To the Editor:

In a recent issue of Blood, the International Lymphoma Study Group (ILSG) presented a list of lymphoid neoplasms derived by consensus, and suggested that it could serve as a practical classification of these tumors for both pathologists and clinicians. Each of the entities on the list represents a clearly recognizable and distinct disease, based on currently available morphologic, immunologic, and genetic techniques, with a characteristic clinical behavior. Dr. Saul Rosenberg, in an accompanying editorial, indicated his concern that this list of neoplasms should not yet be used in clinical practice. We believe that the implementation of a broadly based international consensus on lymphoma classification is long overdue, and that further delay is not warranted. We fear that these concerns may lead to unnecessary hesitation on the part of pathologists and clinicians to recognize these clinicopathologic entities. Therefore, we would like to address these concerns and offer the following clarifications of our proposal.

First, there is concern about the extent to which this list of neoplasms will be accepted by other hematopathologists. The history of lymphoma classification would appear to give credence to this concern, because previous generations of pathologists have been unable to agree on a classification system; even the working formulation did not represent a consensus because it was rejected by 2 of the 12 pathologists involved, Drs. Karl Lennert and Robert Lukes, at the time of its publication. However, we believe that most of the entities in our classification are already being diagnosed by most hematopathologists; our list is just a description of what is already being done. The main reason that a consensus among pathologists on lymphoma classification is now possible is the availability of objective immunophenotyping and genetic data to resolve areas that were controversial when morphology was the only criterion for defining entities. As we stated in our paper, we recognize that our list will require updating and modification, and we look forward to working with other hematopathologists to broaden and build upon this consensus.

A second concern that has been raised is the availability of immunophenotyping and genetic studies, which are an important component of the definition of these neoplasms, in parts of the United States. Our experience as consultants suggests that this concern is not warranted; we find that most practicing pathologists are well aware of the need for special studies on a variety of specimen types, including immunophenotyping of lymphoid and other neoplasms, hormone receptor assays, etc., and are capable of either performing these tests themselves or preserving tissue so that others can perform such studies when needed. Furthermore, a large panel of antibodies for immunophenotyping on paraffin sections is now available and will permit most tumors to be adequately characterized on routinely processed, formalin-fixed, paraffin-embedded biopsy specimens. Finally, immunophenotyping studies are not required to make every diagnosis in every case. As a general principle, morphologic, clinical and immunologic/genetic features are all taken into account in establishing a diagnosis. However, many individual cases of lymphoma can be diagnosed on morphologic grounds alone, providing that histologic sections of reasonable quality are available. In any morphologically or clinically atypical case, immunophenotyping and/or genetic studies may be helpful in establishing a diagnosis. These studies markedly improve diagnostic accuracy and reproducibility among pathologists. It would indeed be a major step backwards to suggest that the immunophenotype should not be part of the definition of a lymphoid neoplasm. We do not think that pathologists should ignore all the advances in immunology and genetics of the last 20 years and continue to classify lymphomas according to the techniques of the 1960s. It strikes us as curiously paradoxical that classification according to a putative cell of origin is intrinsic to virtually all schemes of tumor classification in other organ systems, and yet it is questioned in the United States for lymphomas—the one area in which we actually have objective evidence for the normal counterpart of most of the malignancies.

Another concern is that our classification is not adequately supported by a clinical database. A pathologic classification of neoplasms is, by definition, a listing of distinct disease entities, based on features that can be recognized by pathologists: chiefly morphology, buttressed to a variable extent by special techniques. For pathologists to make the diagnoses, the entities must be defined by these features. Clinical studies to define their clinical spectrum and optimal treatment are essential, but these are not typically the responsibility of the pathologist, and cannot be conducted until pathologists can recognize the entities. It is important to remember that in the working formulation study there was no consensus on the pathologic classification, so that the investigators were working in reverse: defining pathologic entities by clinical prognostic data. This is not the case with our proposal. We did not define any new entities: all of the diseases in our classification have been described in the literature, and for most of them there are numerous studies to show that they have distinctive clinical features. We question the need for more data to show that precursor B- and T-cell neoplasms, B-cell chronic lymphocytic leukemia (B-CLL), Waldenstrom's macroglobulinemia, follicular lymphoma, hairy cell leukemia, plasma cell myeloma, diffuse large B-cell lymphoma, Burkitt's lymphoma, mycosis fungoides, and adult T-cell lymphoma/leukemia (ATL/L) are distinct entities. Even for the more recently described or uncommon entities such as mucosa-associated lymphoid tissue (MALT) lymphoma, mantle cell lymphoma, anaplastic large cell lymphoma, angioimmunoblastic lymphoma, and angiotcentric lymphoma, there is already

