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The World Health Organization Classification of Neoplasms of the Hematopoietic and Lymphoid Tissues: Report of the Clinical Advisory Committee Meeting – Airlie House, Virginia, November, 1997

NL Harris*[,1,2], ES Jaffe[3], J Diebold[4], G Flandrin[5], HK Muller-Hermelink[6], J Vardiman[7], TA Lister[8] and CD Bloomfield[9]

[1]Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts, USA; [2]Harvard Medical School, Boston, Massachusetts, USA; [3]National Cancer Institute, Bethesda, Maryland, USA; [4]Hotel Dieu, Paris, France; [5]Hopital Necker, Paris, France; [6]University of Wurzburg, Wurzburg, Germany; [7]Pritzker School of Medicine, University of Chicago, Chicago, Illinois, USA; [8]Department of Medical Oncology, St Bartholomew's Hospital, London, UK; [9]Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA

Introduction: Since 1995, the European Association of Pathologists and the Society for Hematopathology have been developing a new World Health Organization (WHO) classification of hematologic malignancies. The classification includes lymphoid, myeloid, histiocytic, and mast cell neoplasms.

Materials and methods: The WHO project involves ten committees of pathologists, who have developed lists and definitions of disease entities. A Clinical Advisory Committee (CAC) of international hematologists and oncologists was formed to ensure that the classification will be useful to clinicians. A meeting was held in November 1997 to discuss clinical issues related to the classification.

Results: WHO has adopted the 'Revised European–American Classification of Lymphoid Neoplasms' (REAL), published in 1994 by the International Lymphoma Study Group (ILSG), as the classification of lymphoid neoplasms. This approach to 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 has applied 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.

The CAC meeting, which was organized around a series of clinical questions, was able to reach a consensus on most of the questions posed. The questions and the consensus are discussed in detail below. Among other things, the CAC 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 (IPI).

Conclusion: The experience of developing 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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Introduction

The Society for Hematopathology and the European Association of Hematopathologists have undertaken, as a joint project, the development of a classification of hematological neoplasms for the World Health Organization (WHO). A steering committee composed

*Correspondence: NL Harris, Pathology, Warren 2, Massachusetts General Hospital, Fruit Street, Boston, Massachusetts, MA 02114, USA;
Tel: +617 725 5155; Fax: +617 726 7474;
E-mail: nlharris@partners.org
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of members of both societies has been formed, and ten committees have been 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 are 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. Over 50 pathologists from around the world have been involved in the project since 1995. Proponents of all major lymphoma and leukemia classifications have agreed that if a reasonable consensus emerges from this effort, they will accept the WHO classification of hematological malignancies as the standard. The final classification will be published under the auspices of WHO.[2]

The proposed WHO classification of hematological malignancies stratifies these neoplasms primarily according to lineage: myeloid neoplasms, lymphoid neoplasms, mast cell disorders, and histiocytic neoplasms (Tables 1–5). Within each category, distinct diseases are defined according to a combination of

Table 1 Proposed WHO Classification of Myeloid Neoplasms[a]

Myeloproliferative Diseases (MPD)
- Chronic myelogenous leukemia, Philadelphia chromosome (Ph1) [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 (CMML)
- Atypical chronic myelogenous leukemia (aCML)
- Juvenile myelomonocytic leukemia (JMML)

Myelodysplastic Syndromes (MDS)
- Refractory anemia (RA
  with ringed sideroblasts (RARS)
  without ringed sideroblasts
- Refractory cytopenia (myelodysplastic syndrome) with multilineage dysplasia (RCMD)
- Refractory anemia (myeldysplastic syndrome) with excess blasts (RAEB)
- 5q-syndrome
- Myelodysplastic syndrome, unclassifiable

Acute Myeloid Leukemias (AML)*

I. Acute myeloid leukemias with recurrent cytogenetic translocations
- AML with t(8;21)(q22;q22),AML1(CBFα)/ETO
- Acute promyelocytic leukemia (AML with t(15;17)(q22;q11-12) and variants, PML/RARα)
- AML with abnormal bone marrow eosinophils (inv(16)(p13q22) or t(16;16)(p13;q11), CBFβ/MYH11X)
- AML with 11q23 (MLL) abnormalities

II. Acute myeloid leukemia with multilineage dysplasia
- with prior myelodysplastic syndrome
- without prior myelodysplastic syndrome

