SPECIAL ARTICLE

World Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues: Report of the Clinical Advisory Committee Meeting—Airlie House, Virginia, November 1997

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Purpose: **The European Association of Hematopathologists and the Society for Hematopathology have developed a new World Health Organization (WHO) classification of hematologic malignancies, including lymphoid, myeloid, histiocytic, and mast cell neoplasms.**

Design: **Ten committees of pathologists developed lists and definitions of disease entities. A clinical advisory committee (CAC) of international hematologists and oncologists was formed to ensure that the classification would be useful to clinicians. The CAC met in November 1997 to discuss clinical issues related to the classification.**

Results: **The WHO uses the Revised European-American Lymphoma (REAL) classification, published in 1994 by the International Lymphoma Study Group, to categorize lymphoid neoplasms. The REAL classification is based on the principle that a classification is a list of "real" disease entities, which are defined by a combination of morphology, immunophenotype, genetic features, and clinical features. The relative importance of each of these features varies among diseases, and there is no one gold standard. The WHO classification applies the principles of the REAL classification to myeloid and histiocytic neoplasms. The classification of myeloid neoplasms recognizes distinct entities defined by a combination of morphology and cytogenetic abnormalities. At the CAC meeting, which was organized around a series of clinical questions, participants reached a consensus on most of the questions posed. They concluded that clinical groupings of lymphoid neoplasms were neither necessary nor desirable. Patient treatment is determined by the specific type of lymphoma, with the addition of grade within the tumor type, if applicable, and clinical prognostic factors, such as the International Prognostic Index.**

Conclusion: **The WHO classification has produced a new and exciting degree of cooperation and communication between oncologists and pathologists from around the world, which should facilitate progress in the understanding and treatment of hematologic malignancies.**

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THE SOCIETY FOR Hematopathology and the European Association of Hematopathologists jointly developed a classification of hematologic neoplasms for the World Health Organization (WHO). A steering committee composed of members of both societies was formed, and 10 committees were assigned the task of arriving at a consensus list of myeloid, lymphoid, and histiocytic neoplasms, with descriptions and criteria for diagnosis. A new classification for lymphoid neoplasms was recently proposed,[1] and the goals of the WHO project were to update and revise that classification, with input from additional experts in order to broaden the consensus, and to extend the principles of disease definition and consensus building to the myeloid and histiocytic neoplasms. More than 50 pathologists from around the world were involved in the project, which began in 1995. Proponents of all major lymphoma and leukemia classifications agreed that if a reasonable consensus emerged from this effort, they would accept the WHO classification of hematologic malignancies as the standard.

The proposed WHO classification of hematologic malignancies stratifies neoplasms primarily according to their lineage: myeloid neoplasms (Table 1), lymphoid neoplasms (Tables 2 and 3), mast cell disorders (Table 4), and histiocytic neoplasms (Table 5). Variants and subtypes of selected neoplasms are listed in Tables 6 through 15. Within each category, distinct diseases are defined according to a

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Table 1. Proposed WHO Classification of Myeloid Neoplasms

Myeloproliferative diseases
Chronic myelogenous leukemia, Philadelphia chromosome positive (t(9;22)(qq34;q11), *BCR/ABL*)
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia/hypereosinophilic syndrome
Chronic idiopathic myelofibrosis
Polycythemia vera
Essential thrombocythemia
Myeloproliferative disease, unclassifiable
Myelodysplastic/myeloproliferative diseases
Chronic myelomonocytic leukemia
Atypical chronic myelogenous leukemia
Juvenile myelomonocytic leukemia
Myelodysplastic syndromes
Refractory anemia
With ringed sideroblasts
Without ringed sideroblasts
Refractory cytopenia (myelodysplastic syndrome) with multilineage dysplasia
Refractory anemia (myelodysplastic syndrome) with excess blasts
5q− syndrome
Myelodysplastic syndrome, unclassifiable
Acute myeloid leukemias*
AMLs with recurrent cytogenetic translocations
AML with t(8;21)(q22;q22), AML1(CBF-alpha)/ETO
Acute promyelocytic leukemia (AML with t(15;17)(q22;q11-12) and variants, PML/RAR-alpha)
AML with abnormal bone marrow eosinophils (inv(16)(p13q22) or t(16;16)(p13;q11), CBFβ/MYH11X)
AML with 11q23 (MLL) abnormalities
AML with multilineage dysplasia
With prior myelodysplastic syndrome
Without prior myelodysplastic syndrome
AML and myelodysplastic syndromes, therapy-related
Alkylating agent–related
Epipodophyllotoxin-related (some may be lymphoid)
Other types
AML not otherwise categorized
AML minimally differentiated
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monocytic leukemia
Acute erythroid leukemia
Acute megakaryocytic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Acute biphenotypic leukemias

NOTE: Only major disease categories are listed; subtypes and variants will be discussed in detail in the WHO book.[2]

Abbreviation: AML, acute myeloid leukemia.

*Acute lymphoid leukemias are included under lymphoid neoplasms and in Table 6.

combination of morphology, immunophenotype, genetic features, and clinical syndromes. The relative importance of each criterion differs among the neoplasms, and there is no one gold standard for classification of all hematologic malignancies. The goal was to define disease entities that could be recognized by pathologists and that have clinical relevance.

To ensure that the proposed classification would be of maximal use to oncologists, the steering committee invited expert hematologists and oncologists to form a clinical advisory committee (CAC), with American and European co-chairs. The charge to the CAC was to review the proposed classification and advise the pathologists on its clinical utility. More than 40 hematologists and oncologists from around the world agreed to participate. The proposed classification was circulated, and all participants were invited to submit topics and questions for discussion. A meeting was held in November 1997, at Airlie House, VA, involving the CAC, all pathologists involved in the WHO committees, and the executive committees of the two hematopathology societies.

The meeting was organized around a series of questions developed from those submitted by CAC members and posed by the pathologists. Only controversial issues were discussed; diseases were accepted as previously defined if there were no new questions or data. Only lymphoid and myeloid neoplasms were discussed at the meeting; histiocytic and mast cell tumors were not considered. Participants were invited to present data relevant to each question, and open discussion followed. At the end of each session, the clinicians were asked to arrive at a consensus regarding each question (as well as other issues raised at the meeting); if necessary, a show of hands was taken as a vote. After the meeting, participants were polled to resolve residual questions; several additional meetings of the pathology steering committee and the CAC co-chairs were held for the same purpose. The final classification will be published under the auspices of the WHO.[2]

MYELOID NEOPLASMS

Despite advances in the understanding of genetic factors in the biology of the myeloid neoplasms, particularly the acute leukemias, the classification of these disorders has not been recently updated. Thus, discussion of these disorders generated considerable controversy. At several subsequent meetings of pathologists and the clinical co-chairs, a consensus on the classification emerged. The following summary includes issues raised at the CAC meeting and resolutions achieved subsequently.

