The histologic categorization of lymphoma has been a source of frustration for many years for both clinicians and pathologists. In the last 10 years, much new information has become available about the lymphomas, resulting in recognition of new entities and refinement of previously recognized disease categories, raising the question of whether it is time for a new lymphoma classification. In this paper we report the results of an international review of lymphomas, which we hope may clarify some of the confusion surrounding this topic.

This review was conducted at a meeting of 19 hematopathologists with particular interest and experience in lymphomas (the International Lymphoma Study Group) in Berlin, Germany, in April 1993. At previous meetings in Europe and the United States, we had come to believe that, despite the variety of classification schemes used, many hematopathologists appeared to agree on a rather large number of distinct lymphoma entities that they recognize and diagnose in daily practice. We believed that we could provide a useful service to both pathologists and clinicians struggling with the classification of lymphomas by attempting to arrive at a consensus regarding the categories of lymphoid neoplasia that can be reliably recognized at present.

What emerged from this meeting was, first, that each of us had independently evolved ways of viewing these diseases that were essentially identical. Surprisingly, there was little divergence between European and US participants. Second, it was evident that, while many of these lymphoma entities are recognized in the Kiel Classification, the Lukes-Collins Classification, and the Working Formulation, they often go by different names in different publications and may have variable criteria for diagnosis. Furthermore, we found that many of us had doubts about both the practical feasibility and the scientific validity of distinguishing certain subtypes in these systems. We also found that while some lymphoma categories are easy to recognize, others are disturbingly prone to subjective variability. This feature of lymphoma diagnosis has not been emphasized in previous schemes for classification, which imply that all categories are equally easy for the pathologist to recognize.

Ideally lymphomas, like most other tumors, should be classified according to their presumed normal counterpart, to the extent possible. This should provide the best information about disease biology, natural history, and response to treatment. However, despite extensive study, the definition of lymphoid compartments in humans and movement of cells between these compartments still contains many uncertainties. Furthermore, there are difficulties in defining the full extent of the neoplastic clone in individual cases of lymphoma, and some well-defined lymphoma types lack obvious normal counterparts. Consequently, although differentiation schemes provide useful conceptual frameworks for understanding lymphomas and suggest important new lines of research, our current understanding of both the immune system and the lymphomas appears to be inadequate to support a biologically "correct" lymphoma classification. Thus, a classification strictly based on a theoretical relationship of tumors to normal stages of differentiation is both unrealistic and unnecessary for the practical categorization of human lymphomas.

We concluded that the most practical approach to lymphoma categorization at this time is simply to define the diseases that we think we can recognize with the currently available morphologic, immunologic, and genetic techniques. Thus, a lymphoma classification becomes simply a list of well-defined, "real" disease entities. Many of these entities are associated with distinctive clinical presentations and natural histories, even though treatment options may be limited. Cases that do not fit into one of these defined entities are best left unclassified, reflecting the fact that we do not yet understand everything about lymphomas or the immune system.

In this review, we summarize the entities agreed on at the meeting, giving the major defining histologic, immunologic, and genetic features, their clinical presentations and course, and postulated normal counterpart in the immune system. It is obviously impossible in this space to cover all diseases completely, and more detailed descriptions of most of these entities are available in the literature. Thus, we have focused

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more on some entities than others, particularly those for which our definitions may differ from those of the major classifications, or which are recently described or difficult for nonexperts to understand.

MATERIALS AND METHODS

Disease Categories

We included both Hodgkin’s disease (HD) and non-Hodgkin’s lymphomas (NHL) and lymphoid leukemias, because both solid and circulating phases are present in many lymphoid neoplasms, and distinction between them is artificial. A proposed list of disease entities, together with defining histologic, immunologic, and genetic features and major clinical features, was prepared by three of us (N.L.H., E.S.J., H.S.). This list was circulated to the group of 19 hematopathologists before the meeting in Berlin, Germany, in April 1993. Participants were assigned one or more of the proposed entities before the meeting, asked to review the literature and their own experience, and reach a conclusion regarding (1) whether or not there were sufficient morphologic, immunologic, genetic, and clinical data to justify its inclusion as a distinct disease entity; (2) what the defining criteria were; and (3) what subgroups or grades should be recognized within the entity. Open debate followed each presentation.

Reproducibility Study: Diffuse Large B-Cell Lymphoma

To assess the practicality of subclassifying diffuse large cell lymphomas (as required by both the Kiel Classification and the Working Formulation), a set of slides of 23 diffuse aggressive B-cell lymphomas selected from Oxford was circulated to the participants before the meeting. The cases were confirmed as B-cell lymphomas (as required by both the Kiel Classification and the Working Formulation), a set of slides of 23 diffuse aggressive B-cell lymphomas selected from Oxford circulated to the participants before the meeting. The results were presented during the discussion of diffuse large B-cell lymphoma.

Consensus Development

In a concluding session, a summary of the defining features of each proposed lymphoma entity was presented in tabular form by one of the three organizers. Changes were made to the tables until a final consensus was reached. Only criteria and characteristics that could be agreed on by a majority of the group were included; features or entities that were either unpublished, little known or used, or controversial were not included. The summary tables were used as a basis for the descriptions of the lymphoma entities. The revised tables and manuscript were circulated and approved by all participants.

RESULTS

General Principles

Major Categories

The group was unanimous in agreeing on three major categories of lymphoid malignancies: B-cell, T-cell, and Hodgkin’s disease (HD) (Table 1). Although for a given patient, distinction between B-cell and T-cell neoplasia may not always be clinically relevant, it was the clear consensus that this distinction is a prerequisite for the recognition of biologic entities and should be made whenever possible, and particularly for clinical trials or other studies for publication. Within these three groups, three general categories were proposed: definite, provisional, and unclassifiable. Provisional

<table>
<thead>
<tr>
<th>Table 1. List of Lymphoid Neoplasms Recognized by the International Lymphoma Study Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-Cell Neoplasms</strong></td>
</tr>
<tr>
<td>I. Precursor B-cell neoplasm: Precursor B-lymphoblastic leukemia/lymphoma</td>
</tr>
<tr>
<td>II. Peripheral B-cell neoplasms</td>
</tr>
<tr>
<td>1. B-cell chronic lymphocytic leukemia/prolymphocytic leukemia/lymphoma</td>
</tr>
</tbody>
</table>
| 2. Lymphoplasmacytoid lymphoma/immunocyto
toma |
| 3. Mantle cell lymphoma                 |
| 4. Follicle center lymphoma, follicular |
|   Provisional cytologic grades: I (small cell), II (mixed small and large cell), III (large cell) |
|   Provisional subtype: diffuse, predominantly small cell type |
| 5. Marginal zone B-cell lymphoma        |
| 6. Diffuse large B-cell lymphoma        |
|   Subtype: Primary mediastinal (thymic) B-cell lymphoma |
| 7. Burkitt’s lymphoma                   |
| 8. Unclassifiable B-cell lymphoma       |
| **T-Cell and Putative NK-Cell Neoplasms**|
| I. Precursor T-cell neoplasm: Precursor T-lymphoblastic lymphoma/leukemia |
| II. Peripheral T-cell and NK-cell neoplasms |
| 1. T-cell chronic lymphocytic leukemia/prolymphocytic leukemia |
| 2. Large granular lymphocyte leukemia (LGL) |
|   T-cell type |
|   NK-cell type |
| 3. Mycosis fungoides/Sezary syndrome |
| 4. Peripheral T-cell lymphomas, unspecified* |
|   Provisional cytologic categories: medium-sized cell, mixed medium and large cell, large cell, lymphoepithelial cell |
|   Provisional subtype: Hepatosplenic γδ T-cell lymphoma |
|   Provisional subtype: Subcutaneous panniculitic T-cell lymphoma |
| 5. Angioimmunoblastic T-cell lymphoma (ALD) |
| 6. Angiocentric lymphoma |
| 7. Intestinal T-cell lymphoma (+/- enteropathy associated) |
| 8. Adult T-cell lymphoma/leukemia (ATUL) |
| 9. Anaplastic large cell lymphoma (ALCL), CD30+, T- and null-cell types |

Hodgkin’s Disease

I. Lymphocyte predominance
II. Nodular sclerosis
III. Mixed cellularity
IV. Lymphocyte depletion
VI. Provisional entity: Lymphocyte-rich classical HD

* These categories are thought likely to include more than one disease entity.
categories include entities that have been described in some detail, but with which we had insufficient experience to be confident that they represent distinct diseases. We also believe that it is important to recognize that some cases of lymphoma do not fit into one of the well-recognized or provisional categories, so we included a separate category for unclassifiable cases.

Postulated Normal Counterparts

We also agreed that, although understanding lymphomas may be enhanced by understanding their relationship to the normal immune system, the normal counterpart of many neoplastic lymphoid cells cannot be defined with certainty at present, and that these relationships cannot serve as the sole basis for lymphoma categorization at this time. Therefore, the putative normal counterpart of each tumor is listed, but other than separation into B- and T-cell categories, we have not attempted to organize this list along lines of differentiation within the B- and T-cell systems.

However, we did agree that there are two major categories within both B- and T-cell neoplasms: "precursor" neoplasms, corresponding to lymphoblastic lymphomas and leukemias, and "peripheral" neoplasms, comprising the remainder of B- and T-cell lymphomas and leukemias. The peripheral B- and T-cell neoplasms are organized in this report more or less according to histologic grade: that is, predominant cell size, density of chromatin and proliferation rate, and entities that morphologically resemble one another are grouped together. However, they could be sorted according to a variety of other features, such as clinical aggressiveness, treatment category, histologic pattern, and so forth, depending on the needs of the users.

Nomenclature

For each entity, we proposed a name based either on its putative normal counterpart, its morphologic features, or established usage. Proliferating cells of antigen-independent stages, which are progenitor cells of the entire lymphoid system, are called "lymphoblasts," whereas the cells of later stages are denoted by prefixes that describe their location in lymphoid tissues, their cytologic appearance, or their presumed function in the immune response.

Probable equivalents for each disease entity are given in the Rappaport, Lukes-Collins and Kiel Classifications, and in the Working Formulation, based in part on the summary by Lennert and Feller; these are summarized in Table 2.

Grade and Aggressiveness

We use the term "grade" to refer to histologic parameters such as cell and nuclear size, density of chromatin and proliferation fraction, and the terms "prognostic group" or "aggressiveness" to denote the clinical behavior of a tumor. One important result of our discussions was the recognition that many of these distinct lymphoma entities have a range of morphologic grade and clinical aggressiveness, making it difficult to arrange them according to a spectrum from low to high grade or indolent to aggressive behavior. The most obvious example is that of follicle center (follicular) lymphomas, but also the mucosa-associated lymphoid tissue (MALT)-type lymphomas, angiocentric lymphoma, and even mantle cell lymphoma can apparently have relatively lower and higher grade types. This point may be best understood by analogy to other tumors, such as soft-tissue sarcomas or ovarian tumors, where each tumor is recognized as a distinct entity, within which pathologic criteria can be established to determine its clinical aggressiveness. This concept is contrary to the approach in some lymphoma classifications, which has tended to assume that all lymphomas are related, can transform into one another, and can be considered as a single spectrum of disease, from low to high grade. Although this view has long been known to be incorrect in some respects, it still colors much thinking about lymphomas. We believe it represents an oversimplification that results in confusion rather than clarity.

Immunophenotypes and Genetic Features

Those given are the most characteristic; variations may be seen in individual cases. The notations and abbreviations are as follows: +, over 90% of the cases positive; +/−, over 50% of the cases positive; −/+ , less than 50% of the cases positive; −, less than 10% of the cases positive; TCR-R, T-cell receptor gene rearrangement; IgH-R and IgL-R, Ig heavy/light chain genes rearranged; S Ig, surface Ig; C Ig, cytoplasmic Ig; CD, cluster of differentiation; EMA, epithelial membrane antigen. Morphologic, immunologic, and genetic features that are important in defining the entity or in differential diagnosis are indicated in boldface type.

B-Cell Neoplasms

Precursor B-Cell Neoplasm: Precursor B-Lymphoblastic Leukemia/Lymphoma (B-LBL)

Synonyms. Rappaport: lymphoblastic (formerly diffuse poorly differentiated lymphocytic [PDL]); Kiel: lymphoblastic, B-cell type; Lukes-Collins: undefined cell; Working Formulation: lymphoblastic.

Morphology. Lymphoblasts are slightly larger than small lymphocytes but smaller than the cells of large B-cell lymphoma, with round or convoluted nuclei, fine chromatin, inconspicuous nucleoli, and scant, faintly basophilic cytoplasm (Fig 1). Mitoses are frequent; a starrky-sky pattern may be seen. There is no correlation between morphology and B or T lineage. Thus, immunophenotyping and molecular genetic studies are required to distinguish precursor B- from precursor T-lymphoblastic lymphoma (T-LBL). Although histologic features are usually sufficient to distinguish lymphoblastic from mature B- or T-cell neoplasms, a differential diagnosis with mantle cell lymphoma or myeloid leukemia may arise in rare cases, particularly in adults, and particularly if smears are not available. In these cases, immunophenotyping and molecular genetic studies are helpful.

