Criteria for Involvement of Lymph Node, Bone Marrow, Spleen, and Liver in Hodgkin's Disease

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Summary

The original criteria for the diagnosis and classification of Hodgkin's disease are reviewed in this paper and the critical points of differentiation are reevaluated. For appreciation of the essential morphological features by pathologists, continued use of our original six histological types is recommended, since the four histological types of the Rye classification, although valuable for clinicians, do not convey morphological connotations. The significance of the Reed-Sternberg (R-S) cell variants is reviewed, with emphasis on the fact that the diagnostic R-S cell is only one of a wide variety of R-S variants. Three major problems involving morphological criteria have arisen from limited appreciation of (a) the R-S variants; (b) the identification of the variants of nodular sclerosis; and (c) the precise criteria for differentiating lymphocytic and histiocytic types, mixed and diffuse fibrosis types, and reticular types. The two original criteria for recognition and identification of nodular sclerosis, i.e., lacunar type R-S cells and wide collagen bands, are regarded as the most effective basis for classifying nodular sclerosis, although the distinctiveness of lacunar cells suggests the possibility of reliable identification of nodular sclerosis in a cellular phase without collagen bands. Recognition of the lymphocytic and histiocytic types (lymphocyte predominance) and diffuse fibrosis and reticular types (lymphocyte depletion) is not based simply on the number of lymphocytes but primarily on the character and frequency of R-S cells or the type of fibrosis. The mixed type (mixed cellularity) serves both in an intermediate position between the two extremes and also as an unclassified type for those lesions that are not readily classifiable.

Introduction

In the interim since our proposal of a new approach to the pathological manifestations of Hodgkin's disease and the new histological types (14-16) in their contracted version of the Rye conference (17), a number of confirmatory reports have appeared in the literature (1-4, 6-9, 11-13). These reports have supported our observations on the relationship of the histological types, clinical stages, and survival and have demonstrated the general applicability of this approach. Its effectiveness and reproducibility also has been demonstrated in several studies in which 3 pathologists independently reviewed the biopsy material of large series of cases; either they reached unanimous agreement or 2 of the 3 pathologists have been in accord in the majority of cases (Refs. 3 and 13; R. J. Lukes, C. Nezelof, and C. Gomple, Review of Prolonged Survival Cases of Hodgkin's Disease Treated with Radiation Therapy, in preparation). From these studies and my own experience in 2 of the comparative studies, it is apparent that considerable experience with both the pathological manifestations of Hodgkin's disease and the new histological types is required. In addition, a thorough understanding of the precise criteria for the histological types is essential to achieve a high degree of accuracy and reproducibility in classification for the comparison of reported case series.

Three principal problems have arisen primarily from a lack of appreciation of the morphological criteria for the histological types and deserve critical review: (a) the distinctive character of the R-S1 cell variants in lymphocyte predominance and nodular sclerosis; (b) the essential differential diagnostic features that delineate the histological types; (c) the histological variants of nodular sclerosis, particularly the question of a cellular phase. The advent of laparotomy to determine the extent of Hodgkin's disease also requires redefinition of the minimal evidence of early microscopic involvement of lymph nodes, spleen, liver, and bone marrow. The pathognomonic nature of the diagnostic R-S cell also has been challenged with the observation of R-S-like cells of infectious mononucleosis (18) and in a variety of neoplastic conditions (22).

In this presentation, the problem areas in classification mentioned above will be evaluated and the criteria for each histological type will be reviewed and discussed in relationship to these problems. To those intimately familiar with the criteria, no changes in the basic criteria will be discovered, only redefining and enlargement in critical areas. The principal difficulty with our new approach to the pathology of Hodgkin's disease, in my view, is that it requires the pathologist to restudy the diverse morphological expressions in a large number of biopsies in order to gain an appreciation of the detailed features of the morphological criteria and the histological types. Only in this way is it possible to achieve effectiveness and reproducibility in classifying large series of cases for valid comparison with other published series.

The Problem of Histological Classification

The 4 histological types of Hodgkin's disease recommended at the Rye conference (17) are a contraction of our original 6 histological types (14-16) as shown in Table 1 and have proven useful for clinicians. Unfortunately, for pathologists all

The abbreviations used are: R-S, Reed-Sternberg; L & H, lymphocytic and histiocytic type.
the histological types of the Rye conference do not convey accurate descriptive characterizations of the types and are at times misleading. Many of the lymph node lesions of the lymphocyte predominance type have a prominent or predominant component of histiocytes. In addition, when the lesion of lymphocyte predominance becomes aggressive and is associated with extension to other areas, the change to the mixed cellularity frequently is evidenced by a prominent increase in the number of diagnostic R-S cells with huge nucleoli rather than a decrease in lymphocytes. Similarly, at the opposite end of the spectrum, the development of the lymphocyte depletion type from mixed cellularity on occasion is heralded by a dramatic increase in the number of diagnostic R-S cells before lymphocyte depletion occurs. Because of the complexities of the Hodgkin's disease process, it is most ideal for the pathologist to evaluate the morphological findings initially in terms of our original histological types and translate them for clinicians and publications into types of the Rye conference. In keeping with this belief and for reasons of clarity, this presentation will follow this approach.

Hodgkin's disease is a complex, evolving process with each histological type varying somewhat in expression, suggesting an overlapping array of histological types in a spectrum. The complexity of the process, however, results primarily from 2 unusual features: (a) there are 2 forms of Hodgkin's disease, nodular sclerosis with a number of variants and the remaining interrelated histological types, i.e., L & H (nodular and diffuse), mixed, diffuse fibrosis, and reticular types, and (b) each histological type is variable and may resemble 1 or more of the other histological types. In Chart 1, I have attempted to portray the complexities of the process in Hodgkin's disease as 2 separate series of overlapping circles with each circle representing the variation within a single histological type. The varied expressions of nodular sclerosis are situated in a parallel position to the remaining types demonstrating the similarity of the nodular sclerosis variants to each of the other histological types without any interrelationship. This schematic representation also is used to emphasize the evolving character of the process in 2 parallel noninterrelated series in which the pathologist is required to differentiate both horizontally between the parallel series and vertically between the overlapping histological types, each of which is variable. The principal problems in histological classification in general, therefore, are the separation of nodular sclerosis and its varied expressions from the remaining histological types and the acquisition of extensive experience with the essential criteria that permit critical differentiation between the closely related remaining histological types. The primary criteria for the recognition of nodular sclerosis are the identification of lacunar type R-S cells and the formation of distinctive collagen bands. For the remaining histological types, the frequency of diagnostic R-S cells with huge nucleoli in relationship to the histological features of each type is of paramount importance and of overriding significance.