In the French-American-British (FAB) classification, three main categories of myeloid neoplasms are recognized: acute myeloid leukemias, myelodysplastic syndromes, and myelo-

Table 2. Proposed WHO Classification of Lymphoid Neoplasms

B-Cell neoplasms
Precursor B-cell neoplasm
Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)
Mature (peripheral) B-cell neoplasms*
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma (+/− villous lymphocytes)
Hairy cell leukemia
Plasma cell myeloma/plasmacytoma
Extranodal marginal zone B-cell lymphoma of MALT type
Nodal marginal zone B-cell lymphoma (+/− monocytoid B cells)
Follicular lymphoma
Mantle-cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal large B-cell lymphoma
Primary effusion lymphoma
Burkitt's lymphoma/Burkitt cell leukemia
T-cell and NK-cell neoplasms
Precursor T-cell neoplasm
Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)
Mature (peripheral) T-cell neoplasms*
T-cell prolymphocytic leukemia
T-cell granular lymphocytic leukemia
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia (HTLV1+)
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic gamma-delta T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides/Sezary syndrome
Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type
Peripheral T-cell lymphoma, not otherwise characterized
Angioimmunoblastic T-cell lymphoma
Anaplastic large-cell lymphoma, T/null cell, primary systemic type
Hodgkin's lymphoma (Hodgkin's disease)
Nodular lymphocyte-predominant Hodgkin's lymphoma
Classical Hodgkin's lymphoma
Nodular sclerosis Hodgkin's lymphoma (grades 1 and 2)
Lymphocyte-rich classical Hodgkin's lymphoma
Mixed cellularity Hodgkin's lymphoma
Lymphocyte depletion Hodgkin's lymphoma

NOTE: Only major categories are included. Subtypes and variants will be discussed in the WHO book[2] and are listed in Tables 7 through 16. Common entities are shown in boldface type.

Abbreviations: HTLV1+, human T-cell leukemia virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

*B- and T-/NK-cell neoplasms are grouped according to major clinical presentations (predominantly disseminated/leukemic, primary extranodal, predominantly nodal).

Table 3. Categories of Posttransplant Lymphoproliferative Disorders

Early lesions
Reactive plasmacytic hyperplasia
Infectious mononucleosis-like
PTLD, polymorphic
Polyclonal (rare)
Monoclonal
PTLD, monomorphic (classify according to lymphoma classification)
B-cell lymphomas
Diffuse large B-cell lymphoma (immunoblastic, centroblastic, anaplastic)
Burkitt's/Burkitt-like lymphoma
Plasma cell myeloma
T-cell lymphomas
Peripheral T-cell lymphoma, not otherwise categorized
Other types (hepatosplenic, gamma-delta, T/NK)
Other types, rare
Hodgkin's disease-like lesions (associated with methotrexate therapy)
Plasmacytoma-like lesions

proliferative disorders.[3] The blast count, lineage commitment, and level of differentiation of the neoplastic cells are the major determinants of the categories recognized, using morphologic, cytochemical, and immunophenotypic features. Recently, genetic features (cytogenetic and molecular genetic), as well as other features, such as prior therapy and a history of myelodysplasia, have been shown to have a significant impact on the clinical behavior of these disorders, and these features do not always correlate perfectly with the FAB categories. Thus, a major focus of debate was how to integrate genetic and clinical features with morphology, cytochemistry, and immunophenotype into a classification that could be used by pathologists and have clinical relevance. A key issue, as with the lymphoid neoplasms, was to discriminate between disease entities and prognostic factors. Some genetic abnormalities seem to define distinct diseases, whereas others are prognostic factors within a given disease. Also debated was whether all diseases fit into one of the three major categories or whether additional broad categories are needed.

After discussion, it seemed that a paradigm similar to that adopted for the Revised European-American Lymphoma (REAL) classification could at least tentatively apply to the myeloid disorders; namely, a combination of morphology, immunophenotype, genetic features, and clinical features could be used to define distinct disease entities. The technology of genetic analysis is evolving rapidly, and it is likely that advances in this field will necessitate revisions to

Table 4. Mast Cell Diseases

Cutaneous mastocytosis
Systemic mast cell disease (+/− skin involvement)
Systemic mast cell disease with associated hematologic disorder (+/− skin involvement)
Mast cell leukemia/sarcoma

Table 5. Histiocytic and Dendritic Cell Neoplasms

Macrophage/histiocytic neoplasm
Histiocytic sarcoma
Dendritic Cell neoplasms
Langerhans cell histiocytosis
Langerhans cell sarcoma
Interdigitating dendritic cell sarcoma/tumor
Follicular dendritic cell sarcoma/tumor
Dendritic cell sarcoma, not otherwise specified

any current classification in the near future. The pathologists proposed four major groups of myeloid diseases: myeloproliferative diseases (MPDs), myelodysplastic/myeloproliferative diseases (MD/MPDs), myelodysplastic syndromes (MDSs), and acute myeloid leukemias (AMLs). Within the category of AML, four main groups are recognized: (1) AML with recurrent cytogenetic translocations; (2) AML with myelodysplasia-related features; (3) therapy-related AML and MDS; and (4) AML not otherwise specified.

Myeloproliferative Diseases

MPDs are clonal stem-cell disorders characterized by ''effective'' hematopoiesis that results in elevated peripheral-blood levels of one or more cell lines and hepatosplenomegaly; the marrow is hypercellular with maturation and without dysplasia. Among the MPDs, the prototype is Philadelphia chromosome (Ph1)–positive (*BCR/ABL*$^+$) chronic myelogenous leukemia (CML). The other accepted entities are polycythemia vera, idiopathic myelofibrosis, and essential thrombocythemia. Controversies within this group include the definitions and classification of juvenile myelomonocytic leukemia (JMML; also known as juvenile chronic myeloid leukemia and juvenile chronic myelomonocytic leukemia), chronic myelomonocytic leukemia (CMML), and atypical CML.

Should JMML be a separate category? Should it be classified as an MDS or an MPD? The CAC accepted the conclusions of the International Study Group for Pediatric MDS that JMML is a separate disorder, distinct from adult chronic myeloid or myelomonocytic leukemia. CAC members proposed that the term JMML be adopted. They favored including it in the MPDs; however, the pathologists recommended that a separate category be formed to include JMML and other disorders that combine features of myeloproliferative and myelodysplastic syndromes.

Table 6. Acute Lymphoid Leukemias

Precursor B-cell acute lymphoblastic leukemia (cytogenetic subgroups)
t(9;22)(a34;q11); *BCR/ABL*
t(v;11q23); *MLL* rearranged
t(1;19)(q23;p13) *E2A/PBX1*
t(12;21)(p12;q22) *ETV/CBF*-alpha
Precursor T-cell acute lymphoblastic leukemia
Burkitt-cell leukemia

Table 7. B-Cell Neoplasms, Predominantly Disseminated/Leukemic Types, Variants

B-cell CLL/SLL
Variant: with monoclonal gammopathy/plasmacytoid differentiation
Hairy cell leukemia
Variant: hairy cell leukemia variant

Should CMML be divided into MDS and MPD types? CMML has long been recognized as a disorder that has features of both myelodysplastic and myeloproliferative syndromes. Nearly half the patients present with low or normal neutrophil counts, multilineage marrow dysplasia, no organomegaly, and bone marrow morphology that resembles refractory anemia with excess blasts (RAEB) but with monocytosis. Other patients have marked neutrophilia, monocytosis, and splenomegaly. It has been debated whether this is really two diseases—one an MDS and the other an MPD. However, studies to date have shown no differences in cytogenetic abnormalities, oncogene mutations, in vitro colony growth patterns, or clinical outcome between the two types of CMML. It was the consensus at the meeting that CMML is one disease. The CAC concluded that CMML fits better in the MPD than in the MDS category, but after subsequent discussions, the pathologists recommended that it be included in a separate category, along with JMML, of disorders with both myeloproliferative and myelodysplastic features.