Immunophenotype. Tumor cells are characteristically CD10+ CD19+ CD79a+ CD20+ HLA-Dr+ S Ig− eMu+ CD34+ and may coexpress CD13 and/or 33 in some cases. Antibodies to CD79a (mbl: IgM-associated protein) are useful in identifying CD19+ cases, and can be used on paraffin-embedded sections. Expression of TdT and lack of Ig are useful in distinguishing precursor B-LBL from more mature B-cell neoplasms; CD19, CD22,
<table>
<thead>
<tr>
<th>Kiel Classification</th>
<th>Revised European American Lymphoma Classification</th>
<th>Working Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-lymphoblastic</td>
<td>Precursor B-lymphoblastic lymphoma/leukemia</td>
<td>Lymphoblastic</td>
</tr>
<tr>
<td><strong>B-Lymphocytic, CLL</strong></td>
<td>B-cell chronic lymphocytic leukemia/ prolymphocytic leukemia/small lymphocytic lymphoma</td>
<td>Small lymphocytic, consistent with CLL Small lymphocytic, plasmacytoid</td>
</tr>
<tr>
<td>B-lymphocytic, prolymphocytic leukemia</td>
<td></td>
<td>Small lymphocytic, plasmacytoid</td>
</tr>
<tr>
<td>Lymphoplasmacytoid immunocytoma</td>
<td>Lymphoplasmacytoid lymphoma</td>
<td>Diffuse, small cleaved cell Follicular, small cleaved cell Diffuse, mixed small and large cell Diffuse, large cleaved cell</td>
</tr>
<tr>
<td>Lymphoplasmacytoid immunocytoma</td>
<td></td>
<td>Diffuse, mixed small and large cell</td>
</tr>
<tr>
<td><strong>Centrocytic</strong></td>
<td>Mantle cell lymphoma</td>
<td>Diffuse, small cleaved cell Follicular, small cleaved cell Diffuse, mixed small and large cell Diffuse, large cleaved cell</td>
</tr>
<tr>
<td>Centroblastic, centrocytoid subtype</td>
<td></td>
<td>Diffuse, small cleaved cell Follicular, small cleaved cell Follicular, mixed small and large cell Diffuse, mixed small and large cell</td>
</tr>
<tr>
<td><strong>Centroblastic-centrocytic, follicular</strong></td>
<td>Follicular center lymphoma, follicular</td>
<td>Follicular, predominantly small cleaved cell Follicular, mixed small and large cell Diffuse, small cleaved cell</td>
</tr>
<tr>
<td>Centroblastic, follicular</td>
<td></td>
<td>Diffuse, mixed small and large cell</td>
</tr>
<tr>
<td>Centroblastic-centrocytic, diffuse</td>
<td>Follicular center lymphoma, diffuse, small cell [provisional]</td>
<td>Diffuse, small cleaved cell</td>
</tr>
<tr>
<td>—</td>
<td>Extramedullary marginal zone B-cell lymphoma (low-grade B-cell lymphoma of MALT type)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Monocytoid, including marginal zone immunocytoma</strong></td>
<td>Nodal marginal zone B-cell lymphoma [provisional]</td>
<td>Small lymphocytic Diffuse, small cleaved cell Diffuse, mixed small and large cell Unclassifiable</td>
</tr>
<tr>
<td>—</td>
<td>Splenic marginal zone B-cell lymphoma [provisional]</td>
<td>—</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>Hairy cell leukemia</td>
<td>Extramedullary plasmacytoma</td>
</tr>
<tr>
<td>Plasmacytic</td>
<td>Plasmacytoma/myeloma</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td><strong>Centroblastic (monomorphic, polymorphic and multilobated subtypes)</strong></td>
<td>Diffuse large B-cell lymphoma</td>
<td>Diffuse, large cell</td>
</tr>
<tr>
<td><strong>B-Immunoblastic</strong></td>
<td>Diffuse large B-cell lymphoma</td>
<td>Large cell immunoblastic</td>
</tr>
<tr>
<td>—</td>
<td>Diffuse, large cell</td>
<td>Diffuse, mixed small and large cell</td>
</tr>
<tr>
<td>—</td>
<td>Primary mediastinal large B-cell lymphoma</td>
<td>Diffuse, large cell</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>Burkitt’s lymphoma</td>
<td>Large cell immunoblastic</td>
</tr>
<tr>
<td>—</td>
<td>High-grade B-cell lymphoma, Burkitt-like [provisional]</td>
<td>Small noncleaved cell, Burkitt’s</td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>Small noncleaved cell, non-Burkitt’s</td>
</tr>
<tr>
<td><strong>T-lymphoblastic</strong></td>
<td>Precursor T-lymphoblastic lymphoma/leukemia</td>
<td>Lymphoblastic</td>
</tr>
<tr>
<td>—</td>
<td>T-cell chronic lymphocytic leukemia/ prolymphocytic leukemia</td>
<td>Small lymphocytic Diffuse small cleaved cell</td>
</tr>
<tr>
<td><strong>T-lymphocytic, CLL type</strong></td>
<td>Large granular lymphocytic leukemia</td>
<td>Small lymphocytic Diffuse, small cleaved cell</td>
</tr>
<tr>
<td>—</td>
<td>— T-cell type</td>
<td>Diffuse, large cell</td>
</tr>
<tr>
<td>—</td>
<td>— NK-cell type</td>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td><strong>T-lymphocytic, prolymphocytic leukemia</strong></td>
<td>Mycosis fungoides/Sezary syndrome</td>
<td>—</td>
</tr>
<tr>
<td><strong>Small cell cerebriform (mycosis fungoides, Sezary syndrome)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>Peripheral T-cell lymphomas, unspecified [including provisional subtype: subcutaneous panniculitic T-cell lymphoma]</td>
<td>Diffuse, small cleaved cell Diffuse, mixed small and large cell Diffuse, large cell</td>
</tr>
<tr>
<td><strong>T-cell chronic lymphocytic leukemia</strong></td>
<td></td>
<td>Large cell immunoblastic</td>
</tr>
<tr>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T-immunoblastic</strong></td>
<td>Hepatosplenic γ-δ T-cell lymphoma [provisional]</td>
<td>—</td>
</tr>
<tr>
<td>—</td>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>Diffuse, mixed small and large cell Diffuse, large cell</td>
</tr>
<tr>
<td>Angioimmunoblastic (AILD, LgX)</td>
<td></td>
<td>Large cell immunoblastic</td>
</tr>
</tbody>
</table>
Table 2. Comparison of the Proposed Classification With the Kiel Classification and Working Formulation (Cont’d)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Proposed Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiocentric lymphoma</td>
<td>Diffuse, small cleaved cell</td>
</tr>
<tr>
<td>Intestinal T-cell lymphoma</td>
<td>Diffuse, mixed small and large cell</td>
</tr>
<tr>
<td>Diffuse, mixed small and large cell</td>
<td></td>
</tr>
<tr>
<td>Diffuse, large cell</td>
<td></td>
</tr>
<tr>
<td>Large cell immunoblastic</td>
<td></td>
</tr>
<tr>
<td>Diffuse, small cleaved cell</td>
<td></td>
</tr>
<tr>
<td>Diffuse, mixed small and large cell</td>
<td></td>
</tr>
<tr>
<td>Diffuse, large cell</td>
<td></td>
</tr>
<tr>
<td>Large cell immunoblastic</td>
<td></td>
</tr>
<tr>
<td>Diffuse, large cell</td>
<td></td>
</tr>
<tr>
<td>Large cell immunoblastic</td>
<td></td>
</tr>
<tr>
<td>Large cell immunoblastic</td>
<td></td>
</tr>
<tr>
<td>T-large cell anaplastic (Ki-1+)</td>
<td>Anaplastic large cell lymphoma, T- and null-cell types</td>
</tr>
</tbody>
</table>

When more than one Kiel or Working Formulation category is listed, those in boldface type comprise the majority of the cases.

* Not listed in classification, but discussed as rare or ambiguous type.

CD10, and CD79a are useful in distinction from T-LBL and granulocytic sarcoma.

Genetic features. Ig heavy chain genes are usually rearranged; light chain genes may be rearranged.17,18 Rearrangement of T-cell receptor genes is present in a minority of the cases; cytogenetic abnormalities are variable.20 Antigen receptor gene rearrangements may not be helpful in distinguishing T- from B-precursor neoplasms.

Clinical features. Children are more commonly affected than adults; this disease accounts for about 80% of acute lymphoblastic leukemia and probably less than 20% of lymphoblastic lymphoma. Although the vast majority of precursor B-cell neoplasms present as acute leukemias, with bone marrow (BM) and peripheral blood (PB) involvement, both pathologists and clinicians should be aware that a small proportion present as solid tumors, most often in skin, bone, and lymph nodes, with or without BM or peripheral blood involvement. These solid tumors are histologically indistinguishable from precursor T-lymphoblastic lymphoma.21,22 The disease is highly aggressive but frequently curable with available therapy. Immunophenotypic and cytogenetic features may be useful in predicting outcome: cases with t(1;19) have a worse prognosis, as do cases with t(9;22) or 11q13 abnormalities and those that lack CD10, CD34, or CD24, or express CD13 and CD33; cases with greater than 50 chromosomes have a better prognosis.15,20

Postulated normal counterpart. BM-derived precursor B cell.

Peripheral B-Cell Neoplasms

B-Cell Chronic Lymphocytic Leukemia (B-CLL)/Prolymphocytic Leukemia (B-PLL)/Small Lymphocytic Lymphoma (B-SLL)

Synonyms. Rappaport: well-differentiated lymphocytic, diffuse; Kiel, B-CLL, B-PLL, immunocytoma, lymphoplasmacytoid type; Lukes-Collins: small lymphocyte B, B-CLL: Working Formulation: small lymphocytic, consistent with CLL.

Morphology. Enlarged lymph nodes in patients with B-CLL show a characteristic infiltrate (Fig 2). The predominant cell is a small lymphocyte, which may be slightly larger than a normal lymphocyte, with clumped chromatin, usually a round nucleus, and occasionally a small nucleolus. Larger lymphoid cells (prolymphocytes and paraimmunoblasts) are always present, usually clustered in pseudo follicles (proliferation centers), imparting a pseudofollicular pattern, or less often, distributed evenly throughout the node.21-22 Increased numbers of large cells may be associated with a more aggressive course.23,24 In some cases, the small lymphoid cells show moderate nuclear irregularity, which can lead to a differential diagnosis of mantle cell lymphoma (see below); if

<table>
<thead>
<tr>
<th>B-CLL/SLL</th>
<th>Diffuse with pseudofollicles</th>
<th>Round (may be cleaved)</th>
<th>Prolymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoplasmacytoid</td>
<td>Diffuse</td>
<td>Round (may be cleaved)</td>
<td>Para immunoblasts</td>
</tr>
<tr>
<td>lymphoma</td>
<td>Diffuse, vaguely nodular, mantle zone, rarely follicular</td>
<td>Cleaved (may be round or oval)</td>
<td>Centro blasts</td>
</tr>
<tr>
<td>Follicle center lymphoma</td>
<td>Follicular +/- diffuse areas, rarely diffuse</td>
<td>Cleaved (centrocytes)</td>
<td>Centro blasts</td>
</tr>
<tr>
<td>Marginal zone B-cell lymphoma</td>
<td>Diffuse, interfollicular, marginal zone, occasionally follicular (colonization)</td>
<td>Heterogeneous: round small lymphocytes, cleaved (marginal zone/monocytoid B cells, plasma cells)</td>
<td>Centro blasts</td>
</tr>
</tbody>
</table>

Table 3. Low-Grade B-Cell Lymphomas: Morphologic Features in Differential Diagnosis

<table>
<thead>
<tr>
<th>Lymphoma</th>
<th>Small Cells</th>
<th>Large Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-CLL/SLL</td>
<td>Diffuse with pseudofollicles</td>
<td>Round (may be cleaved)</td>
</tr>
<tr>
<td>Lymphoplasmacytoid</td>
<td>Diffuse</td>
<td>Round (may be cleaved)</td>
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</tr>
<tr>
<td>Marginal zone B-cell lymphoma</td>
<td>Diffuse, interfollicular, marginal zone, occasionally follicular (colonization)</td>
<td>Heterogeneous: round small lymphocytes, cleaved (marginal zone/monocytoid B cells, plasma cells)</td>
</tr>
</tbody>
</table>
Fig 1. Precursor lymphoblastic neoplasms. (A) Precursor B-lymphoblastic lymphoma of lymph node. The tumor cells have irregular nuclei, dispersed chromatin, inconspicuous nucleoli, and scant cytoplasm (Giemsa, original magnification × 872). (B) Precursor T-lymphoblastic lymphoma of lymph node. The appearance is similar to the B-precursor neoplasm (hematoxylin and eosin [H&E], original magnification × 872).