The evolution of the process as indicated in our earlier publications appears to occur in a definite sequence, although the rate of evolution is obviously variable and our ability to study the process in individual cases is limited. Initially, L & H proliferation either of nodular or diffuse type occurs and in time changes to the mixed and, finally, either to diffuse fibrosis or reticular types. In nodular sclerosis, the evolution of the process in general is less clear, but the individual lymph node or tissue site of involvement seems to evolve in a somewhat parallel fashion from a predominance of lymphocytes to a mixed proliferation and, subsequently, either to total sclerosis or to a proliferation consisting predominantly of lacunar type R-S cells. It has been impossible, however, to demonstrate a relationship of the variants of nodular sclerosis to survival and prognosis, possibly because of variations in biopsy sampling. Nevertheless, nodular sclerosis deserves to be regarded separately throughout its course, and it does not appear to change into one of the other histological types because of its distinctive clinical and behavioral features.

### R-S Cells in the Diagnosis and Classification

The R-S cell has long been regarded as diagnostic of Hodgkin's disease. We have demonstrated, however, several significant variants of the R-S cell that lack the huge nucleolus of the diagnostic type and are associated with specific histological types, including the lacunar cell of nodular sclerosis and the distinctive form found in the L & H types (15, 16). We have also described cells morphologically indistinguishable from R-S cells in infectious mononucleosis, which have raised questions regarding pathognomonic nature of the R-S cell for Hodgkin's disease (18).

Appreciation of the pertinent cytological features of the R-S cell variants requires ideally fixed tissue and carefully prepared and stained sections along with considerable experience with a large number of cases of Hodgkin's disease. The diagnostic type of R-S cell has proven to be a reliable

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**Table 1**

<table>
<thead>
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<th>Relationship of classifications</th>
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<tr>
<td><strong>Rye, Lukes et al. (17)</strong></td>
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<tr>
<td>Lymphocyte predominance</td>
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<tr>
<td>Nodular sclerosis</td>
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<tr>
<td>Mixed cellularity</td>
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<tr>
<td>Lymphocyte depletion</td>
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<td>Reticular</td>
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**Chart 1.** Relationship of histological types. The parallel relationship of the nodular sclerosis variants and the remaining histological types are illustrated by 2 parallel, overlapping series of circles. The diagnostic problems involve separating between the 2 series and the overlapping circles.
indication of Hodgkin’s disease, but it is one of a group of polyplody cells found in Hodgkin’s disease. The diagnostic type is a large cell which may be lobated, binucleated, or multinucleated and has a large, inclusion-like nucleolus, frequently with perinucleolar halos (Fig. 1). The cytoplasm is abundant and amphiphilic to amphiphilic, and both the nucleoli and cytoplasm are vividly pyroninophilic. The recent studies of Peckham and Cooper (20) have shown that the diagnostic cell is a nonproliferating end-stage cell in which the huge nucleolus and amphiphilic cytoplasm are a reflection of derangement of RNA synthesis with accumulation of cytoplasmic RNA. The intense pyroninophilia of the cytoplasm in methyl green pyronin-stained sections is useful for this reason in the search for diagnostic R-S cells. The majority of large, abnormal cells found in Hodgkin’s disease are the nondiagnostic variants of the R-S cells since they lack the huge, inclusion-like nucleolus and the abundant amphiphilic and pyroninophilic cytoplasm. The important proliferating cell in Hodgkin’s disease according to the work of Peckham and Cooper (20) is a large, abnormal, mononuclear cell apparently related to the nondiagnostic variants of R-S cells. Nevertheless, from our own observations in the study of a number of case series, the frequency of diagnostic R-S cells with huge nucleoli is of primary prognostic significance, while the remaining R-S cell variants are useful only as indicators of the histological type of Hodgkin’s disease.

There are primarily 3 variants of the R-S cell other than the diagnostic type: the lacunar type of nodular sclerosis; the distinctive polyplon type of the L & H type; and the pleomorphic variant found in the reticular type that exhibits sarcomatosus features. The lacunar variant has been proven to be an extremely reliable indicator of nodular sclerosis. This cell has 2 distinctive features: (a) the abundant, pale to water-clear-appearing cytoplasm with a sharply demarcated peripheral margin; and (b) hyperlobation with small nuclei. The latter feature is common but not consistently found in all cells. The nucleolus is generally small and diagnostic R-S cells with huge nucleoli are rare in many cases. The most distinctive feature, the low-density or water-clear cytoplasm presenting a halo-like effect appears to be partially attributable to the artifact of fixation (Fig. 2). In formalin-fixed tissue, the peripheral portion of the cytoplasm often is retracted from the sharply demarcated peripheral margin, and only a small amount of acidophilic cytoplasm remains in the central perinuclear region. In well-fixed tissue with Zenker’s solution, the cytoplasm is abundant, finely granular, and acidophilic; and usually only a relatively narrow peripheral space is apparent (Fig. 3), although the well-defined margin of the cell remains as in the formalin-fixed tissue. The lacunar cells vary widely in frequency and occur singly or in cohesive clusters. They are dramatically apparent in formalin-fixed tissue in low-magnification fields, but to the unaware they may be unimpressive in Zenker’s fixed specimen. The lacunar cells may be extremely numerous within a biopsy specimen, and yet only a rare diagnostic cell with huge, inclusion-like nucleoli may be found. On occasion, the lacunar cells with large or even huge nucleoli are numerous often in association with increased aggressiveness of the process.

