar connective tissue associated with cellular depletion, particularly of lymphocytes. Both types are generally included together in the granuloma group.

#### NODULAR SCLEROSIS

(Next Slide) This histologic type is characterized by orderly bands of interconnecting collagenous connective tissue that subdivides distinctly abnormal lymphoid tissue partially or entirely into isolated cellular nodules, as in this section of a mediastinal mass. The degree of collagen formation and the character of cellular proliferation vary widely at times, even within the same specimen.

(Next Slide) In this photomicrograph the typical nodule of nodular sclerosis is demonstrated. The cellular nodule is circumscribed by wide bands of dense collagen in the H & E section. While the trichrome stain on the right half demonstrates the collagenous nature of the connective tissue.

(Next Slide) The collagenous character of the circumscribing bands can readily be demonstrated on polarized light with ordinary H & E sections, as demonstrated in this photomicrograph.

(Next Slide) The cellular proliferation in nodular sclerosis, although varying widely is distinctive and exhibits similar variations both in the nodules and in the abnormal lymphoid tissue not subdivided by collagen. The distinctive feature of the cellular proliferation in nodular sclerosis is the unusually large variant of the Reed-Sternberg cell which has abundant, pale to water-clear slightly eosinophilic cytoplasm with well defined cellular borders that present the appearance of the Reed-Sternberg cells situated in a lacuna-like space. These cells have prominent, lobated nucleus often with numerous lobes, delicate, lacy nuclear chromatin and small to medium

size nucleoli. Typical huge nucleoli are infrequent and often difficult to find. The numerous variations of the nodular sclerosing lesion will be discussed in detail later.

#### DIFFUSE FIBROSIS

(Next Slide) 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 usually with numerous 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 stage III or IV 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 with a fibrillar character at times, and in general bears a resemblance to pre-collagen.

(Next Slide) On occasion the fibrosis may be partially or prominently fibroblastic. The process involves lymph nodes irregularly and small loosely cellular portions may remain that contain numerous Reed-Sternberg cells. Differentiation from nodular sclerosis is readily accomplished on the basis of the orderly collagen bands usually found surrounding cellular nodules, and the distinctive large cytoplasmic Reed-Sternberg cells in the nodular sclerosing types. Diffuse fibrosis, by contrast, has disorderly, nonbinucleated connective tissue with cellular depletion.

(Next Slide) Advanced fibrosis in the past has always included both nodular sclerosis and diffuse fibrosis within a single group, most commonly under the term "granuloma." Many years ago Rosenthal separated a F and R type with prominent fibrosis and numerous reticulum cells, but it is difficult to determine whether he was referring to one or both lesions.

## RETICULAR

(Next Slide) The term is employed to refer to the type of lesion in Hodgkin's disease that has a predominant component of Reed-Sternberg cells, although a mixture of cell types may remain. The lesion appears to be intimately related to diffuse fibrosis and also represent an expression of a lymphocytic depletion type. It includes lesions in which the Reed-Sternberg cells may either be pleomorphic and sarcomatous, according to the criteria of Jackson and Parker, or exhibit a simple numerical predominance of characteristic Reed-Sternberg cells. In the reticular type focal necrosis is common and at times a portion of the lymph node may exhibit features of diffuse fibrosis. The reticular type is most commonly observed in autopsy material of post therapy cases in which it represents almost the exclusive residual cell type, usually in association with some degree of diffuse fibrosis. It may be observed in lymph node biopsies from untreated cases in stage III or IV 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 in our series exhibited this manifestation.

(Next Slide) The lesion where Reed-Sternberg cells numerically predominate have been included generally in the granuloma group, according to Jackson and Parker, although Lennert recently suggested the term "reticulo-Hodgkin's" and Rosenthal many years ago emphasized this lesion lymphocytes may be depleted.

## THE RELATIONSHIP OF SURVIVAL TO HISTOLOGIC TYPES

(Next Slide) In this slide the frequency of the histologic types in our recent study of 377 U. S. Army cases which were followed for 15 years, is listed, along with the median survival and a number of survivals at 15 years. Nodular sclerosis with 149 cases or 40% is the most common histologic type. The remaining cases are distributed in a somewhat balanced fashion. The histologic types associated with lymphocytic proliferation, the nodular and diffuse L & H types contain 63 or 16%, while the lymphocytic

depletion types, diffuse fibrosis and reticular, include 68 cases or 18%. The mixed type, intermediate between the extremes, comprises 97 cases or 26%. When we consider the survival data, it is apparent that there is a significant relation between histologic types and median survival. There is a striking difference in median survival between the L & H types with lymphocytic proliferation with 12.4 and 7.4 years, as compared to the lymphocytic depletion types, diffuse fibrosis and reticular, with 0.9 and 2.3 years respectively. The median survival in nodular sclerosis is also significantly longer than mixed, diffuse fibrosis and reticular types.