Fig 2. Lymph node from a patient with B-cell chronic lymphocytic leukemia. (A) Low power view showing characteristic pseudofollicles (proliferation centers) (H&E, original magnification × 22). (B) High magnification showing small lymphocytes, prolymphocytes, and paraimmunoblasts (Giemsa, original magnification × 544).

Fig 3.

Fig 4.
pseudo-follicles and/or prolymphocytes and paraimmunoblasts are present, a diagnosis of B-CLL should be made
(Table 3). B-PLL is characterized by a predominance (>50%) of cells with clumped chromatin but with a prominent central nucleolus and more abundant cytoplasm than typical CLL cells; these cells are best evaluated on smears of peripheral blood or BM.

Most patients whose lymph nodes contain the characteristic infiltrate associated with B-CLL will prove to have BM and PB involvement at the time of the diagnosis or shortly thereafter; however, some are nonleukemic at presentation and it is possible that some may not develop leukemia. A term is needed for these cases, by analogy to granulocytic sarcoma or lymphoblastic lymphoma. The term small lymphocytic lymphoma has in the past been used to encompass not only the nodal counterpart of B-CLL, but also many MALT-type lymphomas and probably also some T-cell neoplasms. We propose that the term small lymphocytic lymphoma be restricted to tumors that show the characteristic morphology and immunophenotype of B-CLL.

Based on our experience and on the literature, it appears that some cases with the characteristic morphology and immunophenotype of B-CLL can have plasmacytoid differentiation, with cytoplasmic Ig and often a small M-component. These cases correspond to the "lymphoplasmacytoid" immunocytoma of the Kiel Classification. The clinical course of these cases does not appear to differ markedly from B-CLL, and we propose that these tumors not be given a separate diagnostic category, but rather be regarded as a variant of B-CLL.

Immunophenotype. The tumor cells of B-CLL have faint SfG, SfD\(^+\), (Clg\(^+\)), B-cell-associated antigen\(^+\) (CD19, 20, 79a), CD5\(^+\), CD23\(^+\), CD43\(^+\), (CD11c\(^-\) (faint), and CD10\(^-\). CD23 is useful in distinguishing B-CLL from mantle cell lymphoma (Table 4). CD22 expression may be weak or undetectable, particularly by flow cytometry. Differences in antigen expression (such as CD11c\(^+\)) may be associated with variations in clinical course; further study of these variants is needed. Cases of B-PLL may be CD5\(^+\), have strong SfG, and more often express CD22.

Genetics. Ig heavy and light chain genes are rearranged; trisomy 12 is reported in one third of the cases, and abnormalities of 13q are seen in up to 25%. (11;14) and bc1-1 rearrangement have been reported; these cases may need further study to rule out the possibility that they are examples of mantle cell lymphoma.

Clinical features. The majority of the cases occur in older adults; this disease comprises 90% of chronic lymphocytic leukemias in the United States and Europe. Most patients have BM and PB involvement at diagnosis; tumor commonly involves multiple nodes, spleen, and liver; extranodal infiltrates may occur. A small M-component may be found in some patients. Occasional patients present with aleukemic nodal involvement, but most will ultimately be found to have or develop marrow and blood infiltration. The clinical course is indolent, and this disease is not usually considered curable with available therapy. Prolymphocytoid transformation or transformation to large cell lymphoma (Richter's Syndrome), may occur; these are usually diffuse large B-cell lymphomas, but cases resembling HD have been reported. B-PLL presents with an unusually high white blood cell (WBC) count and splenomegaly, and has a more aggressive clinical course than typical B-CLL.

Postulated normal counterpart. Recirculating CD5\(^+\) CD23\(^+\) peripheral B cell.

Lymphoplasmacytoid Lymphoma/Immunocytoma

Synonyms. Rappaport: well-differentiated lymphocytic, plasmacytoid, diffuse mixed lymphocytic and histiocytic; Kiel: immunocytoma, lymphoplasmacytic type; Lukes-Collins: plasmacytic-lymphocytic; Working Formulation: small lymphocytic, plasmacytoid, diffuse mixed small and large cell.

Morphology. The tumor consists of a diffuse proliferation of small lymphocytes, plasmacytoid lymphocytes (cells with abundant basophilic cytoplasm, but lymphocyte-like nuclei), and plasma cells, with or without Dutcher bodies, by definition, lacks features of B-CLL, mantle cell, follicle center cell, or marginal zone lymphomas (Table 3). The growth pattern is often interfollicular with sparing of the sinuses.

The terms lymphoplasmacytoid lymphoma, plasmacytoid lymphocytic lymphoma, or immunocytoma do not appear to us to define a single entity, as used in the literature. Many B-CLL neoplasms may occasionally show maturation to plasmacytoid or plasma cells containing Clg, including B-CLL, mantle cell, follicle center, and marginal zone cell lymphomas. We suggest that these cases be classified according to their major features, and not as lymphoplasmacytoid lymphomas. There does appear to be a distinct disorder of small lymphoid cells that show maturation to plasma cells, without features of other lymphoma types, which corresponds to most cases of Waldenstrom's macroglobulinemia. These tumors usually lack CD5 and lack characteristic features of other lymphoma subtypes. They correspond most closely to the lymphoplasmacytic immunocytoma of the Kiel classification. We propose restricting the terms lymphoplasmacytoid lymphoma or immunocytoma to these cases.

Immunophenotype. The cells have surface and cytoplasmic (some cells) Ig, usually of IgM type, usually lack IgD, and are B-cell-associated antigens (CD19, 20, 79a), CD5\(^+\), CD10\(^+\), CD43\(^-\); CD25 or CD11c may be faintly positive in some cases. Lack of CD5 and the
presence of strong cytoplasmic Ig are useful in distinction from B-CLL (Table 4).

Genetic features. Ig heavy and light chain genes are rearranged. No specific abnormality is known.

Clinical features. Lymphoplasmacytoid lymphoma/immunocytoma occurs in the same general age group as B-CLL. Sites involved include BM, lymph nodes, and spleen; less frequently peripheral blood or extranodal sites. The majority of patients have a monoclonal serum paraprotein of IgM type; hyperviscosity symptoms may occur (Waldenstrom’s macroglobulinemia).6,31-34 (Note: other lymphomas may also be associated with serum paraproteins.) The course is indolent and the disease is not generally curable with available treatment. Transformation to large cell lymphoma may occur.

Postulated normal counterpart. CD5+ peripheral B lymphocyte stimulated to differentiate to a plasma cell.

Mantle Cell Lymphoma

Synonyms. Rappaport: intermittently or poorly differentiated lymphocytic, diffuse or nodular (ILL/IDL/PDL); Kiel: centrocytic (mantle cell) lymphoma; Lukes-Collins: small cleaved follicular center cell (FCC); Working Formulation: differentiated lymphocytic, diffuse or nodular (ILL/IDL); Kiel: classification criteria for centrocytic lymphoma*. The tumor occurs in older adults, with a high male-to-female ratio; it is usually widespread at diagnosis. Sites involved include lymph nodes, spleen, Waldeyer’s ring, BM, blood, and extranodal sites, especially the gastrointestinal tract (lymphomatous polyposis).35 The course is moderately aggressive, and it appears to be incurable with available treatment. The median survival ranges from 3 to 5 years; the blastoid variant is more aggressive (median survival 3 years).43 Transformation to a large cell lymphoma composed of centroblast and/or immunoblast-like cells does not appear to occur.

The pattern of mantle cell lymphoma is usually diffuse or vaguely nodular; well-defined follicles as in follicular lymphomas are rarely but occasionally seen. In many cases the tumor involves the mantle zones of at least some reactive follicles; less commonly, a pure mantle zone pattern occurs. Many cases contain individually scattered epithelioid histiocytes, creating a “starry-sky” appearance at low magnification.

We recently proposed the term mantle cell lymphoma to replace centrocytic lymphoma, intermediate lymphocytic lymphoma (ILL), lymphocytic lymphoma of intermediate differentiation (IDL), and mantle zone lymphoma.4 It corresponds to centrocytic lymphoma of the Kiel Classification, which is now believed not to arise from true follicle center centrocytes, but rather possibly from a subset of follicle mantle B cells. In the original Working Formulation study, centrocytic lymphoma was included within the category of diffuse small cleaved cell lymphoma, and comprised the majority of the cases of this subtype. The blastoid variant and some other cases with larger cells may fall within the diffuse mixed or large cleaved cell categories of the Working Formulation; however, the tumor cells do not have basophilic cytoplasm and are distinct from the other lymphomas in these heterogeneous Working Formulation categories.

Immunophenotype. The tumor cells are S IgM+, usually IgD−, λ > κ, B-cell–associated antigen+, CD5+, CD10−/+. CD23−, CD43+, CD11c−. A prominent, disorganized meshwork of follicular dendritic cells (FDC) is present. Absence of CD23 is useful in distinguishing mantle cell lymphoma from B-CLL; Absence of CD23 is useful in distinguishing mantle cell lymphoma from B-CLL; CD5 is useful in distinction from follicle center and marginal zone lymphomas (Table 4).31,33,42,45,46

Genetic features. A chromosomal translocation t(11;14) involves the Ig heavy chain locus and the bcl-1 locus on the long arm of chromosome 11 in the majority of the cases. This translocation results in overexpression of a gene known as PRAD1, which encodes for cyclin D1, a cell-cycle protein that is not normally expressed in lymphoid cells.30,34,44,47-52

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**Follicle Center Lymphoma, Follicular. Provisional**

**Morphology.** This lymphoma is defined as a tumor composed of follicle center cells, usually a mixture of centrocytes (cleaved follicle center cells) and centroblasts (large noncleaved follicle center cells) (Table 3). The pattern is at least partially follicular, but diffuse areas may be present (Fig 4). Sclerosis is common in diffuse areas. Centrocytes typically predominate; centroblasts are usually in the minority, but by definition are always present. Rare lymphomas with a follicular growth pattern consist almost entirely of centroblasts; because the follicular pattern implies a germinal center origin, we include these in the category of follicle center lymphoma.

Examples of the tumor that we define in this manner have been included in different categories in different classifications. By pattern, they would be included in the categories of nodular or follicular lymphomas in the Rappaport Classification and Working Formulation. By cytology they would be included in the categories of follicular center cell lymphoma in the Lukes-Collins Classification and centroblastic/centrocytic lymphoma in the Kiel Classification. However, some of these categories may include lesions other than follicle center lymphoma that may have a nodular pattern (such as mantle cell or MALT-type lymphomas in the Working Formulation), or consist of a monomorphic population of cells believed to be of germinal center origin (Burkitt's lymphoma and some cases of diffuse large FCC lymphoma in the Lukes-Collins classification). The category of centroblastic/centrocytic lymphoma in the Kiel Classification excludes cases of follicle center lymphoma that are follicular but contain a predominance of large cells. Therefore, we propose the term "follicle center lymphoma" to encompass most tumors classified as follicular lymphomas in the Working Formulation, most tumors with a follicular pattern classified as follicle center cell lymphoma in the Lukes-Collins classification, all cases in the Kiel Classification category of centroblastic/centrocytic lymphoma with any follicular pattern, and follicular centroblastic lymphoma.

Both the proportion of centroblasts and the size of the centrocytes vary among cases. Follicle center lymphoma cannot be sharply divided into distinct subtypes, but rather shows a continuous gradation in the number of large cells. Although this has been called "subclassification" in the past, it should be recognized as grading. Although it has been repeatedly shown that an individual pathologist can effectively predict outcome in follicular lymphoma by grading according to proportion of large cells, studies have shown that this is difficult to reproduce among groups of pathologists. By convention in the United States, follicular lymphomas are separated into predominantly small, mixed small and large, and predominantly large cell categories. To avoid this rather unsatisfactory terminology, which implies distinct tumor types, the terms follicular lymphoma, grade I, grade II, and grade III, which are more analogous to terms used for other tumor types, are suggested. We are not able to recommend specific criteria for grading, but suggest that, as with other tumors, each pathologist or institution should adopt a grading scheme and use it consistently, until data from prospective clinical trials are available to suggest a uniform method.

In addition to cellular composition, the proportions of follicular and diffuse areas vary from case to case, and these are also associated with prognosis. The pattern in a given case is usually reported as follicular or follicular and diffuse. **Provisional Subtype: Follicle Center Lymphoma, Diffuse (Predominantly Small Cell)**

**Synonyms.** Rappaport: diffuse poorly differentiated lymphocytic; Kiel: centroblastic/centrocytic, diffuse; Lukes-Collins: diffuse small cleaved FCC; Working Formulation: diffuse small cleaved cell.