The distinctive R-S variant of the L & H type of Hodgkin’s disease has a large polyplony nucleus that is often twisted and overlapping, the nuclear chromatin is extremely fine, and the nucleoli are small or inapparent (Fig. 4). The cytoplasm is pale staining and moderate in amount. The L & H variant of the R-S cell on occasion bears a superficial resemblance to the lacunar cell because of the light staining character of the cytoplasm; but the cytoplasm is considerably less abundant, the nuclei are larger, and they usually do not exhibit hyperlobation with distinctly separate nuclei. The L & H variant of R-S cell may be extremely numerous and constitute 10 to 20% of the cellular population. Diagnostic R-S cells with huge, inclusion-like nucleoli in the same lymph node specimen may be extremely difficult to find, and only diligent search of multiple sections may reveal a small number of acceptable cells of the diagnostic type.

The pleomorphic variant of the R-S cell or the sarcomatosus type exhibits a wide range of bizarre morphological expressions of the diagnostic R-S type, including extreme variations in nuclear number and configuration with giant nucleoli. They usually dominate the cellular proliferation or aggregate in almost tumor nodules.

Criteria for the Histological Types

The histological criteria will be discussed in terms of the classification of Lukes and Butler (15, 16) in relationship to the types of the Rye classification (17). The criteria will be outlined for each histological type in Tables 2 to 7. Of primary importance in all of the histological types are the frequency and character of the diagnostic type of R-S cell: the R-S variants associated with the diagnostic type; the character and amount of fibrosis, whether collagen bands or disorderly connective tissue; and the relative frequency of lymphocytes and other cellular components.

Lymphocyte Predominance. Included within the lymphocyte predominant type of the Rye classification are the nodular and diffuse types of L & H proliferation. The proliferation, portrayed schematically in Chart 2, either occurs in a vaguely nodular fashion distributed throughout the lymph node leaving only a compressed uninvolved portion or extends uniformly and diffusely throughout the node as the diffuse type. The proliferation of lymphocytes and histiocytes has been combined since they are commonly associated in varying proportions, although most frequently the proliferation of lymphocytes predominates. Histiocytes may occur singly or in

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Chart 2. Schematic comparison of lymph node involvement in L & H type, diffuse and nodular. Large, irregular nodules extend throughout the node in the nodular form, while there is uniform involvement in the diffuse form. An occasional reactive follicle may remain in the periphery in each type.

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**Criteria for Involvement in Hodgkin’s Disease**
small aggregates, as in "sarcoid type," or in varying proportions from inconspicuous numbers to the dominant cellular component. Most commonly, however, lymphocytes predominate and on occasion resemble well-differentiated lymphocytic lymphoma or the involvement of lymph nodes in chronic lymphocytic leukemia, particularly in overly thick sections. The lymphocytes are small and have either round, indented, or even cleaved nuclear configuration and scanty cytoplasm. The histiocytes are of the reactive type, with abundant, pale, acidophilic cytoplasm and oval nuclei, with finely dispersed chromatin and small or inconspicuous nucleoli. In general, the histiocytes are distributed randomly in the diffuse type; whereas, in the nodular type they are found within the central portions of the nodules, usually in small numbers. On a few occasions, in my experience, the histiocytes have been extremely numerous within the nodules, and the lesion has superficially resembled a nodular lymphoma of histiocytes. Two types of R-S cells are found in both L & H types, the distinctive variant of the L & H types, and the diagnostic type with huge nucleoli that typically are rare and difficult to find. In both L & H types, active lymphoid follicles are infrequent or absent but, when present are situated in the periphery or the compressed uninvolved portion of the lymph node (Chart 2).

In the following, the criteria for each L & H type of Hodgkin's disease included in lymphocyte predominance will be described separately.

**L & H, Nodular.** This is a distinctive type of Hodgkin's disease that is not generally appreciated, primarily because of its infrequency and the resultant limited experience with the lesion. The process clinically presents as a single, large lymph node, often exceeding 3.0 cm in diameter, rather than as a group of enlarged nodes. The lymph node architecture is obliterated by large, ill-defined, often oval nodules with vaguely demarcated borders, extending through the node from capsule to capsule. Frequently, a small compressed rim of uninvolved lymph node remains in the periphery in which a few identifiable reactive follicles remain (Chart 2). The nodularity may be unimpressive and even overlooked by the unfamiliar observer unless examined in reticulum stain sections in which compressed reticulum fibers about the large nodules are found. The composition of the nodules is somewhat variable but generally consists predominantly of lymphocytes with a few histiocytes and variable numbers of the distinctive L & H variants of R-S cells. On a few occasions, the central portions of the nodules have been composed predominantly of histiocytes with the intermingled R-S cell variants in varying numbers. Between the nodules, the cellularity is predominately lymphocytic and R-S cell variants, and diagnostic R-S cells are found in these areas only when the process appears to be losing its nodularity, becoming diffuse or otherwise changing in aggressiveness.

The cellularity of the nodular type from the above comments is most commonly composed of lymphocytes although histiocytes in small numbers are seen. Other cellular components, such as eosinophils and plasma cells, may be found as a minor component and fibrosis typically is absent, although small foci of hyalized connective tissue have been encountered on a few occasions. Necrosis is absent (Table 2).

The important features of the L & H nodular type are the vague or ill-defined character of the nodularity, the distinctive R-S cell variant of the L & H type, and the distribution of these cells and histiocytes within nodules of lymphocytes. R-S cells of the diagnostic type also are typically rare. The major diagnostic problem is the establishment of the diagnosis because of the difficulty in finding diagnostic R-S cells. Diligent search of multiple sections of numerous blocks typically is necessary. If diagnostic R-S cells are found with ease, however, reexamination of the general features of the lesion is recommended, and the possibility of change to the more aggressive mixed type should be considered. Confusion with a lesion other than Hodgkin's disease, such as lymphocytic lymphoma, well-differentiated, reactive hyperplasia, or chronic lymphocytic leukemia, may occur.

**L & H, Diffuse.** This type presents a problem in classification when the process becomes more aggressive as indicated by an increase in frequency of diagnostic R-S cells. The term lymphocyte predominance is misleading, since emphasis on the frequency of lymphocytes is of secondary importance to the frequency of diagnostic R-S cells with huge nucleoli (Table 3).