It is particularly significant to note when considering survivors that 23 of the 56 or 41% were classified histologically as nodular sclerosis which would be included in the granuloma type of Jackson and Parker. Twenty-one survivors were found in the L & H groups.

## COMPARISON OF HISTOLOGIC CLASSIFICATIONS

(Next Slide) The classifications of Jackson and Parker and the authors are related schematically in this Table. 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 and the L & H types, both nodular or diffuse where histiocytes predominate, and all of the reticular type except the small proportion of cases with a predominance of pleomorphic Reed-Sternberg cells or the sarcoma type.

(Next Slide) Comparative classifications of the 377 cases in our recent study according to the criteria of Jackson and Parker resulted in 30 cases (8%) being classified as paragranuloma, 344 cases (91%) as granuloma and 3 cases (1%) as sarcoma. This represents a distribution similar to that reported in the majority of studies. It is apparent that the granuloma type is a heterogeneous group, encompasses a variety of histologic expressions and includes the overwhelming majority (91%) of the cases of this series.



The prolonged median survival of 11.2 years with paragranuloma and the exceedingly short median survival of 0.6 years with sarcoma are significant, but the groups are small.

The prognostic value of the classification of Jackson and Parker is limited to the paragranuloma group which included only 12 (21%) of the 56 survivors; the remaining 44 (79%) survivors at 15 years exhibited features of granuloma. This finding represents dramatic evidence of the limitations of the classification of Jackson and Parker in prognosis.

(Next Slide) By comparison the histologic classification with our types 44 survivors (79%) are placed in the prognostically favorable histologic groups the L & H types and nodular sclerosis. The relationship of these histologic types to clinical stages is believed to be further indication of their prognostic value.

#### GROSS PATHOLOGY

A few brief comments on the 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.

(Next Slide) 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 nonfiltrative 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.

(Next Slide) In the mediastinum it may resemble a thymoma radiologically except that it is usually located high in the anterior superior mediastinum.

(Next Slide) 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. On a few occasions in our experience the mediastinal masses removed surgically have involved the thymus partially, even though Marshall 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, retractor, grayish-white tissue, intermingled with firm grayish-white, so-called "fish flesh" — appearing, tissue.

(Next Slide) 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.

(Next Slide) 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. The 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.

Pathologic evidence of the extent of lymph node involvement is available essen-

tially 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.

(Next Slide) The nodular character of the involvement of the spleen, 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 adrenal 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 degree 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.

#### 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 and Berman. 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, delay in homograft rejection, and the depletion in

lymphocytes in the inflammatory reactions in the skin window of Rebeck. 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., Aisenber, and R. J. Lukes, J. W. Parker, and H. Wakasa (in preparation). The inverse relationship of lymphocytes and Reed-Sternberg cells observed by Rosenthal and the authors 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 my 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 expression 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.

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, Berman and others, or the (Next Slide) 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 as a sarcomatous type 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 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 to neoplastic induction in Hodgkin's disease is unanswerable at the present time, but require thorough consideration and investigation.

Several types of abnormal reticulum cells that are probably related to Reed-Sternberg cells are observed in association with two of the histologic types that will be described in a subsequent section.

(Next Slide) 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 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.

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 significance 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 lympho-

cytic and histiocytic proliferations should be considered jointly appears justified. This belief is based on the observation that (1) lymphocytes and histiocytes occur consistently together in varying degrees and are difficult to separate; (2) the proliferation of lymphocytes or histiocytes when either predominates may be nodular or diffuse; and (3) 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.

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. It was emphasized as somewhat distinctive by Smetana and Cohen by the term "granuloma with sclerosis," but this term included the two distinctive types of advanced fibrosis identified by the authors, 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 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 Hansen. 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. 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 Hodgkin's disease.

The mixed type appears to be useful to identify the histologic type intermediate between the lymphocytic and histiocytic proliferations at one extreme and the lymphocytic depletion types, diffuse fibrosis and reticular types, at the other extreme.

The sarcoma type of Jackson and Parker 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 appears in general to present a relatively similar rate of progression, particularly in Stage III disease.