Rare lymphomas composed of cells that resemble centrocytes, with a minor component of centroblasts, are entirely diffuse; if both the small and large cells have the phenotype of follicle center cells (see below), it may be assumed that they represent the diffuse counterpart of a follicle center lymphoma. These examples may represent a sampling problem in some cases in which larger biopsies show follicular areas. Most have been called diffuse small cleaved cell lymphoma in the Working Formulation, but some may have sufficient large cells to be called diffuse mixed small and large cell.

**Immunophenotype.** The tumor cells are usually S1g+ (IgM +/− IgD > IgG > IgA), B-cell–associated antigen+, CD10+/-, CD5−, CD23−, CD43−, CD11c− (Table 4). Tightly organized meshworks of FDC are present in follicular areas. BCL-2 protein expression is useful in distinguishing reactive from neoplastic follicles, because it is absent from reactive follicles and present in most follicular lymphomas; however this is not useful in distinguishing follicle center from other types of low-grade B-cell lymphoma, most of which also express BCL-2 protein. Lack of CD5 and CD43 is useful in distinguishing follicle center lymphoma from mantle cell lymphoma, and the presence of CD10 can be useful in distinguishing it from marginal zone cell lymphomas (see below).

**Genetic features.** t(14;18), involving rearrangement of the bcl-2 gene, is present in 70% to 95% of the cases, resulting in expression of this "anti-apoptosis" gene, which is switched off at the translational level in normal germinal center cells; expression of the BCL-2 protein permits accumulation of long-lived centrocytes. This translocation occurs at an early stage of B-cell development, during Ig gene rearrangement, and occasional cells with rearranged bcl-2 genes can be detected in normal lymphoid tissues in some normal individuals. These observations suggest that when a resting B cell that carries the bcl-2 translocation undergoes blast transformation in response to antigen, failure to switch...
off the bcl-2 gene may contribute to development of a lymphoma.

Clinical features. Follicle center lymphoma affects predominantly adults, with an equal male:female incidence. It constitutes as much as 40% of adult NHLs in the United States; the incidence is apparently lower elsewhere. Most patients have widespread disease at diagnosis. Sites involved include predominantly lymph nodes, but also spleen, BM, occasionally PB, or extranodal sites. The clinical course is generally indolent, and it is not usually curable with available treatment. Both the number of centroblasts and the size of the centrocytes appear to correlate with prognosis. Controversy exists over whether cases classified as follicular mixed cell type may be curable with aggressive therapy. Like the proportion of centroblasts, the proportion of the tumor that has a follicular pattern is also related to prognosis. The rare purely diffuse cases appear to have a worse prognosis. Progression to diffuse large B-cell lymphoma may occur.

Postulated normal counterpart. Germinal center B cells, both centrocytes (small cleaved follicular center cells) and centroblasts (large noncleaved follicular center cells), appear to correlate with prognosis.

Marginal Zone B-Cell Lymphoma

(1) Extranodal: Low-grade B-cell lymphoma of MALT type (+/- monocytoid B cells); and (2) Nodal: (+/- monocytoid B cells) (provisional).

Synonyms. Rappaport: (not specifically listed) well-differentiated lymphocytic (WDL) or WDL-plasmacytoid, IDL, ILI, PDL, mixed lymphocytic-histiocytic (nodular or diffuse); Kiel: monocytoid B-cell, immunocytoma (some cases previously classified as centroblastic/centrocytic or centrocytic); Lukes-Collins: small lymphocyte B, lymphocytic-plasmacytic, small lymphocyte B, monocytoid; Working Formulation: (not specifically listed) SLL (some c/w CLL, some plasmacytoid), small cleaved or mixed small and large cell (follicular or diffuse).

Two tumors have been described in recent years, which have sufficient morphologic, immunophenotypic, and clinical similarity to suggest that they may be related. These are the low-grade B-cell lymphoma of MALT type and monocytoid B-cell lymphoma. The nomenclature for these tumors has been confusing: some authorities have used the term monocytoid B-cell lymphoma for both nodal and extranodal disease, and monocytoid B-cell lymphoma of nodal disease, others have restricted monocytoid B-cell lymphoma to nodal disease, and it has not been clear what to call extranodal non-mucosa-associated tumors or nodal tumors with cells that are smaller than typical monocytoid B cells. The tumors show morphologic evidence of differentiation at least in part into cells of marginal zone type, which appear to have the capacity to mature into both monocytoid B cells and plasma cells, and appear to display tissue-specific homing patterns. It seems reasonable to postulate that the different clinical syndromes associated with tumors of this morphologic type may be a result of the homing pattern of the specific neoplastic clone. In addition, proliferation of these cells at certain sites may depend on the presence of activated, antigen-driven T cells. We propose the term "marginal zone B-cell lymphoma" to encompass tumors with these morphologic features, with modifiers to indicate the clinical subtype: extranodal or nodal.

Morphology. Marginal zone B-cell lymphoma is characterized by cellular heterogeneity, including marginal zone (centrocyte-like) cells (small, atypical cells resembling small cleaved follicular center cells or centrocytes, but with more abundant cytoplasm, similar to Peyer’s patch, mesenteric nodal, or splenic marginal zone cells), monocytoid B cells, small lymphocytes, and plasma cells. Occasional large cells (centroblast- or immunoblast-like) are present in most cases. Reactive follicles are usually present, with the neoplastic marginal zone or monocytoid B cells occupying the marginal zone and/or the interfollicular region. Progression to diffuse large B-cell lymphoma may occur.

Immunophenotype. Tumor cells express S1g (M > G or A), lack IgD, and about 40% are Clg–; B-cell–associated antigens (CD19, 20, 22, 79a) are expressed, and the tumors are CD5–, CD10–, CD23–, CD43–, CD11c– (Table 4). Immunophenotyping studies are a useful adjunct to diagnosis, in excluding B-CLL (CD5+), mantle cell (CD5+), and follicle center (CD10+, CD43+, CD11c+, usually Clg–), lymphomas.

Genetic features. No rearrangement of bcl-2 or bcl-1 is seen; trisomy 3 and or t(11;18) have been reported in extranodal cases.

Clinical features. There are two major clinical presentations of lymphoma with the above-described morphologic and immunologic features.

(1) Extranodal marginal zone lymphoma (low-grade B-cell lymphoma of MALT type). These are tumors of adults, with a slight female predominance. Many patients have a history of autoimmune disease, such as Sjogren’s syndrome or Hashimoto’s thyroiditis, or of helicobacter gastritis. It has been suggested that “acquired MALT” secondary to autoimmune disease or infection in these sites may form the substrate for lymphoma development. The majority present with localized stage I or II extranodal disease, involving glandular epithelial tissues of various sites, most frequently the stomach; however, skin and soft tissues may be the presenting site as well. The term “extranodal marginal zone lymphoma” can be used for cases not involving epithelial tissues. Dissemination occurs in up to 30% of the cases, often in other extranodal sites, with long disease-free intervals. Localized tumors may be cured with local treatment. Recent studies suggest that proliferation in some early MALT-type tumors may be antigen-driven, and that therapy directed at the antigen (helicobacter pylori in gastric lymphoma) may result in regression of early lesions. When disseminated, they appear to be indolent and not curable. Transformation to large cell lymphoma may occur.

(2) Nodal marginal zone lymphoma (provisional subtype). The majority of nodal monocytoid B-cell lymphomas
occur in patients with Sjogren’s syndrome or other extranodal MALT-type lymphomas and, therefore, likely represent nodal spread of MALT-type lymphoma. However, tumors with morphologic features identical to those described for extranodal MALT-type or monocytoid B-cell lymphomas have occasionally been reported with isolated or disseminated nodal involvement, in the absence of extranodal disease. Other sites involved include BM and, rarely, PB. The clinical course is indolent, and when disseminated, it is not usually curable with available therapy. Transformation to large cell lymphoma may occur.

Postulated normal counterpart. Marginal zone B cell of extranodal or nodal type with capacity to differentiate into plasma cell and home to certain tissue compartments.

Splenic Marginal Zone Lymphoma, With or Without Villous Lymphocytes ( Provisional Entity)

Synonyms. Rappaport: (not specifically listed) WDL or WDL-plasmacytoid; Kiell: not specifically listed; Lukes-Collins: small lymphocyte B, Lymphocytic-plasmacytic, small lymphocyte B, monocytoid; Working Formulation: (not specifically listed) SLL.

Several cases of splenic lymphoma have been reported, involving both red and white pulp, with a mantle and/or marginal zone pattern in the white pulp, the term “splenic marginal zone lymphoma” has been proposed for this entity. However, it appears to be both morphologically and clinically distinct from extranodal (MALT type) and nodal marginal zone B-cell lymphomas. There is overlap between this entity and an uncommon type of adult chronic B-lymphocytic leukemia, often mistaken for hairy cell leukemia, called splenic lymphoma with villous lymphocytes (SLVL). Preliminary investigation suggests that the spleens of patients with SLVL are identical to those previously reported as splenic marginal zone lymphoma.

Morphology. The characteristic pattern of involvement of both the mantle and marginal zone of the splenic white pulp, usually with a central residual germinal center, which may be either atrophic or hyperplastic. Red pulp involvement may be prominent. The neoplastic cells range from small lymphocytes in the mantle zone to larger cells with irregular nuclei and pale cytoplasm (marginal zone B cells) in the marginal zone.

Immunophenotype. Similar to that of extranodal and nodal marginal zone B-cell lymphomas.

Genetic features. Not well studied; however, trisomy 3 has not been detected.  

Clinical features. Patients typically have BM and PB involvement, usually without peripheral lymphadenopathy, and may have a small M-component. The course is reported to be indolent, and splenectomy may be followed by prolonged remission.

Postulated normal counterpart. Peripheral B cell with differentiation in part to splenic marginal zone cell.

Hairy Cell Leukemia (HCL)

Morphology. Hairy cells are small lymphoid cells with an oval or bean-shaped nucleus, chromatin slightly less clumped than that of a normal lymphocyte, and abundant, pale cytoplasm with “hairy” projections on smear preparations. The BM is always involved; the infiltrate is interstitial, diffuse, and characterized by widely spaced, small nuclei, in contrast to the closely packed nuclei of most other low-grade lymphoid neoplasms involving the marrow. Reticulin is increased, often resulting in a “dry tap.” The diagnosis is best made on BM biopsy; in cases of minimal involvement, immunostaining with anti-B-cell antibodies such as DBA44 or L26 may be useful. In the spleen the tumor involves the red pulp; the white pulp is usually atrophic. Lymph node involvement is uncommon; when present, the infiltrate is diffuse, and may leave spared follicles, resembling marginal zone lymphoma.

Immunophenotype. The tumor cells are S Ig+ (M+/-D, G, or A), B-cell–associated cell antigens* (CD19, 20, 22, 79a), CD5+, CD10-, CD23-, CD11c+ (strong), CD25+ (strong), FMC7+, CD103+ (MLA: mucosal lymphocyte antigen, recognized by HML-1, B-ly7, Ber-ACT, LF61), tartrate-resistant acid phosphatase is present in most cases, but is not specific for the diagnosis. CD103 is the most useful marker for distinguishing HCL from other B-cell leukemias, because CD22, CD11c, CD25, FMC7, and even TRAP can be present in disorders other than HCL. Strong expression of these markers in association with CD103, together with the characteristic morphologic features, are most useful.

Genetic features. Ig heavy and light chain genes are rearranged. No specific abnormality is described.

Clinical features. Patients are adults with splenomegaly and pancytopenia and may have few circulating neoplastic cells. The course is indolent; spontaneous remissions are reported. There is increased susceptibility to infections. The tumor does not respond to conventional lymphoma chemotherapy, but interferon, deoxycoformycin, or 2-chlorodeoxyadenosine can induce long-term remissions.

Postulated normal counterpart. Peripheral B cell of unknown differentiation stage.

Plasmacytoma/Plasma Cell Myeloma

Morphology. Plasmacytoma/myeloma is composed of cells that resemble mature or immature plasma cells (plasmablasts), with no admixture of cells recognizable as lymphoid. Some cases may have “cleaved” nuclei or cells that resemble immunoblasts. Increased cellular immaturity may be associated with a poor prognosis. An “anaplastic” extramedullary stage resembling large cell lymphoma may be a preterminal event in some cases.

Immunophenotype. Tumor cells are S Ig+, C Ig+ (G, A, rare D or E; or light chain only); most B-cell–associated antigens negative (CD19, 20, 22), but CD79a+; CD45+/-, HLA-DR+/-, CD38+, EMA+, CD43+/-, CD56+/--. (CD30 may be detected in paraffin sections using the BerH2 antibody.)  

Genetics. IgH and L genes are rearranged or deleted.

Clinical features. Plasma cell neoplasms are most often disseminated BM tumors of adults (multiple myeloma). Some cases present as solitary bone or extramedullary tumors. The majority of solitary bone plasmacytomas progress to multiple myeloma, whereas only 10% to 20% of solitary extramedullary plasmacytomas show such progression.
Postulated normal counterpart. Plasma cell.