Fig 1. Survival curves for early-stage breast cancer treated with mastectomy and early-stage follicular lymphoma treated with radiation therapy. Breast cancer data adapted from Fisher et al. and follicular lymphoma data adapted from Paryani et al. (●), follicular lymphoma overall survival; (□), breast cancer overall survival; (▲), follicular lymphoma disease-free survival; (○), breast cancer disease-free survival.
ample evidence that they are clinically distinctive. Of course, we would be pleased to see our proposed classification used in large-scale clinical trials. However, some of the uncommon and more controversial entities might not be resolved even in a large study because they would likely be under-represented in many populations. Clearly, the newer and more unusual entities require further investigation, but if pathologists are discouraged from diagnosing these entities, to allow clinicians with a clear knowledge of distinct disease entities, to allow optimal clinical studies and treatment. Clinical studies that group together entities that are biologically distinct may obscure important observations regarding prognosis and interaction with treatment, and can hinder development of novel therapeutic strategies for individual diseases. The emphasis on broad prognostic groups that are defined by survival rather than by pathologic features, as in the working formulation, can lead to the belief that all entities within a group can be considered a single disease, rather than as distinct entities, simply because they have similar survival curves. Overemphasis on survival as a defining feature of a disease, taken to its extreme, could lead to the conclusion that breast cancer and follicular lymphomas need not be distinguished from one another because they have similar survivals

Table 1. Approximate Frequency of Lymphoid Neoplasms in Adult Biopsy Specimens From Centers in the United States and Europe

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Lymph Node %</th>
<th>Bone Marrow %</th>
<th>Spleen %</th>
<th>GI Tract %</th>
<th>Skin %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor T-lymphoblastic leukemia/lymphoma</td>
<td>1-3</td>
<td>5-15</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1-4</td>
</tr>
<tr>
<td>B-cell CLL/PLL</td>
<td>5-10</td>
<td>26-35</td>
<td>25-40</td>
<td>2</td>
<td>5-10</td>
</tr>
<tr>
<td>Lymphoplasmocytoid lymphoma/immunocytoma</td>
<td>1-2</td>
<td>5-10</td>
<td>&lt;1</td>
<td>1-3</td>
<td></td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>2-6</td>
<td>1-3</td>
<td>1-5</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Follicle center lymphoma, follicular</td>
<td>25-40</td>
<td>10-15</td>
<td>20-25</td>
<td>5-10</td>
<td>10</td>
</tr>
<tr>
<td>Marginal zone B-cell lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extramedial (MALT type &lt; monocytoid B cells)</td>
<td>1-5</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>20-50</td>
<td>5</td>
</tr>
<tr>
<td>Nodal (&lt; monocytoid B cells) (provisional)</td>
<td>1-5</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td></td>
<td></td>
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<tr>
<td>Splenic marginal zone lymphoma (provisional)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>&lt;1</td>
<td>5-10</td>
<td>10-25</td>
<td></td>
<td></td>
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<tr>
<td>Plasmacytoma/plasma cell myeloma</td>
<td>&lt;1</td>
<td>30-50</td>
<td></td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>25-35</td>
<td>1</td>
<td>20</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Burkitt’s and Burkitt’s-like (provisional)</td>
<td>1-2</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1-2</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

T/NK-CELL NEOPLASMS: 14% (8-20)