The lymph node architecture is generally obliterated by a proliferation of lymphocytes and histiocytes in varying proportions, although lymphocytes most commonly predominate and frequently only small aggregates or sarcoid type clusters of histiocytes are found. Lymphoid follicles with reaction centers are commonly absent, but on occasion a few small follicles may remain in the periphery as demonstrated in Chart 2. Residual nodules of the nodular L & H type may be discerned if reticulum stains are routinely performed on the lesion exhibiting lymphocytic and histiocytic proliferations. Lymph node lesions initially considered to be of the diffuse type appear to be losing their nodularity, becoming diffuse or otherwise changing in aggressiveness.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Lymphocyte predominance (L &amp; H, nodular)</th>
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<tbody>
<tr>
<td>Architecture</td>
<td>Obliterated</td>
</tr>
<tr>
<td>Follicles</td>
<td>Few in residual compressed node</td>
</tr>
<tr>
<td>Nodules</td>
<td>Large, vaguely outlined</td>
</tr>
<tr>
<td>Cellularity</td>
<td>Lymphocytes and histiocytes in varying proportions</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Eosinophils few</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Typically absent</td>
</tr>
<tr>
<td>R-S cells</td>
<td>None</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Lymphocyte predominance (L &amp; H, diffuse)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architecture</td>
<td>Obliterated</td>
</tr>
<tr>
<td>Follicles</td>
<td>Few or absent</td>
</tr>
<tr>
<td>Nodules</td>
<td>Usually none</td>
</tr>
<tr>
<td>Cellularity</td>
<td>Lymphocytes and histiocytes in varying proportions</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Eosinophils few; occasionally numerous</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Typically absent</td>
</tr>
<tr>
<td>R-S cells</td>
<td>None</td>
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type may have unappreciated nodularity, particularly in unusually thick histological sections. The L & H variant of the R-S cells are distributed in a random fashion unless residual nodularity is found; in these instances they may be concentrated within the nodules. Diagnostic R-S cells are infrequent and typically are difficult to find but generally are not as rare as in the nodular type. If typical diagnostic R-S cells are found with ease, the process has changed in aggressiveness and should be classified as the mixed type, since in my experience the process usually has extended beyond the area of apparent involvement.

Problems in classification are similar to the L & H nodular type. The lesion may be mistaken for chronic lymphocytic leukemia or lymphocytic lymphoma, well differentiated, when histiocytes are infrequent. The principal problem in classification, however, is the distinction between the diffuse L & H type and mixed types, when other cell types, such as eosinophils, plasma cells, and focal fibrosis, are identified, suggesting a mixed cellular proliferation. On occasion, eosinophils are rather numerous, but they do not seem to alter the prognosis and therefore the classification. The distinction is based primarily on the frequency of diagnostic R-S cells with huge nucleoli and the presence or absence of the L & H variants of the R-S cell. The process may also resemble nodular sclerosis when collagen band formation is minimal and the cellular proliferation is predominantly lymphocytic. In the diffuse L & H process, capular thickening and collagen band formation typical of nodular sclerosis are absent, and the L & H variant of the R-S cells lacks the abundant, water-clear cytoplasm and hyperlobation of the lacunar cell.

Nodular Sclerosis. The problem in the identification and classification of nodular sclerosis has related to the minimal degree of sclerosis and the question of a cellular phase of nodular sclerosis. In our initial publications (15, 16), we emphasized that a cellular phase appeared to exist in which only a single band of collagen might be found extending from the thickened capsule in association with the typical cellular proliferation containing the lacunar variant of the R-S cell. We suspected that the process probably began as a cellular proliferation associated with lacunar type R-S cells before the formation of collagen bands. Furthermore, the usual biopsy sampling with a scalene or supraclavicular lymph node was thought most likely to yield a more cellular portion than the underlying mediastinal mass, like the top of the iceberg. With these considerations in mind, we believed that some degree of sclerosis would most commonly be encountered and therefore emphasized that 2 criteria, formation of collagen bands usually in association with a thickened capsule and the lacunar variant of the R-S cell, were required for a diagnosis of nodular sclerosis in order to achieve accuracy and reproducibility. From my experience with over 1000 cases of Hodgkin's disease in the years since our original publication, I believe that these 2 criteria are reliable indicators and still should be required for the diagnosis of nodular sclerosis, since only a small percentage of cases of nodular sclerosis would be misclassified. It is acknowledged that, as a result of sampling problems, lymph node involvement in the cellular phase without collagen bands will be found at times, usually as focal or partial involvement, where advanced degrees of sclerosis may become evident subsequently, as pointed out recently by Kadin et al. (11). The view that advanced degrees of sclerosis should be required as a basic criterion as suggested by Hanson (9) and Cross (4) fails to appreciate the basic nature of the evolving process and the reliability of the lacunar variant of the R-S cell and early collagen band formation as diagnostic criteria for nodular sclerosis.

The 2 essential previously mentioned criteria for nodular sclerosis, however, are oversimplification of the extremely diverse expressions of nodular sclerosis, since nodular sclerosis has a number of variants that may resemble each of the remaining histological types, as shown in Chart 1. In the following, the general criteria will therefore be reviewed in terms of the numerous expressions of the evolving process. The varying degrees of lymph node involvement are portrayed schematically in Chart 3, from the early cellular phase which may reflect even focal involvement to the advanced degrees of sclerosis. The architectural alteration, therefore, varies widely from focal involvement to total sclerotic obliteration. Minimal alteration usually is related to focal thickening of the lymph node capsule from which a thick collagen band extends into the cortex. In the rare cases in which the thickening of the capsule or collagen band formation is absent, small foci of lacunar cells may be observed in nodular aggregates, usually at the corticomedullary junction in an otherwise reactive lymph node (11, 24). The degree of lymph node involvement, therefore, may be focal, i.e., limited to few microscopic areas, partial, involving one portion of a node, or total, with involvement by varying degrees of cellular proliferation and sclerosis. No residual features of lymph node architecture remain at times, only a mass subdivided into nodules by wide bands of collagen of varying thickness as shown in Chart 3.