What should the nomenclature and category be for atypical CML (aCML)? Atypical CML was first recognized as a disease involving predominantly the neutrophil series and lacking Ph1 or the *BCR/ABL* translocation. It has dysplastic as well as proliferative features and often occurs with multilineage dysplasia. The prognosis is significantly worse than that for Ph1$^+$ CML. It is clear that it is clinically, genetically, and morphologically distinct from Ph1$^+$ CML; therefore, the term aCML is suboptimal, implying both a

Table 8. Follicular and Mantle-Cell Lymphomas: Grading and Variants

Follicular lymphoma
Grade 1, 0-5 centroblasts/hpf
Grade 2, 6-15 centroblasts/hpf
Grade 3, > 15 centroblasts/hpf
3a, > 15 centroblasts, but centrocytes are still present
3b, Centroblasts form solid sheets with no residual centrocytes
Variants
Cutaneous follicle center lymphoma
Diffuse follicle center lymphoma
Grade 1, 0-5 CB/hpf
Grade 2, 6-15 CB/hpf
Mantle-cell lymphoma
Variant: blastoid

Table 9. DLBCL, Morphologic Variants and Subtypes

Morphologic variants
Centroblastic
Immunoblastic
T-cell/histiocyte-rich
Lymphomatoid granulomatosis type
Anaplastic large B-cell
Plasmablastic
Subtypes
Mediastinal (thymic) large B-cell lymphoma
Primary effusion lymphoma
Intravascular large B-cell lymphoma

relationship to $Ph1^+$ CML and a chronic process. The CAC was unable to agree on another name, and thought the term aCML could be retained, provided the disease was clearly defined so as to prevent confusion. The pathologists recommended placing aCML with JMML and CMML in a category of MD/MPD.

Should there be a separate category for cases that are neither MDS nor MPD? For reasons mentioned above, the pathologists recommended a fourth category of myeloid neoplasms to contain those cases that are inherently proliferative but show dysplastic features, such as JMML, CMML, and aCML. It was the opinion of the clinicians that such a category was not desirable and that these diseases could be placed in the MPD category. The pathologists contended that these disorders have many common features, including abnormalities of both the granulocytic and monocytic lines and a relatively aggressive course, that distinguish them from the MDS and MPD categories and argued for placing them together.

MPDs: Summary.

1. Should JMML be a separate category? YES
2. Should CMML be divided into MDS and MPD types? NO
3. What should we call aCML? aCML
4. Should there be a separate category for cases that are neither MDS nor MPD? NO CONSENSUS
   - Pathologists proposed a category of MDS/MPD to include JMML, CMML, and aCML.

Acute Myeloid Leukemia and Myelodysplastic Syndrome

What blast count should define AML? According to the FAB standard, AML is defined by the presence of 30% blasts. However, recent studies have indicated that patients with 20% to 30% blasts (classified as RAEB in transformation) have a prognosis similar to that of patients with more than 30% blasts. Thus, there was a consensus that the blast count for the diagnosis of AML should be 20% and the RAEB in transformation category should be dropped.

Table 10. Burkitt's Lymphoma, Morphologic Variants and Subtypes

Morphologic variants
Burkitt-like
With plasmacytoid differentiation (AIDS-associated)
Subtypes, clinical and genetic
Endemic
Sporadic
Immunodeficiency-associated

Table 11. Plasma Cell Disorders: Subtypes and Variants

Monoclonal gammopathy of undetermined significance
Plasma cell myeloma variants
Indolent myeloma
Smoldering myeloma
Osteosclerotic myeloma (POEMS syndrome)
Plasma cell leukemia
Nonsecretory myeloma
Plasmacytoma variants
Solitary plasmacytoma of bone
Extramedullary plasmacytoma

Abbreviation: POEMS, polyneuropathy, organomegaly, endocrinopathy, M-component, skin changes.

Should cytogenetic/molecular categories of AML be recognized as distinct diseases? Several specific cytogenetic abnormalities in AML are associated with characteristic morphology and have distinctive clinical features. With the exception of promyelocytic leukemia/M3 with t(15;17), these genetic abnormalities do not correlate precisely with FAB categories. The consensus of the CAC was that these categories should be recognized as distinct entities within the classification. After discussion, the pathologists agreed that it would be possible to develop morphologic criteria for these categories that would permit them to be recognized, or at least suspected, by pathologists, who should then suggest confirmation by genetic analysis. The following specific categories will be defined: (1) AML with t(8;21)(q22;q22), AML1(*CBF*-alpha)/*ETO*; (2) acute promyelocytic leukemia (AML with t(15;17)(q22;q11-12) and variants, *PML/RAR*-alpha); (3) AML with abnormal bone marrow eosinophils (inv(16)(p13q22) or t(16;16)(p13;q22), *CBF*-beta/*MYH11*); and (4) AML with 11q23 (*MLL*) abnormalities.

Table 12. Immunosecretory Disorders (clinical manifestations of diverse lymphoid neoplasms)

Clinical Syndrome	Underlying Neoplasm
Waldenström's macroglobulinemia	Lymphoplastmacytic lymphoma
Heavy-chain diseases	
Gamma HCD	Lymphoplasmacytic lymphoma
Alpha HCD	Extranodal marginal zone lymphoma (immunoproliferative small intestinal disorder)
Mu HCD	B-cell CLL
Immunoglobulin deposition diseases	
Systemic light-chain disease	Plasma cell myeloma, monoclonal gammopathy
Primary amyloidosis	Plasma cell myeloma, monoclonal gammopathy

Abbreviation: HCD, heavy-chain disease.

Table 13. T-Cell Neoplasms, Disseminated Leukemic Types: Variants

T-cell prolymphocytic leukemia, morphologic variants
Small cell
Cerebriform cell
Adult T-cell leukemia/lymphoma (HTLV1+), clinical variants
Acute
Lymphomatous
Chronic
Smoldering
Hodgkin-like

The specific morphologic features of these disorders will be described in the classification,[2] and these entities will be excluded from the FAB categories used for cases that lack these abnormalities. In addition, cases with these specific cytogenetic abnormalities with low blast counts, which in the past might have been diagnosed as MDS, will now be classified as AML.

Should multilineage dysplasia, prior MDS, and/or prior therapy be included in the classification of AML? Severe multilineage dysplasia, defined as the presence of dysplastic features in two or more cell lines, has been shown to be associated with poor outcome in AML. Similarly, AML arising in patients with a history of MDS also has a poor prognosis. Therapy-related leukemias secondary to alkylating-agent therapy are clearly different from many de novo acute leukemias; they are associated with characteristic cytogenetic abnormalities (3q−, −5, 5q−, −7, 7q−, +8, +9, 11q−, 12p−, −18, −19, 20q−, +21, t(1;7), t(2;11), complex karyotypes) and a worse prognosis and often show multilineage dysplasia or are preceded by a hypoproliferative state with multilineage dysplasia, resembling MDS. Similar cytogenetic abnormalities are often seen in MDS not associated with prior therapy and in de novo acute leukemias, particularly in the elderly. It has been suggested that all of these disorders reflect similar genetic damage, which may be either environmental or iatrogenic. There was a consensus that the presence of multilineage dysplasia at the time of the diagnosis of acute leukemia, a history of myelodysplasia, and prior alkylating-agent therapy were all adverse prognostic factors, which may reflect a common pathogenesis. The committee concluded that multilineage dysplasia, a history of MDS, and a history of alkylating-agent therapy should be included in the classification of AML.