Diffuse Large B-Cell Lymphoma

**Synonyms.** Rappaport: diffuse histiocytic, occasionally diffuse mixed lymphocytic-histiocytic; Kiel: centroblastic, B-immunoblastic, large cell anaplastic (B-cell); Lukes-Collins: large cleaved or large noncleaved FCC, B-immunoblastic; Working Formulation: diffuse large cell cleaved, noncleaved or immunoblastic; occasionally diffuse mixed small and large cell.

**Morphology.** Diffuse large B-cell lymphomas are composed of large cells (nuclei at least twice the size of a small lymphocyte; usually larger than tissue macrophage nuclei) with vesicular nuclei, prominent nucleoli, basophilic cytoplasm and a moderate to high proliferation fraction. In most cases the predominant cell resembles either a centroblast (large noncleaved cell) or an immunoblast; the most common appearance is that of a mixture of centroblast-like and immunoblast-like cells (Fig 7). Other cell types include large cleaved or multilobated cells and anaplastic large cells identical to those of T- or null-cell anaplastic large cell lymphoma. Some cases of large B-cell lymphomas may be rich in small T lymphocytes or histiocytes, creating a resemblance to either T-cell lymphoma or HD of the lymphocyte predominance type. Some of these cases have been placed in the diffuse mixed small and large cell category of the Working Formulation, but we believe they should be considered to be large B-cell lymphomas for clinical purposes.

No correlation has been reported between immunophenotype and histiocytic subtype of B-large cell lymphoma, although cases with anaplastic morphology typically express the CD30 antigen, similarly to T-cell and null-cell anaplastic lymphoma. Further study should be directed at identifying morphologic, immunologic and/or genetic parameters that might define clinically relevant subgroups. This study also suggested important overlap between the definitions of large B-cell lymphoma and so-called small noncleaved cell lymphoma, particularly of the non-Burkitt type.

**Table 5. Reproducibility Study: Subclassification of Large B-Cell Lymphomas**

<table>
<thead>
<tr>
<th>No. of Pathologists in Agreement (%)</th>
<th>No. of Cases Agreed on (%</th>
<th>Consensus Diagnosis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Centroblastic</td>
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<td></td>
<td></td>
<td>Immunoblastic</td>
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<tr>
<td></td>
<td></td>
<td>Large Cell NOS</td>
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<td>1 (4)</td>
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<tr>
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<td>5 (17)</td>
<td>4</td>
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<tr>
<td>9 (75)</td>
<td>11 (48)</td>
<td>9</td>
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<tr>
<td>8 (67)</td>
<td>17 (74)</td>
<td>14</td>
</tr>
<tr>
<td>6 (50)</td>
<td>21 (91)</td>
<td>17</td>
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</table>

23 cases, 4 categories, 12 pathologists. The fourth category (other) was never selected by six or more pathologists; numbers in parentheses are percents.
**Immunophenotype.** Tumor cells are Slg⁺/−, Clg⁺/−, B-cell–associated antigens⁺ (CD19, CD20, CD22, CD79a), CD45⁺/−, CD5−, CD10−, CD11c−.3,140

**Clinical features.** Large B-cell lymphomas constitute 30% to 40% of adult NHLs; the median age is in the sixth decade, but the range is broad, and these tumors may be seen in children.3 Patients typically present with a rapidly enlarging, often symptomatic mass at a single nodal or extranodal site; up to 40% are extranodal. Large cell lymphomas are aggressive but potentially curable with aggressive therapy.8 Although several studies have reported a slightly worse prognosis for immunoblastic than large follicular cell types,8,73 other studies have failed to confirm this.144 Cases of multilobated B-cell type are often extranodal.

**Postulated normal counterpart.** Proliferating peripheral B cells (rearrangement of the bcl-2 gene has been interpreted as evidence for a germinal center origin of some cases).

**Large B-Cell Lymphoma Subtype: Primary Mediastinal (Thymic) Large B-Cell Lymphoma**

**Morphology.** The tumor is composed of large cells with variable nuclear features, resembling centroblasts, large centrocytes, or multilobated cells, often with pale cytoplasm. Less often, the tumor cells resemble immunoblasts. Reed-Sternberg like cells may be present. Many cases have fine, compartmentalizing sclerosis. Both clinically and pathologically (when appropriate tissue can be studied), the tumor usually involves the thymus at presentation.146,147

**Immunophenotype.** The tumor cells are often Ig⁺, but express B-cell–associated antigens (CD19, CD20, CD22, CD79a) and are CD45⁺/−, CD30⁻ (weak CD30 expression with Ber-H2 on frozen sections or microwave treated paraffin sections), CD15⁺.146-149

**Genetic features.** Ig heavy and light chain genes are rearranged.147,150, no specific abnormality is described.

**Clinical features.** Large B-cell lymphoma of the mediastinum appears to be a distinct clinicopathologic entity, with a median age in the fourth decade, a higher incidence in females than males, and a locally invasive anterior mediastinal mass originating in the thymus, with frequent airway compromise and superior vena cava syndrome.151,152 Relapses tend to be extranodal, including liver, gastrointestinal tract, kidneys, ovaries, and central nervous system. Although early studies suggested an unusually aggressive, incurable tumor, others have reported cure rates similar to that for other large cell lymphomas with aggressive therapy.152

**Postulated normal counterpart.** Putative thymic (medullary) B cell.146,153

**Burkitt’s Lymphoma**

**Synonyms.** Rappaport: undifferentiated lymphoma, Burkitt’s type; Kiel: Burkitt’s lymphoma; Lukes-Collins: small noncleaved FCC; Working Formulation: small noncleaved cell, Burkitt’s type.

**Morphology.** Burkitt’s tumor cells are monomorphic, medium-sized cells with round nuclei, multiple (2 to 5) nucleoli, and relatively abundant basophilic cytoplasm, which may give the cells a “cohesive” appearance (Fig 8). Cytoplasmic lipid vacuoles are usually evident on imprints or smears. This tumor has an extremely high rate of proliferation as well as a high rate of spontaneous cell death. A “starry-sky” pattern is usually present, imparted by numerous benign macrophages that have ingested apoptotic tumor cells.

**Immunophenotype.** Tumor cells are SlgM⁺, B-cell–associated antigens⁺ (CD19, CD20, CD22, CD79a), CD10⁺, CD5⁻, CD23⁻.154

**Genetic features.** Most cases have a translocation of c-myc from chromosome 8 to the Ig heavy chain region on chromosome 14 [t(8;14)] or, less commonly, to light chain loci on 2 [t(2;8)] or 22 [t(8;22)]. In African (endemic) cases, the breakpoint on chromosome 14 involves the heavy chain joining region, suggesting that the translocation occurs in an early B cell, before complete Ig rearrangement. In contrast, in nonendemic cases, the translocation involves the Ig heavy chain switch region, suggesting that the translocation occurs at a later stage of B-cell development.155,156 Epstein-Barr virus (EBV) genomes can be demonstrated in the tumor cells in most African cases and in 25% to 40% of the cases associated with acquired immune deficiency syndrome,157-159 but less frequently in non-African, nonimmune deficient cases.

**Clinical features.** Burkitt’s lymphoma is most common in children (approximately one third of non-African pediatric lymphomas); adult cases are often associated with immune deficiency. The male-to-female ratio is 2 or 3 to 1. In African (endemic) cases, the jaws and other facial bones are often involved. In non-African (nonendemic) cases, jaw tumors are less common; the majority of the cases present in the abdomen, most often involving distal ileum, cecum and/or mesentry; ovaries, kidneys or breasts may be involved.160 Rare cases present as acute leukemia with Burkitt’s tumor cells (L3-ALL). The tumor is highly aggressive but potentially curable; prognosis in children correlates with bulk of disease at the time of diagnosis.160

**Postulated normal counterpart.** B cell of unknown differentiation stage.

**Provisional Entity: High-Grade B-Cell Lymphoma, Burkitt-Like**

**Synonyms.** Rappaport: undifferentiated, non-Burkitt; Kiel: not listed; Lukes-Collins: small noncleaved FCC; Working Formulation: small noncleaved cell, non-Burkitt.

**Morphology.** The participants in the meeting noted that several of the cases in the large cell lymphoma reproducibility study set appeared to have morphologic features intermediate between large cell lymphoma with centroblastic or immunoblastic features and typical Burkitt’s lymphoma (Fig 8). All recalled many cases in their own practices in which distinction between large cell and Burkitt’s lymphoma seemed impossible. We believe that these difficult cases comprise many of the cases designated undifferentiated, non-Burkitt’s in the Rappaport classification,162 small noncleaved cell, non-Burkitt type in the Working Formulation,154 for which there is no clear counterpart in the Kiel Classification.
(A category of Burkitt's lymphoma with Clg may correspond to some cases of this entity.6) A recent study63 showed that cases classified as "small noncleaved, non-Burkitt type" lacked c-myc rearrangement and had frequent bcl-2 rearrangement, suggesting that these tumors are probably not related to true Burkitt's lymphoma. Therefore, we propose a provisional category of "high-grade B-cell lymphoma, Burkitt-like" (in preference to "non-Burkitt's")62 for cases in which the cell size and nuclear morphology are intermediate between typical Burkitt's lymphoma and typical large cell lymphoma, in which there is a high proliferation rate, with or without a starry-sky pattern. We believe that this is not a reproducible category, and probably not a single disease entity, but it appears to be necessary for cases that are borderline between large B-cell lymphoma and Burkitt's lymphoma.

**Immunophenotype.** Tumor cells are Slg62- (may have Clg), B-cell-associated antigens+, CD5-, and usually CD10+.154

**Genetic features.** c-myc rearrangement is uncommon; the bcl-2 gene is rearranged in 30%.163

**Clinical features.** Tumors of this description are relatively uncommon and appear to occur mostly in adults, with or without a history of immunosuppression: they involve lymph nodes more often than extranodal sites. Cases classified as small noncleaved, non-Burkitt type in children appear to behave similarly to classic Burkitt's tumor,61 whereas in adults they appear to be highly aggressive and often fatal.

**Postulated normal counterpart.** Proliferating peripheral B cells.

**T-Cell and Putative Natural Killer Cell (NK) Neoplasms**

**Precursor T-Cell Neoplasm: Precursor T-Lymphoblastic Lymphoma/Leukemia (T-LBL)**

**Synonyms.** Rappaport: poorly differentiated lymphocytic, diffuse (modified to lymphoblastic); Lukes-Collins: convoluted T lymphocytic; Working Formulation: lymphoblastic, convoluted or nonconvoluted.

**Morphology.** The tumor cells are morphologically identical to those of precursor B-LBL: lymphoblasts, with round or convoluted nuclei, finely dispersed chromatin, inconspicuous nucleoli, and scant cytoplasm (Fig 1B). Immunophenotyping studies are necessary to distinguish this tumor from precursor B-lymphoblastic neoplasms, and occasionally, from peripheral B- or T-cell neoplasms or granulocytic sarcoma.

**Immunophenotype.** Most cases are CD7+, CD3+ (cytoplasmic CD3 is usually present even when surface antigen is absent); expression of other T-cell-associated antigens (CD2,5) is variable. They express either αβ, γδ, or no T-cell receptor molecules.164,165 Tumors are typically TdT+, CD1a+/−, often CD48 double positive or double negative, Ig−, B-cell-associated antigens+, occasional cases express NK antigens (CD16, 57).166-170

**Genetic features.** Rearrangement of TCR genes is variable;168 IgH rearrangement may be seen;18,165,173 variable cytogenetic abnormalities are reported.20

**Clinical features.** Patients are predominantly adolescent and young adult males, but older adults are occasionally affected.172 It constitutes 40% of childhood lymphomas and 15% of acute lymphoblastic leukemias (defined as >25% BM lymphoblasts). Patients present with rapidly enlarging, symptomatic mediastinal (thymic) masses and/or peripheral lymphadenopathy. Untreated, it is rapidly fatal, usually terminating in acute leukemia; central nervous system involvement is common. The tumor is highly aggressive but potentially curable. Clinically important subtypes may be defined by immunophenotypic profiles: leukemic cases tend to have a more immature phenotype than lymphoma cases,64,166,167 CD2− or NK (CD16+57+) cases may be more aggressive.168-170,173

**Postulated normal counterpart.** Precursor T cells: prothymocyte, early thymocyte, common thymocyte.

**Peripheral T-Cell Neoplasms**

**T-Cell Chronic Lymphocytic Leukemia (T-CLL)/T-Prolymphocytic Leukemia (T-PLL)**

**Synonyms.** Rappaport: WDL, PDL; Kiel: T-lymphocytic; Lukes-Collins: small lymphocyte T, prolymphocytic; Working Formulation: small lymphocytic, c/w CLL, diffuse small cleaved cell; French-American-British (FAB): T-PLL.