Birefringent collagen band formation, with few exceptions, is associated with broad thickening of the overlying capsule, usually as an extension as shown in Chart 3. A central artery is

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**Chart 3. Schematic comparison of lymph node involvement in nodular sclerosis.**

A. Focal involvement including lacunar cells on rare occasions may be observed before any sclerosis. B. In the early cellular phase, there is collagenous thickening of the capsule and extension of 1 band into the node partially involved by a cellular proliferation that includes lacunar type R-S cells. C. Early sclerosis. The degree of sclerosis varies widely and may be limited to a small portion of a node that is totally involved by the typical cellular proliferation containing lacunar cells. D. Advanced sclerosis. The majority of the node or mass is replaced by dense collagen with residual nodular cellular portions containing typical lacunar type R-S cells.
found within the collagen band, depending upon the level sections, and also frequently in the overlying thickened capsule. From this observation, it appears that the lymph node is being revascularized from the periphery. The collagen is readily identified by polarized light or with one of the trichrome stains, with the exception of the early phase of development when the vessel is surrounded by lightly staining, myxomatous-appearing tissue that is positive with acid mucopolysaccharide stains. With an increased degree of sclerosis, the collagen bands extend in the node and subdivide the lymphoid tissue into nodules interconnecting with other bands until the entire lymph node architecture is obliterated and only a sclerotic mass remains. In the early phase, only one band may be found, usually extending from the thickened capsule (Table 4).

The cellular proliferation of nodular sclerosis is diverse in expression and may resemble closely each of the other histological types. The proliferation may be predominantly lymphocytic, mixed, or lacunar cells. The critical differential diagnostic features, therefore, are the distinctive lacunar cell variant of the R-S cell and collagen band formation. It is therefore critical to be familiar with the varied expressions of the lacunar cells in order to differentiate nodular sclerosis from the other histological types.

**Mixed Cellularity (Mixed Type).** Mixed cellularity is identical with the mixed type of our original classification (14–16) and provides an intermediate position between lymphocyte predominance (L & H types) and lymphocyte depletion (diffuse fibrosis and reticular types). It also serves as an unclassified type for those lesions that lack typical features of the remaining types. Focal or partial involvement of lymph nodes without features of nodular sclerosis are also included in the mixed type since in my experience they represent changing disease.

The problems of classification in the mixed type results, not from the failure to recognize the features of the mixed type, but in a lack of appreciation of the criteria for delineating the remaining histological types. Several examples will illustrate the problem. A proliferation of lymphocytes and histiocytes in which diagnostic R-S cells are frequent is classified as the mixed type. A lesion with a prominent but limited degree of fibrosis and lacking the distinctive character of the disorderly connective tissue fails to qualify for diffuse fibrosis. Similarly, a proliferation containing numerous R-S cell variants in which there are few diagnostic R-S cells with huge nucleoli does not qualify for the reticular type but is included in the mixed type. Finally, a small proportion of cases with typical lacunar cells, occurring in clusters or in widely dispersed form but lacking collagen band formation, are included in the mixed type. Although a cellular phase of nodular sclerosis was included in our original descriptions (15, 16), one definite collagen band of significant thickness was required together with the lacunar cells to provide 2 criteria and enhance the accuracy of classification. Recently, Kadin et al. (11) have suggested that nodular sclerosis occasionally may be observed without collagen bands and identified on the basis of the characteristic lacunar cells alone. For accuracy of classification and reproducibility in large series, both lacunar cells and collagen bands are recommended since few cases will be missed. Because artifactually altered cells may simulate lacunar cells, I believe that the possibility of erroneous overinterpretation, particularly with limited experience with nodular sclerosis, looms as the greater danger if the single criterion, lacunar cells, is used. The mixed type is therefore a heterogeneous group representing the central portion of the spectrum ranging from lesions that border on the L & H types at one extreme to those approaching the lymphocyte depletion types of diffuse fibrosis and reticular at the other. It does not interrelate with nodular sclerosis (Table 5).

The architecture of the lymph node of the mixed type is obliterated diffusely by a variable cellular proliferation that is usually accompanied by an increase in disorderly fibrosis. The degree of fibrosis varies in different portions of the lymph node and in individual cases. Almost all cellular elements of the lymphoreticular system may participate in varying proportions presenting a spectrum of proliferation in which the frequency of lymphocytes range from those of the L & H type at one extreme and the lymphocytic depletion types at the other. Histiocytes and eosinophils are generally prominent, but eosinophils at times may be inconspicuous or absent. Focal necrosis may be found, but it is not a common or dominant feature. The capsule and subcapsular sinuses, typically, are unaltered in the partially and focally involved lymph nodes, but the capsule may be thickened and the subcapsular sinuses and cortical sinuses may be obliterated in the diffusely involved nodes, particularly with prominent degrees of fibrosis. Diagnostic R-S cells of lobated, binucleated, or multinucleated type with huge, inclusion-like nucleoli are frequent and generally easily found, often in almost every low-magnification field.

**Lymphocyte Depletion.** The morphological expressions of lymphocyte depletion, the diffuse fibrosis and reticular types,
have presented a problem in classification primarily because of reliance on a decrease in number of lymphocytes as the principal criterion. Of primary importance, however, in the reticular type is the frequency of diagnostic R-S cells with huge nucleoli, while in the diffuse fibrosis type, the distinctive character of the advanced degree of disorderly fibrosis, is of major significance. In addition, diffuse fibrosis and reticular types are closely related, and both may be found in a single lymph node or in the same patient in different areas.

**Diffuse Fibrosis.** This type is the classical morphological expression of immunological failure in Hodgkin's disease and typically is observed in association with rapidly progressive disease, small lymph nodes with cellular depletion, and lymphocytopenia. Immunological studies in this type demonstrate most consistently the absence of delayed hypersensitivity responsiveness and lack of lymphocyte transformation with phytohemagglutinin. The lymph node architecture is altered diffusely in varying degrees by a distinctive type of nonbirefringent fibrosis. In early stages it consists of amorphous, compact material resembling precollagenous material deposited in the reticular framework of the lymph node, leaving the sinusoids and capsule unaltered. Later it becomes compact and hyalinized with a disorderly reticulum fiber distribution. The degree and character of the cellularity varies somewhat with the amount of fibrosis (Table 6).