Table 14. Peripheral T-cell Neoplasms, Primary Extranodal Types: Variants and Subtypes

Mycosis fungoides variants
Pagetoid reticulosis
MF-associated follicular mucinosis
Granulomatous slack skin disease
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
Lymphomatoid papulosis, types A and B*
Primary cutaneous ALCL
Borderline lesions

*Lymphomatoid papulosis is not considered a neoplasm.

Table 15. Peripheral T-Cell Neoplasms, Predominantly Nodal Types: Variants

Peripheral T-cell lymphoma not otherwise categorized, variants
Lymphoepithelioid (Lennert's)
T-zone
Anaplastic large cell lymphoma T-null cell type, variants
Lymphohistiocytic
Small cell

The specific cytogenetic abnormalities common to MDS, alkylating-agent–related AML, and poor-prognosis AML (3q−, −5, 5q−, −7, 7q−, +8, +9, 11q−, 12p−, −18, −19, 20q−, +21, t(1;7), t(2;11), complex karyotypes) likely reflect a common pathogenesis of these lesions, distinct from that of other de novo AMLs. However, there was no consensus on the role of these abnormalities in defining disease entities within the classification. Our understanding of this issue will likely improve in the near future, necessitating a change in the major groupings. However, for the present, cytogenetic abnormalities indicative of poor prognosis should be recognized as prognostic factors within each category of AML.

Therapy with topoisomerase II inhibitors (epipodophyllotoxins and doxorubicin) is also associated with secondary leukemias, which are often myeloid but may be lymphoid. They typically show cytogenetic abnormalities associated with de novo AML—most commonly translocations involving 11q23 (*MLL*) but also occasionally t(8;21), inv(16), or t(15;17). These cases should also be recognized in the classification as distinct from alkylating-agent–related secondary leukemias.

Should refractory cytopenia with multilineage dysplasia be a separate category? MDSs are clonal stem-cell disorders characterized by ineffective hematopoiesis that results clinically in peripheral-blood cytopenias; the marrow is variably hypercellular, and patients show poor responses to chemotherapy and have an increased risk of progression to acute leukemia. Refractory anemia and refractory anemia with ring sideroblasts were defined in the FAB classification as having dysplasia largely restricted to the erythroid line. Recent studies have shown that patients with MDS and less

Table 16. Proposed Categories of Unclassifiable Hematologic Malignancies

Hematologic malignancy, unclassifiable
Myeloid neoplasm, unclassifiable
Myeloproliferative disease, unclassifiable
Myelodysplastic syndrome, unclassifiable
Acute myeloid leukemia, unclassifiable
Lymphoid neoplasm/lymphoma, unclassifiable
B-cell lymphoma, unclassifiable
T-cell lymphoma, unclassifiable
Hodgkin's disease, unclassifiable
Histiocytic neoplasm, unclassifiable

than 5% blasts but with significant dysplasia involving granulocytic and megakaryocytic lines have a worse prognosis and are more likely to die of marrow failure or progress to acute leukemia (similar to RAEB) than patients with MDS who lack these features. Thus, the committee agreed that a separate category is needed for these cases. Multilineage dysplasia is defined as the presence of dysplastic features in two or more cell lines. Refractory anemia (with or without ring sideroblasts) will continue to be defined as a disorder involving the erythroid line only. MDS will exclude cases of low-blast-count leukemias that show one of the following AML type cytogenetic abnormalities: t(8;21), inv(16), or t(15;17). Because of the distinctive morphologic and clinical features of the 5q− syndrome, the pathologists agreed that this should be a separate category within MDS.

AML and MDS: Summary.

1. What blast count should define AML? 20%
   - (eliminate RAEB in transformation)
2. Should cytogenetic/molecular categories be recognized as distinct diseases? YES
   - t(8;21)(q22;q22), AML1(*CBF*-alpha)/*ETO*
   - Acute promyelocytic leukemia t(15;17)(q22;q11-12), *PML/RAR*-alpha and variants
   - AML with abnormal bone marrow eosinophils (inv(16)(p13q22) and variants, *CBF*-beta/*MYH11*)
   - 11q23, *MLL* abnormalities
3. Should severe multilineage dysplasia, prior therapy, and/or prior MDS be included in classification of AML? YES
4. Should MDS with multilineage dysplasia be a separate category? YES

LYMPHOID NEOPLASMS

The proposed WHO classification of lymphoid neoplasms adopts the REAL classification, proposed by the International Lymphoma Study Group. The REAL classification is based on the premise that a classification should attempt to define distinct disease entities, using all available information, including morphology, immunophenotype, genetic features, and clinical features. There is no single gold standard, and the importance of various criteria for both definition and diagnosis differs among different diseases. On the basis of 3 years of experience with the REAL classification and input from the committees, several changes were proposed for the WHO classification. These included changes in nomenclature, division of heterogeneous categories, and adoption of ''provisional'' entities as ''real.'' The proposed WHO classification recognizes B-cell neoplasms, T-cell/natural-killer (NK)–cell neoplasms, and Hodgkin's disease (HD). The T- and B-cell neoplasms were stratified into precursor, or lymphoblastic, neoplasms (acute lymphoblastic leukemia [ALL] and lymphoblastic lymphoma) and mature (peripheral) B- and T-cell neoplasms. The mature B- and T-cell neoplasms were informally grouped according to their major clinical presentations: predominantly disseminated/leukemic, primary extranodal, and predominantly nodal diseases. The pathologists sought input from the clinicians on these changes as well as on issues that remained controversial or problematic, such as grading of follicular lymphoma, how to define Burkitt-like lymphoma, subclassification of large B-cell lymphomas and mature T-cell lymphomas, and the desirability of clinical groupings of the non-Hodgkin's lymphomas.

Precursor Neoplasms

Should the FAB terms (L1, L2, L3) be retained? There was a consensus that the FAB terms are no longer relevant, since L1 and L2 morphology do not predict immunophenotype, genetic abnormalities, or clinical behavior. L3 is generally equivalent to Burkitt's lymphoma in leukemic phase and should be diagnosed as such.

Are lymphoblastic leukemias and lymphoblastic lymphomas a single disease with different presentations? There was a consensus that the precursor neoplasms presenting as solid tumors and those presenting with marrow and blood involvement are biologically the same disease with different clinical presentations. The presence of bone marrow and peripheral-blood involvement are principally prognostic factors/staging issues and not classification issues, although the biologic basis for the different clinical presentations is not fully understood. Most precursor lymphoid neoplasms present as leukemia; thus, it was agreed that the classification should retain the term ALL for the leukemic phase of precursor neoplasms of T and B types (Table 6).

Should genetic abnormalities be included in the classification? Genetic abnormalities are important prognostic factors within precursor B lymphoblastic neoplasms (t(9;22)(q34;q11), *BCR/ABL*; 11q23, *MLL*; t(1;19)(q23;p13), *E2A/PBX1*; t(12;21)(p12;q22); *ETV/CBF*-alpha). Pathologists who attempt to diagnose these neoplasms should be familiar with the types and significance of genetic abnormalities that can be seen. Genetic analysis should form part of (or an addendum to) the pathology report whenever feasible (Table 6).

Precursor Neoplasms: Summary.

1. Should the FAB terms (L1, L2, L3) be retained? NO
2. Are acute lymphoblastic leukemias and lymphoblastic lymphomas a single disease with different clinical presentations? YES
   - Retain the term leukemia for ALL of precursor T and B types.
3. Should cytogenetics be included in classification? YES
   - Cytogenetics should be included as prognostic factors within each subtype.