III. Acute myeloid leukemia and myelodysplastic syndrome, therapy related
- Alkylating agent related
- Epipodophyllotoxin related (some may be lymphoid)
- Other types

IV. Acute myeloid leukemia 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 myelofiborisis

Acute Biphenotypic Leukemias

[a]Only major disease categories are listed; subtypes and variants will be discussed in detail in the text; *Acute lymphoid leukemias are included under lymphoid neoplasms and in Table 7

Table 2 Proposed WHO Classification of Lymphoid Neoplasms*[a]

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 lymphoma/Burkitt cell leukemia

T 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 γδ 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 lymphoma (Hodgkin disease)
- Nodular lymphocyte predominance Hodgkin lymphoma
- Classical Hodgkin lymphoma
  Nodular sclerosis Hodgkin lymphoma (Grades 1 and 2)
  Lyphocyte-rich classical Hodgkin lymphoma
  Mixed cellularity Hodgkin lymphoma
  Lymphocyte depletion Hodgkin lymphoma

*More common entities are underlined; **B- and T/NK-cell neoplasms are grouped according to major clinical presentations (predominantly disseminated/leukemic, primary extranodal, predominantly nodal); [a]Only major categories are included. Subtypes and variants are shown in tables 6–15

Table 3 Categories of post-transplant lymphoproliferative disorders (PTLD)

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

Table 4 Mast cell diseases

- Cutaneous mastocytosis
- Systematic mast cell disease (+/− skin involvement)
- Systematic 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 (NOS)

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

In order to ensure that the proposed classification will be of maximum use to oncologists, the Steering Committee invited expert hematologists and oncologists to form a Clinical Advisory Committee, with American and European co-chairs. The charge to the committee was to review the proposed classification and advise the pathologists on its clinical utility. Over 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, Virginia, to which the Clinical Advisory Committee and all pathologists involved in the WHO committees, as well as the Executive Committees of the two hematopathology societies, were invited.

The meeting was organized around a series of questions, developed from those submitted by Clinical Advisory Committee members as well as those posed by the pathologists. Only issues that were controversial were discussed; diseases for which there were no new questions or data were accepted as previously defined. Only lymphoid and myeloid neoplasms were discussed at this 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 present were asked to arrive at a consensus regarding each question (as well as on other issues raised at the meeting); if necessary a show of hands was taken as a vote. Following the meeting, a poll of the participants, as well as several additional meetings of the pathology Steering Committee and the co-chairs of the Clinical Advisory Committee, were held to resolve residual questions.

Myeloid neoplasms

Although there have been many 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 updated recently. Thus, the discussion of these disorders generated considerable controversy and several subsequent meetings of pathologists and the clinical co-chairs occurred, during which a consensus on the classification emerged. The following summary includes both issues raised at the Clinical Advisory Committee 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 myeloproliferative 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 a 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 can be used by pathologists and will have clinical relevance. A key issue, as with the lymphoid neoplasms, is to discriminate between

disease entities and *prognostic factors*. Some genetic abnormalities appear to define distinct diseases, while others are prognostic factors within a given disease. Another issue debated was whether all diseases fit into one of the three major categories, or whether additional broad categories are needed.

After discussion, it appeared that a paradigm similar to that adopted for the REAL classification of lymphoid neoplasms can at least tentatively apply to the myeloid disorders; namely, that a combination of morphology, immunophenotype, genetic featues and clinical features is used to define distinct disease entities. The technology of genetic analysis is moving rapidly, and it is likely that advances in this field will necessitate revisions to any current classification in the near future. The pathologists propose four major groups of myeloid diseases: myeloproliferative diseases (MPD), myelodysplastic/myeloproliferative diseases (MD/MPD), myelodysplastic syndromes (MDS), and acute myeloid leukemias (AML). Within the category of AML, four main groups are recognized: I. AML with recurrent cytogenetic translocations; II. AML with myelodysplasia-related features; and III. Therapy-related AML and MDS. An additional clinical group is recognized: IV. AML not otherwise categorized.