**Morphology.** Most chronic T-cell leukemias have cells with prominent nucleoli, some nuclear irregularity, and more abundant cytoplasm than typical B-CLL, so that they fall into the category of prolymphocytic leukemia (T-PLL). However, some cases have smaller cells that may resemble B-CLL.30,174,175 The cells are usually nongranular, but have focal granular paranuclear positivity on acid phosphatase and acid nonspecific esterase stains (Fig 9). Lymph node involvement is diffuse and paracortical, with sparing of follicles; it differs from B-CLL in lack of pseudofollicles. Prominent small vessels of the high endothelial venule type (HEV) may be numerous, and often contain atypical small lymphoid cells.176 Splenic red pulp and hepatic sinusoids may be infiltrated. BM involvement is usually diffuse, and the marrow may show increased reticulin.

**Immunophenotype.** In contrast to other CD4+ T-cell leukemias (ATL/L and MF/SS), the tumor cells are CD7+, as well as other T-cell-associated antigens (CD2,3,5), most cases are CD4+ (65%), some are CD4+8+ (21%), rare cases are CD4−8+, and they are CD25+−,30,175,177

**Genetic features.** Clonal rearrangements of TCR genes: inv 14 (q11;q32) in 75%; trisomy 8q.

**Clinical features.** T-CLL/PLL comprises 1% of CLL but up to 20% of PLL. Patients have a high white count (>100,000), and a high frequency of cutaneous or mucosal infiltrates. BM, spleen, liver, and lymph nodes may be involved. It is more aggressive than B-CLL, and not usually curable with available therapy.175

**Postulated normal counterpart.** Circulating peripheral T cell.

**Large Granular Lymphocyte (LGL) Leukemia, T-Cell and NK-Cell Types**

**Synonyms.** Rappaport: SLL, CLL; Kiel: T-CLL; Lukes-Collins: small lymphocyte, T; Working Formulation: small lymphocytic, consistent with (c/w) CLL; FAB: T-CLL, T-LGL.
**Morphologic features.** This disorder corresponds to cases described as T8 lymphocytosis with neutropenia, CD8+, or Tγ lymphoproliferative disease, and CD8+ T-CLL. Peripheral blood cells have round or oval nuclei with moderately condensed chromatin and rare nucleoli, eccentrically placed in abundant pale blue cytoplasm with azurophile granules (Fig 10). The cells are acid phosphatase positive, with a granular pattern, and are nonspecific esterase negative or weakly positive. BM infiltration is usually sparse, with mild to moderate lymphocytosis as well as focal aggregates, sometimes resembling B-cell lymphoma. There may be a myeloid maturation arrest or erythroid hypoplasia. Splenic red pulp and hepatic sinuses may be infiltrated.

**Immunophenotype.** Two types: T-cell and NK-cell have been reported. T cells: CD2+ CD3+ CD5- CD7- TCRAβ+ CD4- CD8+. CD16+ CD56+ CD57+/-. NK cells: CD2+ CD3- TCRAβ+ CD4- CD8+ CD16- CD56+/-. CD57+.

**Genetic features.** T-cell cases show clonal rearrangements of TCR genes. NK-cell cases are germline, and clonality is not proven in most cases. Association with EBV is reported in aggressive Asian cases.

**Clinical features.** Patients with both types have mild to moderate, stable lymphocytosis (5 to 20,000/mm³), often with neutropenia; anemia is seen in T-cell cases. T-cell cases usually have mild to moderate splenomegaly, without significant lymphadenopathy or hepatomegaly; most NK-cell cases lack all of these. The course is usually indolent, with morbidity related to cytopenias rather than tumor burden. Occasional patients with both types have a more aggressive course. The EBV+ Asian cases have a more acute presentation and a more aggressive course.

**Postulated normal counterpart.** T-cell type: peripheral CD8+ T lymphocyte with suppressor but no NK function. NK-cell type: NK-cell.

**Mycosis Fungoides/Sezary Syndrome (MF/SS)**

**Synonyms.** Rappaport: mycosis fungoides/Sezary syndrome; Kiel: small cell, cerebriform; Lukes-Collins: cerebriform T; Working Formulation: mycosis fungoides.

**Morphology.** Tumor cells are predominantly small cells with cerebriform nuclei, with a minority of larger cells with similar nuclei, which infiltrate the epidermis, circulate in the blood, and involve the paracortex of lymph nodes. The infiltrate is invariably accompanied by interdigitating and Langerhans’ cells. The BM is usually normal.

**Immunophenotype.** Tumor cells express T-cell–associated antigens (CD2β+5); approximately one third are CD7+; most cases are CD4+, but rare CD8+ cases are reported. CD25 is usually negative, but positive cases have been reported. S-100+ CD1a+ interdigitating and Langerhans’ cells are present.

**Genetic features.** TCR genes are clonally rearranged.

**Clinical features.** Patients are usually adults who present with multiple cutaneous plaques or nodules, or with generalized erythroderma; lymphadenopathy is usually a late occurrence. Peripheral blood involvement may be subtle in MF or prominent in Sezary’s syndrome. As a terminal event, a large cell lymphoma may develop, which is morphologically and immunophenotypically similar to anaplastic large cell lymphoma (ALCL). An association with HD and lymphomatoid papulosis has also been reported.

**Postulated normal counterpart.** Peripheral epidermotropic CD4+ T cell.

**Peripheral T-Cell Lymphomas, Unspecified (Provisional Cytologic Categories: Medium-Sized Cell, Mixed Medium and Large Cell, Large Cell)**

**Synonyms.** Rappaport: diffuse PDL, diffuse mixed lymphocytic-histiocytic, histiocytic; Kiel: T-zone lymphoma, lymphoepithelioid cell lymphoma, pleomorphic, small, medium, and large cell, T-immunoblastic; Lukes-Collins: T-immunoblastic lymphoma; Working Formulation: diffuse small cleaved cell, diffuse mixed small and large cell, large cell immunoblastic (polymorphous or clear cell).

Peripheral T-cell lymphomas typically contain a mixture of small and large atypical cells. They make up as many as half of the cases usually classified as diffuse mixed small and large cell type and an unknown proportion of cases classified as large cell immunoblastic in the Working Formulation. We find, as have others, that peripheral T-cell lymphomas can be difficult to understand and subclassify. Problems include their rarity in Western material, their apparent heterogeneity, and the difficulty of identifying the neoplastic cell population without a reliable immunophenotypic marker of T-cell malignancy. A number of distinct clinical syndromes have been defined, which correspond to recognizable morphologic subtypes of T-cell neoplasia, and we have described these as distinct entities. Once these have been separated out, there remains a large group of nonlymphoblastic, non-CLL T-cell lymphomas, which likely constitute the majority of cases of peripheral T-cell lymphoma.

Although the Kiel Classification defines multiple subtypes within this broad category, members of the group find it difficult to subclassify these cases with confidence, and suspect that other pathologists may share this experience. Further clinicopathologic studies are required to confirm the feasibility and clinical relevance of subclassification of peripheral T-cell lymphomas. For the time being, we found it most practical to lump these cases as “peripheral T-cell lymphomas, unspecified.”

**Morphologic features.** Peripheral T-cell lymphomas of unspecified type show a diffuse or occasionally interfollicular proliferation that ranges from atypical small cells to medium-sized or large cells; most contain a mixed population of small and large atypical cells, and even those with a predominance of medium-sized or large cells often contain a broad spectrum of cell sizes (Fig 11). Admixed eosinophils or epithelioid histiocytes may be numerous. (Lymphoepithelioid cell [Lennert’s] lymphoma is considered a cytologic category of peripheral T-cell lymphoma.) The neoplastic cells often have irregular nuclei, and vary considerably in size and shape, with occasional large, hypochromatic cells that may resemble Reed-Sternberg cells. True RS cells are rare or absent. For lack of other criteria, we propose stratifying these cases by the number of large cells, as medium-sized cell, mixed medium and large cell,
and large cell types, recognizing that this is imprecise and not reproducible.

Two subtypes of peripheral T-cell lymphoma appear to have sufficiently distinctive morphology, immunophenotype, and clinical behavior to warrant recognition as provisional entities: hepatosplenic gamma-delta (γδ) T-cell lymphoma, and subcutaneous panniculitic T-cell lymphoma. Immunophenotype. T-cell--associated antigens are variable (CD3+/-, CD2+/-, CD5+/-, CD7+/-), CD4 > CD8, may be CD4--CD8--; B-cell--associated antigens are lacking (may express CD45RA and lack CD45RO; rare CD20+ T-cell lymphomas are reported).

Genetic features. TCR genes are usually but not always rearranged; Ig genes are germline.

Clinical features. These tumors comprise less than 15% of lymphomas in most European and US studies, but are more common in other parts of the world. Patients are usually adults with generalized disease, occasionally with eosinophilia, puritis or hemophagocytic syndromes; lymph nodes, skin or subcutis, liver, spleen and other viscera may be involved. The clinical course is usually rather aggressive, although potentially curable; relapses are more common than in B-cell lymphomas of similar histologic grades. This category includes heterogeneous diseases that require further definition.

Postulated normal counterpart. Peripheral T cells in various stages of transformation.

Peripheral T-Cell Lymphoma, Specific Variants

Four subtypes of peripheral T-cell lymphoma were considered by the group to have sufficiently clear defining features—morphologic, immunologic, genetic, and/or clinical—to be reliably recognized as distinct entities by most pathologists. These include angioimmunoblastic T-cell lymphoma, angiocentric lymphoma, intestinal T-cell lymphoma, and adult T-cell lymphoma/leukemia (HTLV1+). Although relatively uncommon in the United States and Europe, they are occasionally encountered in routine practice, and should be recognized.

Angioimmunoblastic T-Cell Lymphoma

Synonyms. Rappaport: not listed (diffuse mixed lymphocytic-histiocytic, histiocytic); Kiel: T-cell, angioimmunoblastic (AILD); Lukes-Collins: IBL-like T-cell lymphoma; Working Formulation: not listed (diffuse mixed small and large cell, diffuse large cell, large cell immunoblastic).

Morphology. Although initially proposed to be an abnormal immune reaction (angioimmunoblastic lymphadenopathy with dysproteinemia [AILD]), this entity is now generally accepted as a T-cell lymphoma, because most cases show clonal rearrangements of T-cell receptor genes. The morphologic features are similar to those described for angioimmunoblastic lymphadenopathy. The nodal architecture is effaced; peripheral sinuses are typically open and even dilated, but the abnormal infiltrate often extends beyond the capsule into the perinodal fat. Reactive follicles with germinal centers are usually absent. The node typically has a pale, or depleted appearance at low power. There is a proliferation of small, arborizing HEV, many of which show thickened or hyalinized PAS+ walls (Fig 12). Expanded aggregates of FDC, visible on immunostained sections, surround the proliferating blood vessels, and may have the appearance of "burnt-out" germinal centers. The lymphoid infiltrate usually appears relatively sparse, compared with other lymphomas, probably because of the large number of FDC. The lymphoid cells are a mixture of small lymphocytes, immunoblasts, and a characteristic type of atypical "clear" cell, which usually has a round to slightly indented nucleus and abundant, pale or clear cytoplasm (Fig 12). These cells occur singly or in small aggregates or sheets. Epitheliod histiocytes, plasma cells, and eosinophils may be admixed.

Immunophenotype. Tumor cells express T-cell-associated antigens and usually CD4; expanded FDC clusters are separated from other T-cell lymphomas.

Genetic features. TCR genes are rearranged in 75%; IgH in 10%; EBV genomes are detected in many cases; trisomy 3 and/or 5 may occur.

Clinical features. This is a relatively rare disorder, but is clinically distinctive. Patients typically have a systemic disease, with generalized lymphadenopathy, which is rarely massive, fever, weight loss, skin rash, and polyclonal hypergammaglobulinemia. The course is moderately aggressive, with occasional spontaneous remissions or protracted responses to steroids, and infectious complications. Progression to high grade lymphoma of T- or occasionally B-cell type occurs.

Postulated normal counterpart. Peripheral T cell of unknown subset in various stages of transformation.

Angiocentric Lymphoma

Synonyms and related disorders. Rappaport: not listed (diffuse PDL, mixed lymphocytic/histiocytic or histiocytic); Lukes-Collins: not listed (T-immunoblastic sarcoma); Kiel Classification: not listed (T, pleomorphic small, medium and large cell); Working Formulation: not listed (diffuse small cleaved, mixed small and large cell, diffuse large cell, large cell immunoblastic); other, angiocentric immunoproliferative lesion (grades 2 and 3), polymorphic reticulosis, lethal midline granuloma, midline malignant reticulosis, nasal T cell lymphoma, lymphomatoid granulomatosis (some cases).