**Reticular.** There are 2 morphological expressions of this type. In one form, diagnostic R-S cells with huge nucleoli are numerous and may be the predominant component; while in the 2nd, R-S cells are extremely pleomorphic and bizarre or sarcomatous. Problems in classification have arisen principally with the nonsarcomatous variety in differentiating reticular from mixed and nodular sclerosis. The distinction is dependent upon the difficult judgment of frequency of diagnostic R-S cells. Here an appreciation of the variants of R-S cells is essential. When a number of R-S cells with huge nucleoli can be found in almost every high-magnification field in an otherwise mixed cellular proliferation, the process usually has become extremely aggressive and should be regarded as the reticular type. If, however, the R-S cells are of the lacunar type, even though they may dominate every field and many have huge nucleoli, the lesion is classified as nodular sclerosis. Pathologists often have encountered difficulty with nodular sclerosis in this situation, particularly with aggressive infiltrative masses where collagen bands may be infrequent and the lacunar cells are extremely variable and even pleomorphic (Table 7).

**Focal and Partial Involvement of Lymph Nodes.** Involvement of lymph nodes, either focal or partial (Chart 4), is observed principally with mixed and nodular sclerosis but also on occasion with the reticular type. Focal or partial involvement, in my experience, represents changing disease and evidence of recent involvement of the node, either as an extension in the lymph nodes of a single region or as the initial lymph node in a new region. Rarely is it the only focus of involvement of Hodgkin's disease apparent clinically as reported by Strum and Rappaport (23). When a lymph node exhibiting limited involvement is discovered, morphological evidence of Hodgkin's disease usually will be apparent in adjacent larger and deeper nodes. With this guidance, biopsy of a carefully selected representative lymph node will yield more meaningful information for classification and staging. In addition, the size of the lesion when focal may be insufficient to permit accurate classification. In the absence of a more representative biopsy, focal Hodgkin's disease should be regarded as an indication of changing disease and the mixed type, unless there is evidence of nodular sclerosis. The partially involved nodes appear to represent either enlargement of a single focus or confluence of multiple, small, enlarging foci; involve sizable portions or the majority of nodes and generally are readily classifiable.

Small foci of involvement, whether single or multiple, are situated usually in cortical tissue in the interfollicular region, often near the corticomedullary junction, and are unrelated to sinusoids. Although they may appear as a single focus within an otherwise reactive lymph node, careful search of multiple sections often will reveal multiple foci in similar locations. Generally, these small foci are rather well defined and are distinctly different from the surrounding reactive lymphoid tissue. The size varies considerably, but they may be discernible when as small as a high-magnification field. Because of the limited size of the foci, accurate classification according to the histological types is difficult. Generally, however, they exhibit features of the mixed, nodular sclerosis, or reticular histological types. Diffuse fibrosis, as a result of its aggressive nature and rapidity of development, involves the majority of lymph nodes. In nodular sclerosis, small foci may be found that consist of clusters of lacunar cells, either in a mixed cellular proliferation or as aggregations of lacunar cells in a nodule of lymphocytes. With few exceptions, these foci containing distinctive lacunar cells are associated with adjacent collagen bands and thickening of the overlying capsule, and usually areas of nodular sclerosis are found elsewhere in the lymph node, either in the same section or in deeper sections. Focal involvement in Hodgkin's in my experience essentially does not occur as scattered R-S cell variants, including diagnostic R-S cells, in otherwise reactive lymphoid tissue, but as a discrete focus. The worrisome lymph node reactions that contain atypical cells and plague pathologists with rare

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**Table 5**

<table>
<thead>
<tr>
<th>Architecture</th>
<th>Diffusely obliterated</th>
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<tbody>
<tr>
<td>Cellularity</td>
<td>Partial involvement common</td>
</tr>
<tr>
<td>R-S cells</td>
<td>Varies widely; may resemble L &amp; H, diffuse fibrosis, and reticular types</td>
</tr>
<tr>
<td>Includes unclassifiable lesions</td>
<td></td>
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**Table 6**

<table>
<thead>
<tr>
<th>Architecture</th>
<th>Partially to totally obliterated</th>
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</thead>
<tbody>
<tr>
<td>Cellularity</td>
<td>Disorderly distributed reticulum fibers</td>
</tr>
<tr>
<td>R-S cells</td>
<td>Diagnostic type often rare</td>
</tr>
<tr>
<td>Includes foci of reticular type on occasions</td>
<td></td>
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The mononuclear cell may be accepted as indicated in this Symposium's committee report on morphological criteria. Lymph nodes have not presented a problem in interpretation when the cell has a huge nucleolus similar to the diagnostic general features of one of the histological types in a discrete disease. I believe the following criteria are sufficient: the view that proof of involvement of these sites need not be as stringent as required for initial diagnosis of Hodgkin's disease, but they have raised some difficult new problems regarding the determination of involvement of spleen, bone marrow, and lymph nodes on minimal evidence for staging purposes in patients with established diagnosis of Hodgkin's disease. Previously unappreciated lesions also have been encountered, such as the granulomas of spleen and liver reported by Kadin et al. (10, 11) and lymphocytic portal infiltrate in the liver associated with small bile ductule proliferation. In general, the diagnosis of Hodgkin's disease can readily be established and the lesions can be classified according to the histological types if the sites of involvement are not extremely small. When the foci of involvement are small, particularly in biopsy specimens of liver and bone marrow, the general features of the discrete lesion of Hodgkin's disease are discernible, and only a few abnormal polyploid cells and no ideal diagnostic R-S cells are found. It is my view that proof of involvement of these sites need not be as stringent as required for initial diagnosis of Hodgkin's disease. I believe the following criteria are sufficient: the general features of one of the histological types in a discrete focus; one of the polyploid variants of the R-S cell without the diagnostic type in which there are huge, inclusion-like nucleoli. The mononuclear cell may be accepted as indicated in this Symposium's committee report on morphological criteria when the cell has a huge nucleolus similar to the diagnostic type. The postlymphangiographic changes in the sinusoids of lymph nodes have not presented a problem in interpretation since the multinucleated giant cells are situated in sinusoids and readily distinguishable from R-S cells. In the portions of lymph node involved by Hodgkin's disease, the sinusoids usually were not distended and apparently had not been permeated by the contrast material.