- t(9;22)(q34;q11), *BCR/ABL*; 11q23, *MLL*; t(1;19)(q23;p13), *E2A/PBX1*; t(12;21)(p12;q22), *ETV/CBF*-alpha.

Mature B and T/NK Neoplasms

As for the precursor neoplasms, the proposed classification considers lymphomas and lymphoid leukemias of the same cell type as one disease with different clinical presentations or stages. For the mature B and T/NK neoplasms, this question is primarily relevant to B-cell chronic lymphocytic leukemia (CLL) and B-cell small lymphocytic lymphoma (SLL). Although patients in some locations may be seen by different physicians based on their presentation (eg, patients with peripheral-blood involvement [leukemias] are seen by hematologists and those with tissue involvement [lymphomas] are seen by oncologists), there was a consensus that the two diseases are biologically the same (Table 7).

Follicular Lymphoma

Should the nomenclature be changed to follicular lymphoma? The WHO committee proposed to change the nomenclature from follicle center lymphoma to follicular lymphoma. The CAC overwhelmingly approved this proposal. For the rare case of purely diffuse lymphoma that seems to be of follicle center origin (predominance of centrocytes, rare centroblasts, *BCL2* rearranged), the term follicle center lymphoma, diffuse, will be retained as a separate category. This diagnosis should only be made if both small and large cells are B cells and preferably with demonstration of some indicator of follicle center derivation, such as *BCL2* rearrangement or CD10 expression (Table 8).

Should follicular lymphoma be graded by the number of large cells? The following points were made. First, follicular lymphoma of grade 1 (follicular small cleaved) and grade 2 (follicular mixed) are more closely related to each other than to grade 3 follicular lymphoma (follicular large cell), since in sequential biopsies, transitions are seen from grade 1 (follicular small cleaved) to grade 2 (follicular mixed) and vice versa but rarely from grade 1 to grade 3 (follicular large cell). Second, patients with grade 3 tend to have earlier relapses (worse freedom from relapse) than do patients with grades 1 and 2 but similar overall survival, and this inferior freedom from relapse may be obliterated by doxorubicin-containing therapy. Third, grade 3 follicular lymphoma is not the same disease as diffuse large B-cell lymphoma (DLBCL) because it has a higher relapse rate, although it also has a slightly better overall survival. Finally, pathologists discriminate poorly between follicular lymphoma of grades 1 and 2, but they may be better able to discriminate between these and grade 3 cases. Several studies suggest that the Berard criteria[3] for the diagnosis of grade 3 follicular lymphoma (> 15 centroblasts/high-power field [hpf]) may best define the group of cases with a potential for early relapses that may be prevented by doxorubicin-containing chemotherapy. There was no consensus on whether this is warranted as initial therapy for these patients. It was also noted that factors other than histologic grade affect outcome in patients with follicular lymphoma, including clinical features summarized in the International Prognostic Index and potential biologic markers such as Bcl-2 protein expression and *P53* mutations.

In summary, there was a consensus that follicular lymphoma should be categorized into at least two grades and that what is currently recognized as grade 3 (follicular large cell) should be discriminated from lower-grade cases. Although there are minor differences in natural history and response to treatment between grades 1 and 2 follicular lymphoma, there was a consensus that these did not mandate different approaches to treatment and thus were not of great clinical importance. Nonetheless, there was concern that changing the nomenclature would be potentially confusing and that a three-grade system should be retained. The pathologists were encouraged to define clinically relevant and reproducible criteria for such grading. After discussion, the pathologists concluded that since only the Berard cell-counting method has been repeatedly tested in the literature, it should be recommended for use (grade 1, zero to five centroblasts/hpf; grade 2, six to 15 centroblasts/hpf; and grade 3, > 15 centroblasts/hpf). Ten to 20 hpfs, within different follicles, are counted; these are representative follicles, not those selected for having the most numerous large cells.[4]

Should diffuse areas be reported? Several oncologists were of the opinion that diffuse areas in all grades of follicular lymphoma do seem to have an impact on prognosis. There was a consensus that diffuse areas should be reported and quantified according to the recommendations of the REAL classification, ie, predominantly follicular (> 75% follicular), follicular and diffuse (25% to 75% follicular), and predominantly diffuse (< 25% follicular). However, it is not clear what the implications of these features for treatment would be. In grade 3 follicular lymphoma, diffuse areas represent areas of DLBCL and should be reported as such (eg, follicular lymphoma, grade 3/3 [75%] with DLBCL [25%], not follicular lymphoma, grade 3, follicular and diffuse). The presence of DLBCL in any follicular lymphoma will dictate more aggressive therapy.

Follicular Lymphoma: Summary.

1. Change nomenclature from follicle center lymphoma to follicular lymphoma? YES
2. Should follicular lymphoma be graded by the number of large cells? YES
3. Are two grades adequate for clinical practice? YES

- However, three grades will be used to avoid confusion.

4. What should be method of grading? NO CONSENSUS
   - Pathologists recommended the cell-counting method, ie, for grade 1, one to five centroblasts/hpf; for grade 2, six to 15 centroblasts/hpf; and for grade 3, more than 15 centroblasts/hpf.
5. Should diffuse areas be reported? YES
6. How should diffuse areas be quantified? NO CONSENSUS
   - Pathologists recommended criteria suggested in the REAL classification, ie, follicular (> 75% follicular), follicular and diffuse (25% to 75% follicular), and predominantly diffuse (< 25% follicular).
   - Areas of DLBCL should be classified separately. An example of suggested terminology is follicular lymphoma, grade 3/3 (75%), with DLBCL (25%).

Marginal Zone Lymphomas

Should the term extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) or MALT-type lymphoma be applied only to a lymphoma composed mostly of small cells? What should the terminology be for large-cell lymphoma in a MALT site? The term high-grade MALT lymphoma, which is used by some pathologists to denote either transformation of a low-grade MALT lymphoma or any large B-cell lymphoma in a MALT site, is confusing to clinicians, who have come to regard the term MALT lymphoma to be synonymous with a lesion that may respond to antibiotic therapy for eradication of *Helicobacter pylori*. Because patients with a component of large-cell lymphoma may not respond to antibiotic therapy, the oncologists were concerned that use of this term could result in undertreatment of extranodal large-cell lymphoma. Furthermore, recent data show that the types of cytogenetic abnormalities seen in low-grade MALT lymphomas differ from those seen in primary large-cell lymphoma of the stomach, raising the question of whether these primary lymphomas are really related to low-grade MALT lymphomas. Therefore, the oncologists preferred that the term MALT lymphoma be used only for the low-grade lymphoma originally described as low-grade B-cell lymphoma of MALT. Areas of large-cell lymphoma, if present, should be separately diagnosed as DLBCL. Primary large-cell lymphomas of MALT sites should be diagnosed as DLBCL, not as high-grade MALT lymphoma.

