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## The Changing Classification of Non-Hodgkin's Lymphomas

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Non-Hodgkin's lymphomas will be diagnosed an estimated 50,000 times this year in the United States.<sup>1</sup> This makes them the most common tumors of the immune system. Unfortunately, they are increasing steadily in frequency and have been doing so since 1950. The mortality rate has been rising in a corresponding fashion, reflecting our lack of new therapies.

In any illness for which more than one treatment is effective, the ability to identify and classify subgroups of patients is important. In non-Hodgkin's lymphomas, many treatments are beneficial in that they cure some patients, frequently prolong life, and alleviate symptoms. However, the treatments (e.g., cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone [CHOP]; fludarabine; interferon; radiotherapy; and bone marrow transplantation, to name a few) vary widely in complications, intensity, and cost. Because all treatments are not useful to all patients, it is necessary to divide the non-Hodgkin's lymphomas into clinically relevant subgroups.

Previous systems used to subdivide the non-Hodgkin's lymphomas were based on morphology. Early in

this century, the recognition of the Reed-Sternberg cell made it possible for physicians to distinguish between Hodgkin's disease and the non-Hodgkin's lymphomas. Subsequent systems, as exemplified by the Rappaport classification, made subdivisions based on pattern of cell growth and cell size and shape. Lukes and Collins, in the system given their names, and the Kiel classification developed by Karl Lennert added immunologic subgrouping when the existence of T and B lymphocytes became known.

In an attempt to allow translation among the various systems in use, the Working Formulation was developed. It was made up largely of the Rappaport subgroups using Lukes and Collins terminology. With this background, it is not surprising that the Working Formulation was much more popular in North America than in Europe.

Recently, increasingly sophisticated biologic observations have made possible the identification of previously unrecognized groups of patients with similar clinical characteristics and treatment outcomes. For example, patients with small-cell, B-cell lymphoma who have the translocation t(11;14) with the break point on chromosome 11 at the locus for the cyclin D1 gene form a group with a distinct clinical-pathologic entity now called mantle cell lymphoma.

Similarly, recognition that small

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**Table**  
**The Frequency of Occurrence of Major Subtypes**  
**of Non-Hodgkin's Lymphoma**

Subtype	Frequency (%)
Diffuse large B-cell	31
Follicular	22
Marginal zone, MALT	8
Peripheral T-cell	7
Small lymphocytic (B-cell)	7
Mantle cell	6
Primary mediastinal large B-cell	2
Anaplastic large T/NK-cell	2
High-grade, B-cell Burkitt's-like	2
Marginal zone, nodal	2
Lymphoblastic, T-cell	2
Burkitt's	<1

MALT = mucosa-associated lymphoid tissue.  
 Data from the Non-Hodgkin's Lymphoma Classification Project.<sup>3</sup>

cell, B-cell, CD5-negative lymphomas of the stomach were associated with *Helicobacter pylori* infection helped the acceptance of the concept of MALT (mucosa-associated lymphoid tissue) lymphoma. The International Lymphoma Study Group (ILSG) has proposed that lymphomas in the future be grouped as clinical-pathologic entities rather than only as morphologic

subgroups.<sup>2</sup>

A group of investigators from around the world has tested this new concept.<sup>3</sup> Approximately 1,400 lymphomas from patients in North America, Europe, Africa, and Asia were grouped according to the ILSG proposal. The frequency found for the major subtypes is listed in the Table.

This system led to the identifica-

tion of clinically relevant subgroups, and the diagnoses were made much more accurately than they were using previous systems.<sup>3</sup> However, the fact that the most common lymphoma in the new classification (diffuse large B-cell lymphoma) almost certainly represents more than one clinical-pathologic entity shows that work remains to be done.

Another important observation of the international study mentioned earlier was that the diagnosis of a specific subtype of lymphoma is not enough information for good patient care. The prognosis of any subgroup is related to

the clinical characteristics found in the International Prognostic Index.<sup>4</sup> An accurate diagnosis combined with a prognostic grouping based on the International Prognostic Index makes it possible for clinicians to identify clinically useful subgroups of patients for whom intelligent therapeutic decisions can be made.

The future for clinical investigation of the diagnosis and management of patients with non-Hodgkin's lymphoma appears promising. This group of illnesses has taught us much about the principles and practice of oncology and will likely teach us much more.

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**References**

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