**Extranodal Involvement (Spleen, Bone Marrow, Liver, and Lung).** The laparotomy studies initiated in the past few years have yielded important new information about Hodgkin's disease, but they have raised some difficult new problems regarding the determination of involvement of spleen, bone marrow, and lymph nodes on minimal evidence for staging purposes in patients with established diagnosis of Hodgkin's disease. Previously unappreciated lesions also have been encountered, such as the granulomas of spleen and liver reported by Kadin et al. (10, 11) and lymphocytic portal infiltrate in the liver associated with small bile ductule proliferation. In general, the diagnosis of Hodgkin's disease can readily be established and the lesions can be classified according to the histological types if the sites of involvement are not extremely small. When the foci of involvement are small, particularly in biopsy specimens of liver and bone marrow, the general features of the discrete lesion of Hodgkin's disease are discernible, and only a few abnormal polyploid cells and no ideal diagnostic R-S cells are found. It is my view that proof of involvement of these sites need not be as stringent as required for initial diagnosis of Hodgkin's disease. I believe the following criteria are sufficient: the general features of one of the histological types in a discrete focus; one of the polyploid variants of the R-S cell without the diagnostic type in which there are huge, inclusion-like nucleoli. The mononuclear cell may be accepted as indicated in this Symposium's committee report on morphological criteria when the cell has a huge nucleolus similar to the diagnostic type. The postlymphangiographic changes in the sinusoids of lymph nodes have not presented a problem in interpretation since the multinucleated giant cells are situated in sinusoids and readily distinguishable from R-S cells. In the portions of lymph node involved by Hodgkin's disease, the sinusoids usually were not distended and apparently had not been permeated by the contrast material.

**Spleen.** Involvement of the spleen in Hodgkin's disease consists of discrete nodules situated in the white pulp and vary from microscopic foci to confluent, grossly evident nodules. In the pretherapy state, the nodules may exhibit the feature of any of the histological types in my experience with the exception of lymphocyte predominance (L & H, nodular and diffuse) and are generally readily classifiable. Small foci of involvement are apparent, usually as enlarged Malpighian bodies distinctive from the remaining white pulp as a result of an increase in connective tissue and the presence of R-S cell variants (Fig. 5). In patients with the established diagnosis of nodular sclerosis and splenic involvement, the foci contain identifiable lacunary type R-S cells and usually collagen bands. When the areas of involvement are large, the nodules may be subdivided by interconnected collagen bands. In the remaining histological types, the histological features are generally quite distinctive. In the spleens involved by diffuse fibrosis, a large proportion of the Malpighian bodies are depleted of lymphocytes and replaced by compact precollagenous material that exhibits disorderly reticulum formation. In these cellular-depleted nodules, R-S cells may be infrequent and difficult to find. In the reticular type, large, confluent, partially necrotic nodules are composed predominantly of diagnostic R-S cells.

**Bone Marrow.** Involvement of bone occurs principally as 2 types: the radiologically evident distinctive form and the microscopic type detected on random biopsy or in sections of marrow aspiration particles. The distinctive lesions as demonstrated by Musshoff (19) are frequently associated with contiguously involved lymph nodes in patients with nodular sclerosis. In bone lesions of this type, the lacunar R-S cells often predominate and are identifiable in properly fixed and decalcified specimens. The microscopic foci of involvement detected in random studies in my experience are an expression of widely disseminating disease in agreement with Musshoff's observations (19) and most commonly exhibit the features of diffuse fibrosis. In this type, illustrated in Fig. 7, the distinctive character of the abnormal, poorly organized, precollagen type of connective tissue is usually striking, and there is an increase focally in disorderly reticulum fibers. Abnormal mononuclear cells and R-S cell variants may be in evidence as in Fig. 6, but the diagnostic R-S variant with huge nucleoli may be difficult to find. For the determination of disseminated marrow involvement on random biopsy, features of diffuse fibrosis associated with polyploid R-S cell variants or large, abnormal mononuclear cells with huge nucleoli are sufficient evidence. In the less common involvement with the mixed or reticular types, abnormal R-S cell variants usually are found with less difficulty as a component of the histological type.

**Liver.** Biopsies of the liver obtained at laparotomy have revealed 3 types of lesions: Hodgkin's disease of nodular sclerosis, mixed, diffuse fibrosis, and reticular types; the granulomas of uncertain origin reported by Kadin et al. (10, 11); and portal lymphocytic infiltration associated with

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**Table 7**

<table>
<thead>
<tr>
<th>Lymphocyte depletion (reticular)</th>
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<tr>
<td>Observed in 2 forms:</td>
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<tr>
<td>1. Predominance of diagnostic R-S cells</td>
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<tr>
<td>2. Sarcomatous R-S cells predominate</td>
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<tr>
<td>Architecture</td>
</tr>
<tr>
<td>Partially to totally obliterated</td>
</tr>
<tr>
<td>Cellularity</td>
</tr>
<tr>
<td>Depends on type</td>
</tr>
<tr>
<td>Fibrosis</td>
</tr>
<tr>
<td>Disorderly nonbirefringent</td>
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<tr>
<td>Prominent if lesion overlaps with diffuse fibrosis type</td>
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**Chart 4.** Comparison of focal and partial lymph node involvement. A. The focal type is limited to small, discrete areas, usually in the corticomedullary region of a reactive lymph node. B. In the partial type, the degree varies widely and involves principally the deeper cortex and medulla, leaving portions of the cortex uninvolved.
proliferation of small bile ductules, also of uncertain origin. The lesions of Hodgkin’s disease present no particular difficulty in diagnosis and classification when they are of considerable size and sufficient tissue is available for examination. If the lesion is a focus discovered only on microscopic examination as shown in Fig. 6, the important decision regarding hepatic dissemination may be difficult and search of multiple sections of the lesion is often required. In general the criteria for involvement are similar to those for small foci elsewhere. Evidence of a discrete lesion with features of one of the histological types is essential as well as conclusive evidence of a R-S cell variant, although a diagnostic R-S cell is not required. A large, abnormal mononuclear cell with a huge nucleolus is an acceptable form. Particular caution must be used in interpreting small portal lymphocytic lesions in which there are a few abnormal mononuclear cells. Because of the disseminated nature of hepatic involvement, the lesions generally will exhibit features of the more progressive histological types or nodular sclerosis rather than of lymphocyte predominance. Moreover, nonspecific infiltration of portal areas by lymphocytes in Hodgkin’s disease is common and often striking in degree. The granulomas reported by Kadin et al. (10, 11) are similarly frequent, but they are readily distinguishable from Hodgkin’s lesions.