Should marginal zone/MALT lymphoma be graded by the proportion of large cells? The issue of grading MALT lymphoma has not been studied extensively. Several early reports suggested that cases with up to 25% large cells did not have a worse prognosis than cases with fewer large cells. However, a recent report of patients treated primarily with antibiotics found that the presence of increased transformed cells (5% to 10% with clusters of < 20 cells) conferred a slight but significantly worse prognosis compared with cases with less than 5% large cells. Cases with high-grade areas consisting of sheets of blasts (> 20 cells) behaved similarly to large-cell lymphoma with no low-grade component. In addition, it was reported at the meeting that the international non-Hodgkin's lymphoma classification project found that the presence of more than 5% large cells in an extranodal marginal zone lymphoma conferred a worse prognosis, as did areas of DLBCL. The consensus of the committee was that increased numbers of large cells may be of prognostic importance in MALT lymphoma and warrant further study. The WHO classification should specify criteria for grading so that its significance can be tested in future clinical studies. In cases of marginal zone B-cell lymphoma (low-grade MALT lymphoma) with coexisting DLBCL, a separate diagnosis of DLBCL should be made. The principle is therefore similar to that for follicular lymphoma: the tumors are graded according to the number of large cells, but when confluent areas of large cells are present, this indicates transformation to DLBCL.

Marginal zone lymphomas of nodal and splenic type: Are they "real"? There was a consensus that recent data support the recognition that two other types of lymphoma, called marginal zone lymphomas, are distinct from MALT lymphoma and from each other. Splenic marginal zone lymphoma seems to be the tissue counterpart of splenic lymphoma with villous lymphocytes. Patients are typically older adults with bone marrow and blood involvement and an indolent clinical course. Nodal marginal zone lymphoma (which often has a prominent monocytoid B-cell component) must be distinguished from both MALT lymphoma with lymph node involvement and from other lymphomas (particularly follicular and mantle cell lymphoma) with a marginal zone pattern or a component of monocytoid B cells. Nodal marginal zone lymphoma seems to have a high rate of early relapse and overall survival similar to or slightly worse than that of follicular lymphoma.

Marginal Zone Lymphomas: Summary.

1. Should the term, extranodal marginal zone B-cell lymphoma of MALT or MALT-type lymphoma be applied only to a lymphoma composed mostly of small cells and not to large-cell lymphoma in a MALT site? YES
2. Should the term high-grade MALT lymphoma be used? NO
   - Suggested terminology: DLBCL (with or without areas of marginal zone/MALT-type lymphoma).

3. Should extranodal marginal zone B-cell lymphoma of MALT type be further graded/stratified based on the number of large cells? RESEARCH QUESTION
   - Criteria should be given so that additional studies can be conducted.
4. Are nodal and splenic marginal zone lymphoma distinct diseases that should be recognized and defined in the classification? YES

B-Cell Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Are B-cell CLL and SLL one disease at different stages? As for the precursor neoplasms and Burkitt's lymphoma, the committee agreed with the pathologists that B-cell CLL and SLL are one disease at different stages, not two separate entities, and that they should be listed together in the classification.

Are cases of B-cell CLL with plasmacytoid differentiation (lymphoplasmacytoid immunocytoma in the Kiel classification) a different disease from typical CLL? Data from several groups using the Kiel classification suggest that plasmacytoid differentiation may be an adverse prognostic factor in B-cell CLL; the committee concluded that the available data do not support calling it a different disease and that further study is needed to determine whether plasmacytoid differentiation is an adverse prognostic factor in CLL. Therefore, recognition of this feature is not required for diagnosis for clinical purposes, but criteria for diagnosing plasmacytoid differentiation should be agreed on, if possible, for future studies.

B-Cell CLL/SLL: Summary

1. Are B-cell CLL and SLL one disease at different stages? YES
2. Is plasmacytoid differentiation an indication of a different disease? NO
3. Is plasmacytoid differentiation a prognostic factor? RESEARCH QUESTION

Mantle-Cell Lymphoma

Should mantle-cell lymphoma be subclassified/graded for clinical purposes? A number of studies have found morphologic heterogeneity in mantle-cell lymphoma in both pattern and cytology and have suggested that some features may predict outcome. For example, cases with a mantle zone pattern have been less aggressive in some studies but not in others, and cases with blastic or blastoid morphology have had a worse prognosis in some reports. It was the consensus of the committee that, since no effective therapy currently exists for any type of mantle-cell lymphoma, stratification by morphologic features was not required for clinical diagnostic purposes at this time. However, the different cytologic types and patterns should be included in the WHO book on the classification, so that variant cases will be recognized as mantle-cell lymphoma for diagnosis and graded similarly for research studies.

Mantle-Cell Lymphoma: Summary. Should mantle-cell lymphoma be subclassified/graded for clinical purposes? By cytology? NO By pattern? NO

- Different cytologic types and patterns should be included so that they will be recognized as mantle-cell lymphoma for diagnosis and graded similarly for research.

Large B-Cell Lymphoma and Burkitt-Like Lymphoma

Should morphologic subclassification of DLBCL be required? There was a consensus on the part of the CAC that neither biologic nor clinical data at present support a requirement for subclassification of DLBCL according to the criteria of the Working Formulation or the Kiel classification. Data from the Kiel group suggest that immunoblastic lymphoma as defined in the updated Kiel classification ($>$ 90% immunoblasts) has a worse prognosis than centroblastic lymphoma. Other data suggest that staining for bcl-6 (centroblastic) and syndecan-1/CD138 (immunoblastic) or evidence of *BCL6* rearrangement (centroblastic) may help to discriminate between immunoblastic and centroblastic lymphoma. Nonetheless, neither reliable pathologic or biologic criteria for subclassification nor distinctive therapies that can be recommended for clinical practice are available at this time. For these reasons, the committee agreed that these categories should remain optional at this time. However, there was agreement that the pathologists should develop criteria for subclassification, so that these categories can be tested in future clinical studies (Table 9).

Should Burkitt-like or non-Burkitt's lymphoma be a subtype of DLBCL, a subtype of Burkitt's lymphoma, or a distinct category? What should be the defining criteria? The pathologists proposed to define Burkitt-like lymphoma as a subtype of large B-cell lymphoma. However, there was a clear consensus among the oncologists that this would be a mistake. Abundant data indicate that, in children, cases classified as Burkitt-like (or non-Burkitt) behave identically to Burkitt's lymphoma and would be undertreated if treated like large B-cell lymphoma. In adults, the biology of cases classified as Burkitt-like is less clear, but this may reflect the heterogeneity of the diagnostic criteria. In the international non-Hodgkin's lymphoma study, Burkitt-like was a nonreproducible category, with only about 50% agreement among the pathologists; the major areas of overlap were DLBCL and Burkitt's lymphoma. The oncologists urged that the category of Burkitt-like lymphoma be reserved for tumors that should

be treated like Burkitt's lymphoma, ie, very high-grade tumors. The committee concluded that Burkitt-like lymphoma should be listed as a morphologic variant of Burkitt's lymphoma in the WHO classification. The term atypical Burkitt's lymphoma was proposed for this variant; however, the steering committee subsequently decided that the term Burkitt-like was preferable, since the relationship to Burkitt's lymphoma is not known in all cases. Thus, the category of Burkitt's lymphoma will include classic Burkitt's lymphoma and a variant, Burkitt-like lymphoma. In addition, three subcategories, ie, endemic, nonendemic, and immunodeficiency-associated, were proposed to reflect the major clinical and genetic subtypes of this disease (Table 10).