Morphologic features. This disorder is characterized by an angiocentric and angioinvasive infiltrate, usually composed of a mixture of normal-appearing small lymphocytes and variable numbers of atypical lymphoid cells and immunoblasts, along with plasma cells and occasionally eosinophils and histiocytes. A characteristic feature is invasion of vascular walls and, usually, occlusion of lumina by lymphoid cells with varying degrees of cytologic atypia (Fig 13). The vascular occlusion is usually associated with prominent ischemic necrosis of both tumor cells and normal tissue. Cases with features of pulmonary lymphomatoid granulomatosis have been considered to belong to this entity; however, recent studies suggest that at least some pulmonary
cases may be EBV-associated B-cell proliferations, and therefore a distinct disease category.\textsuperscript{218}

**Immunophenotype.** The atypical cells in most cases express pan-T antigens (CD2\textsuperscript{+} CD5\textsuperscript{-/-} CD7\textsuperscript{+/-}) but are often CD3\textsuperscript{+}, may be CD4\textsuperscript{+} or CD8\textsuperscript{+}, and are often CD56\textsuperscript{+}.\textsuperscript{219-221} In some pulmonary cases with features of lymphomatoid granulomatosis, the atypical cells express B-lineage antigens.\textsuperscript{218}

**Genetic features.** TCR and Ig genes are usually germ-line; EBV genomes are usually present.\textsuperscript{217,220,222,223} In some
pulmonary cases, clonal Ig gene rearrangement has been shown, and EBV genomes are present in B cells.218

Clinical features. Angiocentric lymphoma is a rare disorder in the United States and Europe, but is more common in Asia. It may affect children or adults. Extranodal sites are invariably involved, including nose, palate, and skin.217,220,216,222 Cases with pulmonary and central nervous system involvement may represent a different entity (see above). The clinical course appears to depend on the proportion of large cells, and may be indolent or aggressive.217 Hemophagocytic syndromes may occur. Some cases of the aggressive variant of NK cell leukemia/lymphoma may be related to this disorder.224

Postulated normal counterpart. NK cell, ? unknown peripherally T-cell subset.

Intestinal T-Cell Lymphoma (With or Without Enteropathy)

Synonyms. Rappaport: not listed (diffuse mixed lymphocytic-histiocytic, histiocytic); Lukes-Collins: not listed (T-immunoblastic sarcoma); Kiel: not listed (T, pleomorphic small, medium and large cell); Working Formulation: not listed (diffuse small cleaved cell, diffuse mixed small and large cell, diffuse large cell, large cell immunoblastic); other, malignant histiocytosis of the intestine, ulcerative jejunitis.

Morphology. This disorder was originally termed "malignant histiocytosis of the intestine," but has since been conclusively shown to be a T-cell lymphoma.225 On gross examination, jejunal ulcers are present, often multiple, and often with perforation. A mass may or may not be present. The tumors contain a variable admixture of small, medium/ mixed, large or anaplastic tumor cells, often with a high content of intraepithelial T cells in adjacent mucosa. Adjacent mucosa may or may not show villous atrophy.209 Early lesions may show mucosal ulceration with only scattered atypical cells and numerous reactive histiocytes, without formation of large masses.

Immunophenotype. Tumor cells are CD3+CD7+ CD8−/− CD4+ CD103+. (MLA: HML-1, LFGL1, Bly7, Ber-Act8).226

Genetic features. TCRβ genes are clonally rearranged.225

Clinical features. This disease occurs in adults, often with a history of gluten-sensitive enteropathy, but occasionally as the initial event in a patient found to have typical histologic features of sprue in the resected intestine, or less commonly, without evidence of enteropathy. It is uncommon, in most areas of the United States and Europe, but is seen with increased frequency in areas in which gluten-sensitive enteropathy is more common. Patients present with abdominal pain, often associated with jejunal perforation; stomach or colon are affected less often. The course is aggressive and death usually occurs from multifocal intestinal perforation caused by refractory malignant ulcers.

Postulated normal counterpart. Intestinal intraepithelial T cell in various stages of transformation.

Adult T-Cell Lymphoma/Leukemia (ATL/L)

Synonyms. Rappaport: diffuse PDL, mixed lymphocytic-histiocytic, or histiocytic; Lukes-Collins: T-immunoblastic sarcoma; Kiel: pleomorphic small, medium and large cell types (HTLV1+); Working Formulation: diffuse small cleaved cell, mixed small and large cell, diffuse large cell, large cell immunoblastic.

Morphology. This disease is defined as a T-cell neoplasm caused by HTLV1.227,221 The histology is variable. The pattern in lymph nodes is diffuse; usually there is a mixture of small and large atypical cells with pronounced polymorphism and nuclear pleomorphism216,220,222 (Fig 14A). Multinucleated giant cells resembling Reed-Sternberg cells in some cases may cause a resemblance to HD.216 Cells with hyperlobated nuclei ("clover leaf" or "flower" cells) are common in the peripheral blood20 (Fig 14B). Marrow infiltration is diffuse, and ranges from sparse to marked.

Immunophenotype. Tumor cells express T-cell-associated antigens (CD2,3,5+); but usually lack CD7; most are CD4+ CD25+; rare CD8+ cases have been reported.

Genetic features. TCR genes are clonally rearranged; clonally integrated HTLV1 genomes are found in all cases.228,224

Clinical features. The majority of patients are adults, who have antibodies to HTLV1. Most cases occur in Japan, but an endemic focus is found in the Caribbean, and sporadic cases are found in the United States.229-232 Several clinical variants have been described.235 Most common is the "acute" form, which presents with a high white blood cell count, hepatosplenomegaly, hypercalcemia, and lytic bone lesions; median survival is less than 1 year. The rare lymphomatous form is characterized by isolated lymphadenopathy without leukemia. A chronic form with lower white blood cell count, without hypercalcemia or hepatosplenomegaly, has slightly longer survival, and rare smoldering cases have mild lymphocytosis, which is demonstrably clonal, but a very indolent course.236 Both chronic and smoldering forms often have skin rashes.

Postulated normal counterpart. Peripheral CD4+ T cell in various stages of transformation.

Anaplastic Large Cell (CD30+) Lymphoma (T- and Null-Cell Types)

Synonyms. Rappaport: not listed (histiocytic, diffuse); Kiel: large cell anaplastic (T and null types); Lukes-Collins: T-immunoblastic sarcoma; Working Formulation: not listed (diffuse large cell immunoblastic); possible other names: malignant histiocytosis, sinusoidal large cell lymphoma, regressing atypical histiocytosis.

This tumor was originally recognized by application of the Ki-1 (CD30) antibody; tumors strongly expressing the antigen had a characteristic morphology, now known as anaplastic large cell lymphoma (ALCL).229,237 Although other lymphomas of either T-cell or B-cell type may strongly express CD30,229,138,139 we believe there is sufficient evidence that the anaplastic type is a distinct clinicopathologic entity to warrant its inclusion in any lymphoma categorization attempt.

Morphologic features. The tumor is composed of large blastic cells with pleomorphic, often horseshoe-shaped or multiple nuclei with multiple (usually) or single prominent nucleoli. Multinucleated forms may resemble Reed-Sternberg cells (Fig 15). The tumor cells are usually much larger
than the cells of usual large cell lymphomas, with more abundant cytoplasm. The cells grow in a cohesive pattern and often preferentially involve the lymph node sinuses, as well as extranodal sites, such as soft tissue, bone, and skin. There is a variable admixture of granulocytes and macrophages. A lymphohistiocytic variant occurs, in which reactive histiocytes predominate and the rare neoplastic cells may be smaller than classic ALCL cells, and a small cell variant has been described recently, whose relationship to classic ALCL remains to be determined. Many cases of ALCL were previously diagnosed as malignant histiocytic tumors, regressing atypical histiocytosis, metastatic carcinoma, melanoma, sarcoma, or lymphocyte-depleted HD.

The majority of tumors with the morphologic features described above express one or more T-cell-associated antigens, many express neither T- nor B-cell-associated antigens and some cases express B-cell antigens. The group has included the B-cell cases among the morphologic variants of B-large cell lymphoma, rather than considering it a distinct disease. Although the literature on this topic is confusing, because of variations in case definition, there is evidence that the T and ‘null’ cases likely represent different antigenic expressions of the same disease; however, there may be two distinct clinical and possibly biological entities within this category (see below).

**Immunophenotype.** The tumor cells are CD30+, CD45+, CD25+, EMA+, CD15+, CD3+, other T-cell–associated antigens variable, CD43+, CD45RO+, CD68– (when studied using PGM1); KP1 may stain some cases), and lysozyme. About 50% have been reported to express H and Y blood group antigens, detected with a monoclonal antibody, BNI9. Primary cutaneous cases are reported to lack EMA and express the cutaneous lymphocyte antigen (CLA, HECA-452).

**Genetic features.** Cytogenetic studies on a small number of cases of the systemic form have shown a t(2;5); cytogenetic studies on primary cutaneous cases have not been reported. Fifty percent to 60% of the cases have TCR rearranged; 40% to 60% have no rearrangement of TCR or Ig genes.

**Clinical features.** Anaplastic large cell lymphoma is a relatively rare tumor, but may be diagnosed with increasing frequency as its features are more widely recognized. Cases
have been reported in all age groups; 15% to 30% of the cases in unselected series are under age 20. Most cases arise "de novo"; however, some patients have a history of other lymphomas including mycosis fungoides or HD. There is growing evidence for two distinct forms of primary ALCL: a systemic form, which may involve lymph nodes or extranodal sites, including the skin, but is not localized to the skin, and a primary cutaneous form, without extracutaneous spread at the time of the diagnosis. Tumors that present with systemic extracutaneous disease (with or without skin involvement) have a bimodal age distribution in children and adults, are clinically more aggressive, and are EMA+ and cutaneous lymphocyte antigen (CLA, HECA-452) negative. Primary cutaneous tumors occur predominantly in adults, may spontaneously regress, lack EMA and express the CLA, and may represent a continuous spectrum with lymphomatoid papulosis type A. Although the primary cutaneous form appears to be indolent and incurable, the systemic form appears to behave similarly to other large cell lymphomas, being moderately aggressive but potentially curable with aggressive therapy. Late relapses may be seen.

Postulated normal counterpart. Extrafollicular CD30+ blasts.

Provisional Entity: ALCL Hodgkin's-Like (Hodgkin's-related)

Morphologic features. This tumor is composed of confluent sheets of tumor cells, and a cohesive, often sinusoidal growth pattern, similar to classic ALCL; but with architectural features that resemble HD of the nodular sclerosis type (NSHD), such as capsular thickening, nodular growth of tumor cells, and sclerotic bands. These cases are apparently usually classified by the American pathologists in the group as either NSHD (syncytial, lymphocyte depleted, or NSII type) or lymphocyte depletion (LDHD), reticular type ("Hodgkin's sarcoma") (see below).

Immunophenotype. Identical to classic ALCL; tumors are usually EBV-.

Genetic features. Not known.

Clinical features. Patients are young adults with aggressive nodal disease, and often with bulky mediastinal masses; according to European studies they do not do well with conventional therapy for HD, but may have a good response to very aggressive therapy, such as third generation chemotherapy regimens for high-grade NHLs. We believe that further study is required to define this possible entity and its relationship to HD on the one hand and classic ALCL on the other.

Postulated normal counterpart. Not known (as for ALCL or NSII).

Hodgkin's Disease

Lymphocyte Predominance (Paragranuloma)

Synonyms. Lukes et al: lymphocytic and/or histiocytic, nodular, lymphocytic and/or histiocytic, diffuse (some cases); Lennert and Mohr: paragranuloma, nodular or diffuse.

Sufficient evidence has emerged in recent years to warrant recognition of this subtype of HD as a distinct entity. Although it resembles other types of HD in having a minority of putative neoplastic cells in a background of benign inflammatory cells, it differs both morphologically, immunophenotypically, and clinically from classic HD (Table 6). Because the category of diffuse lymphocyte predominance in the Rye Classification probably includes cases more closely related to classic HD (see lymphocyte-rich classic HD, below), the older term, paragranuloma, has been suggested as a way of denoting this distinctive tumor.

Lymphocyte predominance HD usually has a nodular growth pattern with or without diffuse areas; it is rarely purely diffuse; nodularity may be more easily recognized using immunohistologic stains with anti-B cell or anti-FDC antibodies. Progressively transformed germinal centers are often seen in the same or other nodes. The atypical cells have vesiular, polylobated nuclei and small nucleoli (see below); these have been called L&H cells (lymphocytic and/or histiocytic) or "popcorn" cells. Although these cells may be very numerous, usually no diagnostic Reed-Sternberg cells are found. The background is predominantly lymphocytes with or without epithelioid histiocyte clusters; plasma cells are infrequent, and eosinophils and neutrophils are rarely seen. Occasional sclerosis may cause lesions to resemble nodular sclerosis.

Immunophenotype. The atypical cells are CD45+, B-cell-associated antigens+ (CD19, 20, 22, 79a), CDw75+, EMA++, CD15-, CD30++, and are usually Ig- by routine techniques, although one study reported light chain restriction. J-chain has been shown in many cases. Small lymphocytes in the nodules are predominantly B cells with a mantle zone phenotype; numerous T cells are present, with CD57+ T cells surrounding the L&H cells. A prominent meshwork of FDC is present within the nodules.