Myeloproliferative diseases

Myeloproliferative diseases (MPD) are clonal stem cell disorders that are characterized by 'effective' hematopoiesis, resulting in elevated peripheral blood levels of one or more cell lines and hepatosplenomegaly; there is marrow hypercellularity with maturation and without dysplasia. Among the myeloproliferative disorders, the prototype is Philadelphia chromosome (Ph1)+[BCR/ABL+] chronic myelogenesis 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 (also known as juvenile chronic myeloid leukemia and juvenile chronic myelomonocytic leukemia), chronic myelomonocytic leukemia and atypical CML.

Should juvenile myelomonocytic leukemia be a separate category? Should it be classified as MDS or MPD? The Clinical Advisory Committee accepted the conclusions of the international study group for pediatric MDS that this is a separate disorder, distinct from adult chronic myeloid or myelomonocytic leukemias. It has been proposed that the name 'juvenile myelomonocytic leukemia (JMML)' be adopted. The committee favored including it in the myeloproliferative disorders; however, the pathologists recommend that a separate category be formed to include this and other disorders that combine features of myeloproliferative and myelodysplastic syndromes.

Should chronic myelomonocytic leukemia (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 organomegly 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 a MDS and the other a 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 of the meeting that this is one disease. The committee concluded that it fits better in the MPD than in the MDS category, but after subsequent discussions, the pathologists recommend that it be included in a separate category, with JMML, of disorders with both myeloproliferative and myelodysplastic features.

What should be the nomenclature and category for atypical CML? This disease was first recognized as a disease involving predominately the neutrophil series, that lacked Ph1 or BCR/ABL translocation, which has dysplastic as well as proliferative features, often with multilineage dysplasia. The prognosis is significantly worse than that of Phl+CML. It is clear that it is clinically, genetically and morphologically distinct from Ph1+CML and the name, atypical CML (aCML), is therefore suboptimal, implying both a relationship to Ph1+CML and a chronic process. The committee was unable to agree on another name and felt that the term aCML could be retained, provided a clear definition of the disease was provided in order to prevent confusion. The pathologists recommend placing this disease with JMML and CMML in a category of 'myelodysplastic/myeloproliferative' diseases.

Should there be a separate category for cases that are neither MDS or MPD? For reasons mentioned above, the pathologists recommend a fourth category of myeloid neoplasms, to contain those cases that are inherently proliferative but show dysplastic features, including JMML, CMML and aCML. It was the opinion of the clinicians present that such a category was not desirable, and that these diseases could be placed in the MPD category. However, the pathologists contended that these disorders have many features in common, including abnormalities of both granulocytic and monocytic lines and a relatively aggressive course, that distinguish them from the MDS and MPD categories and argue for placing them together.

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 'atypical CML'? Atypical CML
4. Should there be a separate category for cases that are neither MDS nor MPD? NO CONSENSUS

- Pathologists propose a category of MDS/MPD, to include JMML, CMML, aCML.

Acute Myeloid Leukemia (AML) and Myelodysplastic Syndromes (MDS)

What blast count should define AML? The FAB standard has been 30% blasts. However, recent studies have indicated that patients with 20–30% blasts (classified as refractory anemia with excess blasts in transformation, RAEB-T) have a prognosis similar to that of patients with >30% blasts. Thus, there was a consensus that the blast count for the diagnosis of AML should be 20% and the category of RAEB-T should be dropped.

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 Clinical Advisory Committee 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, which would permit them to be recognized, or at least suspected, by pathologists, who should then suggest confirmation by genetic anlaysis. The specific categories that will be defined are:

1. AML with t(8;21)(q22;q22), AML1(CBFα)/ETO
2. Acute promyelocytic leukemia (AML with t(15;17)(q22;q11-12) and variants, PML/RARα)
3. AML with abnormal bone marrow eosinophils (inv(16)(p13q22) or t(16;16)(p13;q22), CBFβ/MYH11)
4. AML with 11q23 (MLL) abnormalities.

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

Should multilineage dysplasia, prior MDS, and/or prior therapy, be included in classification of AML? Severe multilineage dysplasia, defined as the presence of dysplastic features in the cells of two or more lines, have been shown to be associated with poor outcomes in AML. Similarly, AML arising in patients with a history of MDS also have 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, as well as 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, or 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 classificaiton of AML.