Lung. The lesions of Hodgkin’s disease in the lung in untreated patients may present the features essentially of any of the histological types except the L & H types. The lesions of nodular sclerosis are most commonly encountered because of the proximity to the mediastinum, the spread of the lesion by contiguity, and the frequent occurrence of regional lesions by this histological type as shown by Musshoff (19). As in other sites of involvement, the diagnosis and classification is not difficult if the specimen and lesion are of considerable size and technically undistorted. The criteria for lung involvement is similar to that used for other sites for staging purposes in established cases of Hodgkin’s disease. For the initial diagnosis of Hodgkin’s disease, the criteria used for lymph nodes, including diagnostic R-S cells, are required.

Discussion

The histological manifestations of Hodgkin’s disease present a challenging array of morphological expressions to the pathologist for interpretation. Our attempt to classify this complex disease and provide usable criteria for reproducible results has received considerable support (1–4, 6–9, 11–13). Admittedly, pathologists have encountered difficulties. These appear solvable, but it is required that pathologists review large numbers of cases comparatively while learning our new approach. The restudy of the histological manifestations of Hodgkin’s disease appears necessary in order to acquire an appreciation of the R-S cell variants and the range of variations within each histological type. From my own experience, including studies of large case series including 2 other experienced pathologists, a lengthy restudy period or new look at Hodgkin’s disease has been required. Once this adaptation has been achieved, our original criteria have proven effective in classification and the results can be quite reproducible, depending upon the degree of experience of the individual pathologist. In review of large case series for publication, 3 pathologists experienced with the criteria would achieve the most ideal results as recommended by Coppleson et al. (3), but I believe that one interested pathologist experienced with our new approach to Hodgkin’s disease can be accurate and effective. Although the original criteria appear to be reasonably reliable, there is need for further reevaluation and consideration of other approaches as proposed by Cross (5). It seems unlikely, however, that the complex system of Cross (5) will be meaningful. Vascular invasion, reported by Rappaport and Strum (21), appears to be an additional useful criterion for increased aggressiveness of the disease.

The broad range of expressions of nodular sclerosis have evoked much attention and undoubtedly considerable work is necessary to define further its subtypes in terms of prognostic significance. Unquestionably, the 2 criteria we described for nodular sclerosis, collagen band formation and lacunar type R-S cells, are a great oversimplification of the histological expressions. The degree of collagen formation varies widely from a single band to total sclerosis, although Hanson (9) and Cross (4) emphasized that rather advanced degrees of collagen formation were essential for recognition of the lesion. Kadin et al. (11) and Strum and Rappaport (24) have provided convincing evidence recently of nodular sclerosis in the form of cellular nodules containing the distinctive lacunar type R-S cell without collagen band formation. Nevertheless, for accuracy and reproducibility I believe that both collagen band formation and lacunar type R-S cells should be required for the diagnosis of nodular sclerosis, since this cellular phase is uncommon and few cases in my experience will be misclassified in large case series. Advanced degrees of collagen formation involving the thymus in nodular sclerosis now appears to account for the lesion previously regarded as granulomatous thymoma (6, 12). Through the years every lesion proposed as a granulomatous thymoma, in my experience, has exhibited features of nodular sclerosis. In all the expressions of nodular sclerosis, the lacunar variant of the R-S cell exhibits its distinctive morphological features and provides a most reliable criteria for the experienced pathologist to interpret all the expressions of this intriguing process. The criteria for classifying the remaining histological types are numerous, but the frequency of the diagnostic R-S cell with huge nucleoli is of paramount importance and provides the basis of precise delineation between the L & H and mixed types and between the mixed and reticular types. The distinctive character of the L & H variant of R-S cell and the peculiar appearance of the fibrosis in diffuse fibrosis type are not generally appreciated. Only careful study of their features will enable the pathologist to achieve a high degree of effectiveness with our new approach to the pathology of Hodgkin’s disease.

References

Robert J. Lukes


Fig. 1. The typical binucleated and multinucleated cells with inclusion-like nucleoli and deeply staining cytoplasm (b, c, and d) present the features of the diagnostic R-S cell and are compared with the diagnostically unreliable mononuclear form (a). LACH S-65-13924. H & E, x 850.

Fig. 2. These lacunar type R-S cells exhibit the pale cytoplasm with artifactual vacuolization and retraction, typically found in tissue fixed in formaldehyde. RJL 197-68. H & E, x 800.

Fig. 3. An aggregate of lacunar type R-S cells in tissue fixed in Zenker's solution have a narrow, peripheral, clear zone; prominent granular cytoplasm; and a variable number of nuclei. The distinctive cytoplasmic character of lacunar cells may be lost with Zenker's fixation. RJL 93-71. H & E, x 800.
Fig. 4. L & H variant of R-S cell. These fragile polyplloid cells have large, convoluted, twisted, overlapping nuclei with finely distributed chromatin, small nucleoli, and a small amount of pale, indistinct cytoplasm. RJL 165-71. H & E, x 800.

Fig. 5. Spleen. A minimal focus of involvement in the white pulp. Several multinucleated cells resembling R-S cells are found in a slightly enlarged Malpighian body in association with slight increase in reticulum. RJL 237-67. H & E, x 400.
Fig. 6. A small focus of Hodgkin’s disease in the liver. Scattered lobated and multinucleated cells are found in a discrete cellular focus exhibiting a prominent increase in connective tissue. LACH 70-5264. H & E, x 160.

Fig. 7. A focus of diffuse fibrosis in the bone marrow. The distinctive abnormal "precollagenous" character of the fibrosis typical of this type is seen in association with R-S variants. RJL 79-71. H & E, x 500.
Criteria for Involvement of Lymph Node, Bone Marrow, Spleen, and Liver in Hodgkin's Disease

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