At present, there are no readily available immunophenotypic criteria that can be used in this differential diagnosis. However, participants observed that probably both the morphology and the biology of Burkitt's lymphoma are defined by the presence of c-*myc* rearrangement and overexpression, which results in all cells being perpetually in cycle. The gold standard for the diagnosis of Burkitt's lymphoma should be the presence of the translocation t(8;14)(q24;q32) and its variants or c-*myc* rearrangement. Cytogenetic analysis is recommended in all leukemic cases. If cytogenetic or Southern blot analysis is not available in solid tumors, it seems likely that the most reasonable surrogate for c-*myc* rearrangement is proliferation fraction. Therefore, it was suggested that, for cases in which cytogenetic analysis is not available, Burkitt's lymphoma or Burkitt-like lymphoma should not be diagnosed without a Ki-67 fraction close to 100%. Thus, the definition of Burkitt-like lymphoma is a lymphoma that morphologically resembles Burkitt's lymphoma but has more pleomorphism or large cells than classical Burkitt's lymphoma and, in addition, has a proliferation fraction of greater than 99%.

Do we need separate categories for clinical subtypes of DLBCL? There are multiple distinct clinical presentations of DLBCL, several of which have unique clinical behavior. These include mediastinal/thymic large B-cell lymphoma, primary CNS lymphoma, and primary effusion lymphoma. Of particular concern to pathologists is the category of cutaneous B-cell lymphomas, most of which have an indolent clinical course. Lymphomas in the marginal zone/MALT lymphoma category are easily recognized by pathologists as low grade. However, the other major category, called cutaneous follicle center lymphoma in the recently proposed classification from the European Organization for Research and Treatment of Cancer, has a range of morphology, from a clearly low-grade lesion resembling nodal follicular lymphoma to a diffuse proliferation with numerous large cells that may be called DLBCL by pathologists. This type of lymphoma, which is typically localized to the head and trunk, responds well to local therapy (excision or radiation), and typically does not disseminate to lymph nodes, comprised 70% of cutaneous B-cell lymphomas in the European Organization for Research and Treatment of Cancer study. There is concern that if the distinctive histologic and clinical features of cutaneous follicle center lymphoma are not recognized by both pathologists and oncologists, these patients will be overtreated with aggressive chemotherapy.

The consensus of the committee was that separate classifications of lymphomas at specific extranodal sites are not needed for clinical purposes. However, the site of involvement should be clearly stated in the pathology report, and oncologists are obliged to understand the distinctive clinical features of lymphomas at various sites. Distinct entities, such as primary mediastinal (thymic) B-cell lymphoma, primary effusion lymphoma, and intravascular lymphoma, should be described in the WHO book[2] and listed as subtypes of DLBCL (Table 10). The committee recommended that the distinctive clinical features of B-cell lymphomas in the skin be indicated in the descriptions of each lymphoma subtype (Table 8).

Large B-Cell Lymphoma and Burkitt-like Lymphoma: Summary.

1. Should morphologic subclassification of DLBCL be required? NO
   - Criteria for subclassification should be standardized for future studies.
2. Should the category of Burkitt-like lymphoma be a subtype of large B-cell lymphoma? NO
   - Burkitt-like lymphoma will be considered a variant of Burkitt's lymphoma.
   - The major criteria are (a) morphology intermediate between Burkitt's lymphoma and large-cell lymphoma; (b) t(8;14)(q24;q32) and variants, c-*myc* rearrangement; and (c) proliferation fraction (Ki-67) greater than 99%.
3. Do we need separate categories for clinical subtypes of DLBCL? NO
   - Location should be indicated in report.

Lymphomas in immunodeficiency states: Do we need a separate classification? Most lymphomas that occur in immunodeficiency states are also seen in nonimmunosuppressed patients, but they have some distinctive features in immunodeficient patients. For example, in human immunodeficiency virus (HIV)–positive patients, primary CNS lymphoma is always Epstein-Barr virus (EBV)–positive, in contrast to sporadic CNS lymphoma. HD is more aggressive and always EBV^+ in HIV^+ patients. The recently described primary effusion lymphoma, which was initially thought to be unique to HIV^+ patients, has been reported in HIV^- patients as well. T-cell lymphomas in HIV^+ patients also do

not seem to be distinctive. A recently described plasmablastic lymphoma is distinctive, and its relationship to myeloma remains to be determined.

The polymorphic posttransplant lymphoproliferative disorders seem to be a unique form of lymphoproliferation that does not occur in immunologically normal individuals. It was suggested that EBNA-2 expression in these lesions indicates that the proliferation is EBV-driven and may respond to reduced immunosuppression.

In summary, the committee suggested that a separate classification was not needed for immunodeficiency-associated lymphomas but that the specific types of lymphomas that occur in immunodeficiency states and their distinctive features in these conditions should be indicated in the WHO book.[2] In addition, the pathologists thought that a separate classification of posttransplant lymphoproliferative disorders would be useful, because of their distinctive biologic and clinical features (Table 3).

Lymphomas in Immunodeficiency States: Summary. Do we need a separate classification? NO

- Note the frequency of specific types in immunodeficiency states.
- Posttransplant lymphoproliferative disorders are distinctive and need a separate classification.
- EBV status may be important in determining prognosis and treatment.

Peripheral T/NK-Cell Neoplasms

Are clinical syndromes integral to the definition of T-/NK-cell neoplasms? Many distinct T-cell and/or NK-cell diseases vary in cytologic composition (small to large to anaplastic). Immunophenotypic variation exists within disease entities, and many antigens are shared by different diseases. Specific cytogenetic features are not defined for most entities, and even T-cell receptor types (alpha-beta *v* gamma-delta) or T versus NK lineage are not sufficient to define distinct disease entities. To a greater extent than is appreciated for B-cell neoplasms, it seems that clinical syndromes, and particularly location (nodal *v* extranodal and specific extranodal sites), are important in determining the biologic behavior of the disease. The committee agreed that clinical syndromes seem to be integral to the definition of T- and NK-cell neoplasms.

Should peripheral T-cell lymphoma, unspecified, be subclassified (according to the Kiel classification) for clinical purposes? According to the available data, there seems to be no immediate justification or clear criteria for recognizing cytologic subtypes within the broad category of peripheral T-cell lymphoma, unspecified. However, given the marked differences in clinical behavior between primary extranodal T-/NK-cell lymphomas and primary nodal lymphomas, it is likely to be clinically relevant to subdivide the unspecified category into nodal and extranodal types. Both pathologists and oncologists will need to continue to address this area in further studies (Tables 14 and 15).

Peripheral T-/NK-Cell Lymphomas: Summary.

1. Are clinical syndromes integral to the definition of peripheral T-/NK-cell neoplasms? YES
2. Is cytologic subclassification of peripheral T-cell lymphoma required for clinical purposes? NO

Anaplastic Large-Cell Lymphoma

Should cutaneous and systemic anaplastic large-cell lymphoma (ALCL) be considered one disease or two? What should the terminology be for the cutaneous type? There is evidence that most cases of ALCL of T-cell type presenting with disease localized to the skin are different from systemic ALCL: the clinical course is indolent, they lack the translocation t(2;5)(p23;q35), are ALK protein–negative, and seem to form a spectrum with lymphomatoid papulosis. Although some members of the committee held that the clinical course was not predictably indolent, there was general agreement that, at least for the purposes of further study, cutaneous and systemic ALCL should be considered distinct categories. There was significant concern, however, about the proposed term primary $CD30^+$ cutaneous lymphoproliferative disorder, a term that includes lymphomatoid papulosis, cutaneous ALCL, and $CD30^+$ cutaneous T-cell lymphomas that do not have typical anaplastic morphology. Oncologists thought that including lymphomatoid papulosis in a classification of lymphomas would imply to patients and insurers that this is a malignancy, whereas it typically has a benign clinical course.