Genetic features. Ig and TCR genes are germline; large cells are EBV- in most cases.

Clinical features. The tumor occurs at all ages, adults more commonly than children, males more than females. It usually involves peripheral lymph nodes, with sparing of the mediastinum; it is usually localized at diagnosis, but may rarely be disseminated. Survival is long, with or without treatment, for localized cases. Late relapses have been reported to be more common than in other types of HD; it may be associated with or progress to large B-cell lymphoma. Prospective clinical studies using different
forms of treatment should be attempted to determine the optimal approach to this disorder.

Postulated normal counterpart. Undefined peripheral B cell.

Nodular Sclerosis

Morphologic features. The tumor has at least a partially nodular pattern, with fibrous bands separating the nodules in most cases; diffuse areas are common, as is necrosis. The characteristic cell is the lacunar type RS cell, which may be very numerous; diagnostic RS cells are usually also present (Fig 16). The background contains lymphocytes, histiocytes, plasma cells, eosinophils, and neutrophils. Subclassification according to the number of atypical cells may be clinically relevant; several grading schemes exist (NSI/II, symphytic variant, lymphocyte depleted, cellular phase).

Immunophenotype. Tumor cells are CD15+, CD30+, CD45- (may be positive in frozen sections); usually B-cell- and T-cell-associated antigens are negative, EMA- 170-278. CD15 and CD30 may be difficult to detect in paraffin sections in some cases unless microwave antigen-retrieval techniques are used. Expression of B-cell- and T-cell-associated antigens has been reported in a variable number of cases, usually in a minority of the cells. The diagnosis is made on routine sections, and immunophenotyping studies are at best an adjunct to the diagnosis. In a morphologically typical case, immunophenotyping studies are not needed, and failure to detect CD15 or CD30 or expression of a B- or T-cell-associated antigen should not preclude a diagnosis of HD.

Genetic features. Ig and TCR genes are usually germline, but rearrangements of Ig genes are reported in some cases, usually with faint bands. Tumor cells are EBV+ in about 40% of the cases. bcl-2 rearrangement has been detected with the polymerase chain reaction in a variable proportion of the cases in some laboratories, but not in others; these rearrangements have not been proven to be in the neoplastic cells.

Clinical features. This variant is most common in adolescents and young adults, but can occur at any age; females equal or exceed males. The mediastinum is commonly involved; stage and bulk of disease have prognostic importance. It is often curable.

Postulated normal counterpart. Unknown; activated lymphoid cell of an as yet unidentified B-cell or T-cell subset, or of a primitive lymphoid cell.

Mixed Cellularity

Morphologic features. The infiltrate is diffuse or vaguely nodular, without band-forming sclerosis, although fine interstitial fibrosis may be present. RS cells are of the classic type, although some lacunar cells may be seen (Fig 16). The infiltrate contains lymphocytes, histiocytes, eosinophils, neutrophils and plasma cells.

Immunophenotype. Tumor cells are CD30+, CD15+, CD45- (may be positive in frozen sections), usually B-cell- and T-cell-associated antigens negative, EMA-. CD15 and CD30 may be difficult to detect in paraffin sections in some cases unless microwave antigen-retrieval techniques are used. Expression of B-cell- or T-cell-associated antigens has been reported in a variable number of cases, usually in a minority of the cells. The diagnosis is made on routine sections, and immunophenotyping studies are at best an adjunct to the diagnosis. In a morphologically typical case, immunophenotyping studies are not needed, and failure to detect CD15 or CD30 or expression of a B- or T-cell-associated antigen should not preclude a diagnosis of HD.

Genetic features. Ig and TCR genes are usually germline, but rearrangements of Ig genes are reported in some cases, usually with faint bands. Tumor cells are EBV+ in the majority of the cases (60% to 70%), and in non-industrialized countries. Clonal sheets of Reed-Sternberg cells and variants may occur and rarely predominate ("reticular" variant or "Hodgkin's sarcoma"). The borderline between the reticular variant and ALCL is not sharp, and may be a matter of definition. Further studies are required to resolve this issue.

Immunophenotype. Tumor cells are CD30+, CD15+, CD45-, B-cell-associated antigens and T-cell-associated antigens-, EMA-. Because the histologic differential diagnosis often includes B- or T-large cell lymphoma or ALCL, absence of T- and B-cell markers are usually required for the diagnosis.

Genetic features. Ig and TCR genes are germline. (If rearrangements are found, the tumor is usually classified as a B-cell or T-cell lymphoma.)

Clinical features. This is the least common variant of HD and is most common in older people, in human immunodeficiency virus-positive (HIV+) individuals and in non-industrialized countries. It frequently presents with abdominal lymphadenopathy, spleen, liver and BM involvement, without peripheral adenopathy. The stage is usually advanced at diagnosis; however, response to treatment is reported not to differ from other subtypes.

Postulated normal counterpart. Unknown; activated lymphoid cell of an as yet unidentified B-cell or T-cell subset, or of a primitive lymphoid cell.

Provisional Entity: Lymphocyte-Rich Classical HD

Synonyms. Lukes et al257: subset of diffuse lymphocyte predominance; Lennert and Mohri258: lymphocyte predominant mixed cellularity.

Morphologic features. This is defined a diffuse tumor with relatively infrequent Reed-Sternberg cells, which are of the classic type, rather than the variants seen in nodular LPHD; some lacunar cells may be present, in a background
of lymphocytes, with infrequent eosinophils or plasma cells. There is morphologic overlap with diffuse lymphocyte predominance, the cellular phase of NS, and mixed cellularity. In contrast to diffuse LPHD, the Reed-Sternberg cells have the morphology and immunophenotype of classic RS cells, and therefore we believe these lesions should not be classified as true lymphocyte predominance. The immunophenotype, genetic features, and clinical features are similar to NS and MCHD.

Unclassifiable Cases

For the well-defined disease categories to be meaningful, it is important not to “squeeze” into them cases that do not fulfill diagnostic criteria. Therefore, unclassifiable cases are defined as those that do not fit into either a definite or provisional category: they may be T cell, B cell, or undefined, they may be borderline between HD and NHL, and they may be either high or low histologic grade, based on proliferation fraction and proportion of transformed (blast) cells. At least the following categories should be recognized: (1) B-cell lymphoma, unclassifiable: low-grade (predominantly small cells), or high-grade (mixed small and large or predominantly large cells); (2) T-cell lymphoma, unclassifiable: low-grade (predominantly small cells), or high-grade (mixed small and large or predominantly large cells); (3) HD, unclassifiable; (4) malignant lymphoma, unclassifiable: low-grade or high-grade.

A case may be unclassifiable because of poor histologic preparation, inadequate immunophenotyping or molecular genetic studies, or because despite complete analysis with available techniques it does not fit clearly into any of the well-defined disease categories. The latter group is clearly the most important for future growth of knowledge. For each case, the reason for inability to classify should be stated.

DISCUSSION

The current lack of consensus on lymphoma classification causes problems for practicing pathologists and clinicians, and creates difficulty in interpreting published studies. Several alternatives could be considered: (1) update the International Working Formulation to incorporate newly described entities; (2) adopt the Kiel Classification, which has recently been updated, as the standard international standard; or (3) develop a new lymphoma classification.

It has been suggested that the Working Formulation, the most widely used method for lymphoma diagnosis in the United States, and the basis for most American lymphoma clinical trials, be updated to include new entities. Arguments in favor of this course include the relative simplicity of the Working Formulation, which make it easy to understand and apply, the belief that its prognostic groups make it uniquely clinically relevant, and the fact that it has been used in many clinical trials in the last decade. Nonetheless, there are several arguments against revising the Working Formulation. One major reason is that the Working Formulation was not intended by its authors to be a free-standing classification scheme, but rather a method of translating between existing classifications. At the time it was developed, six schemes were in use in various parts of the world; pathologists could not reach a consensus, and the NCI-sponsored study failed to show a clear advantage in survival prediction or reproducibility of any one classification. Thus, the Working Formulation was proposed as an inclusive scheme, in which all categories in all existing classifications could find a place. However, since publication of the Working Formulation in 1982, most of the six classifications have not continued in use; only the Kiel and Lukes-Collins classifications are widely used. Thus, it is not clear what remains for the Working Formulation to “translate” between.

A second problem is that the Working Formulation categories were defined by survival data based on a group of patients treated on chemotherapy protocols used in the 1970s. Because its categories were based on survival data from a defined patient population, it is difficult to see how it can be formally revised without reference to the original slides and patient data. Furthermore, a classification based solely on response to treatment available 10 to 20 years ago may not have continued relevance as new therapies become available.

Finally, the morphologic diagnoses in the Working Formulation were based solely on review of hematoxylin and eosin-stained sections; no special stains or immunologic data were available. Many of the advances in lymphomas in recent years have involved immunologic and genetic studies, which are not available on the Working Formulation material. For all of the above reasons, we believe that updating the Working Formulation is impractical.

The Kiel Classification, used in Europe and elsewhere, has recently been updated. It could be argued that this classification, which is widely used outside of the United States, should be adopted as the new international standard classification. The Kiel Classification is based on the postulated relationship of neoplastic lymphoid cells to their normal counterparts in the immune system, and uses both detailed morphologic analysis and immunologic studies to define specific disease entities. It contains many well-defined entities that are now accepted throughout the world, and thus could serve as a basis for an international consensus classification. However, it excludes primary extranodal lymphomas other than mycosis fungoides and does not address some issues of concern to North Americans, such as the morphologic and clinical heterogeneity of follicular lymphomas, which appear to be more common in the United States than in Europe. Finally, it requires morphologic subclassification of entities such as large B-cell lymphoma and peripheral T-cell lymphomas, which may be difficult and poorly reproducible.

For these reasons, we took the approach of determining what experienced hematopathologists—none of whom had been involved in developing one of the existing classifications—were actually doing in their daily practice. We assumed that entities that we could all agree on could be recognized by others, and that entities that we could not define or diagnose reliably would likely cause difficulty for other pathologists. This approach to lymphoma categorization is not intended to replace either the Kiel Classification or the Working Formulation. We have built on existing classifications and many other published studies, and simply produced a compilation of existing knowledge in a practical form.
Most of the entities listed are already included in the updated Kiel Classification. Our list can be used in conjunction with the Working Formulation, because many of the diseases recognized fall within one or another of the Working Formulation categories. Conversely, American hematologists and oncologists may conclude that the Working Formulation has outlived its usefulness and that more specific disease entities, such as those listed here, should be recognized in clinical trials. Because our effort builds on current European and American classifications, we have termed it the "Revised European-American Lymphoma Classification."

We have described a large number of disease entities, which may alarm those who believe that a lymphoma classification must be simple. Given the complexity of the immune system, it should not be surprising that its tumors are numerous and complex. It is necessary to "split" before meaningful "lumping" can occur. If several morphologically, immunologically, and genetically distinct neoplasms prove to respond identically to currently available treatment, they can be "lumped" for the purposes of clinical treatment selection. However, if new forms of treatment become available, particularly if these are directed against antigenic or genetic features, it will be important to recognize and study each disease separately. For those who argue that oncologists cannot possibly remember a large number of diseases or incorporate new ones into their thinking, we call to mind the large and (to pathologists) bewildering array of new drugs and combinations that oncologists seem to understand and respond to without difficulty. If the entities that we describe here are indeed real diseases, the relevance and utility of this approach will be readily apparent, and no one will complain about the large number of diseases to study and treat. If appropriate studies are conducted, proposed entities that are not real diseases will soon be eliminated.

This study should be regarded as a preliminary effort to bring some order to the chaos of lymphoma categorization, and constitutes merely a framework for further study. Specifically, we have made no attempt to determine the reproducibility of diagnosis of these various categories, either among different pathologists or by the same pathologist over time. We note that no prior tumor classification has been done with existing classifications of lymphoma, they have shown disappointing results. We expect that reproducibility studies should be undertaken, and should in general be a more frequent activity in the pathologic diagnosis of tumors.

We have also not made a systematic attempt to determine the utility of these histologically and immunologically defined categories in predicting clinical outcome. Our clinical data are taken from studies already published in the literature, many of them conducted by pathologists rather than clinicians. We believe that systematic application of the criteria presented here to defined groups of patients, in collaboration with our clinical colleagues, is imperative. Several of us are associated with cooperative clinical groups studying lymphomas in both the United States and Europe, and we plan to undertake this important next step in the near future.

Finally, we recognize that the list of entities presented here is likely to contain errors both of omission and commission: we have included some provisional entities that may not prove to be real diseases, and excluded some recently defined or controversial entities that may prove to be real in the future. Thus, a critical feature of any tumor classification is that it be periodically reviewed and updated to incorporate new information. A model for this activity has been the FAB group in its approach to leukemias. Either our informal group or a larger group, composed of subcommittees of the major Hematopathology associations or the World Health Organization, should undertake this task.

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