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Lymph Node %</th>
<th>Bone Marrow %</th>
<th>Spleen %</th>
<th>GI Tract %</th>
<th>Skin %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor T-lymphoblastic lymphoma/leukemia</td>
<td>1-4</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>T-cell CLL/PLL</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>5</td>
</tr>
<tr>
<td>Large granular lymphocyte leukemia (LGL)</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycosis fungoides/Sezary syndrome</td>
<td>1</td>
<td></td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral T-cell lymphomas, unspecified</td>
<td>5-7</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>2-3</td>
<td>10-20</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma (AILD)</td>
<td>1-4</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiocentric lymphoma</td>
<td>&lt;1</td>
<td></td>
<td>&lt;1</td>
<td></td>
<td>&lt;1</td>
</tr>
<tr>
<td>Intestinal T-cell lymphoma</td>
<td></td>
<td></td>
<td></td>
<td>1-5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>ATL/L</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td></td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma (ALCL), CO39+</td>
<td>1-10</td>
<td>1-2</td>
<td>&lt;1</td>
<td>1-5</td>
<td>5-15</td>
</tr>
</tbody>
</table>

Data is from the Departments of Pathology, Stanford University, Stanford, CA; John Radcliffe Hospital, Oxford, UK; Herlev Hospital, Copenhagen, Denmark; and Universita degli Studi, Bologna, Italy.

Abbreviations: GI, gastrointestinal; PLL, prolymphocytic leukemia; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

In response to a concern about the lack of information on the incidence of the various disease entities, several members of the ILSG have reanalyzed their own material, to determine the frequency of the entities in their patient populations (Table 1). Although preliminary, these data give some idea of the relative frequency with which these diagnoses may be made in Western adult populations. Not surprisingly, B-cell lymphomas comprise 85% of the neoplasms, and T-cell lymphomas 15%; the two largest categories are follicle center lymphoma, follicular (35%-40%) and diffuse large B-cell lymphoma (25%-30%). Thus, pathologists and oncologists can be assured that the majority of the adult nodal lymphomas that they will see are the two most familiar categories already known from other classifications. Within the T-cell lymphomas, the most common types are mycosis fungoides, anaplastic large cell lymphoma, and peripheral T-cell lymphomas, unspecified. However, the frequency of these neoplasms differs in various extranodal sites and in pediatric populations, as well as in other parts of the world; a detailed discussion of these variations could be the topic of another review.

One question that arises about any disease classification is whether it can be reproducibly used by less-experienced pathologists. The reproducibility of prior lymphoma classifications has been tested in the past, and all have been found to be poorly reproducible. We believe that oncologists dealing with lymphomas in the United States in the past two decades have been deprived of the excitement of learning to know and treat distinct diseases, because of the failure of pathologists to define them clearly and agree on these definitions.
fact, the National Cancer Institute study that produced the working formulation included a reproducibility study that tested the agreement between the proponents of each classification and a panel of six independent pathologists. The results indicated a poor rate of concurrence (0.21 to 0.65). Notably, the authors of the report concluded that the introduction of immunologic techniques might improve diagnostic accuracy and permit a "transition away from subtle morphologic distinctions alone to a more functional (and technologic) basis" for diagnosis. Subsequent studies have indeed shown that the addition of immunophenotyping data to morphology significantly improves reproducibility among pathologists, and we are confident that a list of well-defined entities such as the one we proposed will be more reproducibly diagnosed than the more ambiguous categories of the working formulation.

In summary, we hope that our list will be helpful to both pathologists and clinicians working with patients with lymphoid neoplasms. Although it is presented as a proposal, we believe that it represents what is currently possible—and what is already being done—in lymphoma diagnosis. In this fast-moving field, everything is perennially preliminary, and no classification can keep pace with developments in biology, diagnosis, and therapy. We believe that our approach—establishing a consensus among experts on the defining criteria for currently recognizable neoplasms—represents the best approach to lymphoma classification yet offered in the literature. We have not discarded previous classifications, nor have we proposed anything original; we have compiled from the literature and our own experience the best that each classification has to offer, and added other entities not included in existing classifications. This is the largest group of pathologists ever to agree on a lymphoma classification. For the future, we urge our colleagues in the major hematopathology societies to develop joint committees on classification, to use the expertise of their members in continuing to update the list of defined entities, and we encourage our clinical colleagues to incorporate these entities into clinical trials.

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REFERENCES

Lymphoma classification proposal: clarification [letter; comment] [see comments]

NL Harris, ES Jaffe, H Stein, PM Banks, JK Chan, ML Cleary, G Delsol, C De Wolf-Peeters, B Falini and KC Gatter