In conclusion, the committee agreed that primary cutaneous ALCL should be included in the list of neoplasms and that a discussion of $CD30^+$ cutaneous lymphoproliferative diseases should be included in the WHO book[2] with a discussion of lymphomatoid papulosis and borderline lesions. Because it is difficult to predict using morphology alone which disease the patient has, pathologists will often be forced to use the term $CD30^+$ cutaneous lymphoproliferative disease on the pathology reports, with the understanding that clinical criteria must be added to determine whether the patient has a locally progressive disease that requires treatment (ALCL) or a relapsing condition that needs no treatment (lymphomatoid papulosis).

What is the gold standard for defining ALCL? Given the recent availability of an antibody to the ALK protein, which is highly associated with the translocation t(2;5)(p23;q35), the question was raised whether this can be used as the

defining criterion for ALCL. Clinically, cases with the translocation t(2;5) and/or ALK positivity seem to represent a homogeneous group with a relatively good prognosis. However, others observed that experience with ALK antibodies is limited and they are only now becoming commercially available. In addition, there are cases with typical morphology and immunophenotype that are ALK- or t(2;5)-negative. The committee concluded that a single gold standard for the diagnosis of ALCL does not exist; the diagnosis requires both morphology and immunophenotype, and at least at present, restricting the diagnosis to ALK^+ cases does not seem to be justified. It was suggested that ALK staining be done in all cases to the extent possible and that cases be designated as ALCL ALK^+ or ALK^-, at least for research purposes. In addition, pathologists need to be aware of the rather broad morphologic spectrum of ALCL.

ALCL: Summary.

1. Is cutaneous ALCL different from systemic ALCL? PROBABLY YES
   - However, the distinction between them is not always straightforward, and the cutaneous type is not always indolent.
2. Should lymphomatoid papulosis be added to the list of lymphoid neoplasms? NO
   - It should be discussed in the WHO book along with borderline cases.
3. Is there a gold standard for the diagnosis of ALCL? NOT YET
   - The morphologic spectrum of ALCL needs to be better understood by pathologists.
   - Cases should be listed as ALK^+ or ALK^- for research.

Hodgkin's Disease

Grading of nodular sclerosis HD: Should it be required for clinical use? Data on the clinical impact of grading nodular sclerosis HD according to the British National Lymphoma Investigation criteria (grade 1, few Reed-Sternberg cells; grade 2, many Reed-Sternberg cells) have shown conflicting results, with some studies showing that grade 2 cases are associated with a worse outcome and others showing no difference in outcome. The committee recommended that grading not be required for clinical purposes in routine diagnosis but that the classification include clear criteria so that this question can be tested in future studies.

Nomenclature: HD or Hodgkin's lymphoma? Because it is now clear that HD is a clonal proliferation of (in most cases) B cells, and therefore qualifies as a lymphoma, the pathologists proposed that the name be changed to Hodgkin's lymphoma. Opinion of the committee was divided on this score, with some arguing that patients become confused as to whether they have a lymphoma or not when the term disease is used, and others standing on tradition and resisting unnecessary change. No consensus was reached.

Lymphocyte-rich classical HD: Is it a "real" subtype? Little clinical data exist on the lymphocyte-rich classical HD subtype, proposed as provisional in the REAL classification. The committee agreed that it was important to separate these cases from nodular lymphocyte-predominance HD for clinical purposes and that it would be valuable to separate them from other types of classical HD for clinical research purposes.

ALCL, HD-like: is it real? The pathologists proposed to drop the provisional ALCL, HD-like, category from the REAL classification, believing that there is probably no true biologic borderline between HD (in most cases a B-cell process) and ALCL (in most cases a T-cell process). Some cases of ALCL may have a nodular growth pattern and areas of fibrosis and thus resemble HD of nodular sclerosis type. Some cases of nodular sclerosis HD may have increased numbers of malignant cells and therefore resemble ALCL. However, this resemblance does not indicate a biologic relationship. Pathologists should strive to resolve morphologically difficult cases by immunophenotyping and, if necessary, molecular genetic studies. In a case that is morphologically on the borderline between HD and ALCL, expression of CD15 with or without B-cell antigens favors HD, whereas the absence of CD15 and expression of T-cell antigens or ALK protein favor ALCL. Detection of the T-cell receptor gene or *NPM/ALK* rearrangement would confirm T-cell lymphoma, and the absence of rearrangements would favor HD. Cases that cannot be resolved by a combination of morphologic, immunophenotypic, and genetic studies should be considered unclassifiable. Clinical judgment should be used to determine whether to rebiopsy or to treat with a regimen that would be suitable for both HD and ALCL.

HD: Summary.

1. Should grading of nodular sclerosis HD be required for clinical use? NO
   - Criteria need to be clearly defined for future studies.
2. Should lymphocyte-rich classical HD be a separate category? YES
   - Clinical features need further study.
3. Is ALCL, HD-like, a real entity? NO
   - Pathologists should use immunophenotyping and molecular genetic techniques to classify morphologically borderline cases as either HD or ALCL; unresolved cases should be called unclassifiable.
4. Should we change the name from HD to Hodgkin's lymphoma? NO CONSENSUS
   - Proposal: allow both (HD/Hodgkin's lymphoma).

CLINICAL GROUPINGS OF B- AND T-/NK-CELL LYMPHOMAS

Are Clinical Groupings Useful for Clinical Practice?

The committee concluded that grouping the B- and T-/NK-cell neoplasms into prognostic categories would serve no clear purpose and could hamper understanding of the specific features of some of the diseases. There are no groups of diseases that require identical treatment, and if treatment must be individualized to a specific disease, grouping serves no purpose and may be misleading. The entities listed in the classification are clearly defined and clinically relevant, and it is necessary for oncologists and pathologists dealing with these diseases to understand each of them.

Is a Shorter List of Diseases Necessary for Clinicians?

The committee also discussed whether a shorter list of common diseases should be prepared for clinical use. There was a clear consensus that the complete list of neoplasms should have more common entities highlighted, to draw the attention of nonexperts to the diseases they are likely to encounter in practice. Opinion was split on the need for a short list, and a poll taken after the meeting showed a majority of the oncologists favored one comprehensive list with common entities highlighted.

Clinical Groupings of Lymphoid Neoplasms: Summary

1. Are clinical groupings necessary or useful? NO
2. Should common entities be indicated in bold? YES
3. Should a short list of common entities be included for clinicians? NO

UNCLASSIFIABLE HEMATOLOGIC MALIGNANCIES

Even with the advances in immunophenotyping and genetic analysis, some hematologic malignancies still defy classification. A case may be unclassifiable because of an inadequate tissue sample, because special studies are not available, because the tissue is poorly preserved, or because even with complete analysis it does not fit into one of the categories recognized in the classification. For each case, the reason for the inability to classify it should be stated in thepathology report. Suggested categories and terminology for unclassifiable cases are listed in Table 16.

CONCLUSION

The committee concluded that the approach to the classification of hematologic malignancies proposed by the International Lymphoma Study Group in the REAL classification and adopted now in the WHO classification represents a significant advance in our ability to identify and treat specific disease entities. This approach leaves room for identifying new entities and subtypes and for incorporating new data into diagnostic criteria, disease definition, and nomenclature. It has also produced a new and exciting degree of cooperation and communication between oncologists and pathologists from around the world that should facilitate accumulation of new knowledge, and which will hopefully continue in the future. After the WHO classification is completed, it will be important to develop a mechanism for updating it, to avoid the confusion that has often resulted in the past from the existence of multiple classifications.

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APPENDIX

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