The specific cytogenetic abnormalities common to both 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* AML. 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 adriamycin) is also associated with secondary leukemias, which are often myeloid but may be lymphoid. These 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? Myelodysplastic syndromes are clonal stem cell disorders characterized by ineffective hematopoiesis, resulting clinically in peripheral blood cytopenias; the marrow is variably hypercellular and patients show poor responses to chemotherapy, with an increased risk of progression to acute leukemia. The terms, refractory anemia (RA) and refractory anemia with ring sideroblasts (RARS) were defined in the FAB classification as having dysplasia largely restricted to the erythroid line. Recent studies have shown that cases of MDS with <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 those lacking 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 the cells of two or more 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 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, it was agreed by the pathologists that this should be a separate category within MDS.

SUMMARY:
1. What blast count should define AML? 20%
   - (eliminate RAEB-T)
2. Should cytogenetic/molecular categories be recognized as distinct diseases? YES
   - t(8;21)(q22;q22), AML1 (CBFα)/ETO
   - Acute promyelocytic leukemia t(15;17) (q22;q11-12), PML/RARα and variants
   - Acute myeloid leukemia with abnormal bone marrow eosinophils (inv(16)(p13q22) and variants, CBFβ/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 Revised European–American Classification of Lymphoid Neoplasms (REAL), proposed by the International Lymphoma Study Group (Table 2). This 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 one 'gold standard' and the importance of various criteria for both definition and diagnosis differ among different diseases. Based on experience with using this classification for several years and on input from the committees, several changes were proposed for the WHO version. These include some changes in nomenclature, splitting some categories that were believed to be heterogeneous and adopting some 'provisional' entities as 'real'. The proposed classification recognizes B-cell neoplasms, T/NK-cell neoplasms, and Hodgkin disease. The T- and B-cell neoplasms are stratified into precursor, or lymphoblastic, neoplasms (acute lymphoblastic leukemia and lymphoblastic lymphoma) and mature ('peripheral') B- and T-cell neoplasms. The mature B- and T-cell neoplasms are 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, and also on some issues that remain controversial or problematic, such as grading of follicular lymphoma, how to define 'Burkitt-like' lymphoma, subclassification of large B-cell lymphoma and mature T-cell lymphomas and the desirability of clinical groupings of the non-Hodgkin lymphomas.

Precursor neoplasms

Should the FAB terms (L1,2,3) be retained? There was a consensus that these 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 lymphoma in leukemic phase, and should be diagnosed as such (Table 6).

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, but with different clinical presentations. The presence of bone marrow and peripheral blood involvement are principally prognostic factors/staging issues, not classification issues, although the biological basis for the different clinical presentations is not fully understood. Most precursor lymphoid neoplasms present as leukemia and thus it was agreed that the classification should retain the term, acute lymphoblastic leukemia (ALL), for the leukemic phase of precursor neoplasms of T and B types.

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/CBFα)], and pathologists who undertake to diagnose these neoplasms should be familiar with the types and significance of genetic abnormalities that can be seen. The genetic analysis should form part of (or an addendum to) the pathology report whenever feasible.

SUMMARY: *Precursor neoplasms*
1. Should the FAB terms (L1,2,3) 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

Table 6 Acute lymphoid leukemias

Precursor B-cell acute lymphoblastic leukemia (cytogenetic subgroups)
t(9;22)(q34;q11); BCR/ABL
t(v;11q23); MLL rearranged
t(1;19)(q23;p13) E2A/PBX1
t(12;21)(p12;q22) ETV/CBFα
Precursor T-cell acute lymphoblastic leukemia
Burkitt cell leukemia

3. Should cytogenetics be included in classification? YES
   - 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/CBFα.

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 and B-cell small lymphocytic lymphoma. Although patients in some locations may be seen by different physicians based on their presentation (e.g. those presenting with peripheral blood involvement — leukemias — being seen by hematologists and those presenting with tissue involvement — lymphomas — by oncologists), there was a consensus that they are biologically the same diseases.

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 Clinical Advisory Committee overwhelmingly approved this proposal. For the rare case of purely diffuse lymphoma that appears 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 7).

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/FSC) and grade 2 (follicular mixed/FM) are more closely related to each other than to grade 3 (follicular large cell/FLC) since, in sequential biopsies, transitions are seen from grade 1 (FSC) to grade 2 (FM) and vice versa, but rarely from grade 1 to grade 3 (FLC). Second, patients with grade 3 (FLC) tend to have earlier relapses (worse freedom from relapse/FFR) than grades 1 and 2, but similar overall survival (OS), and this inferior FFR may be obliterated by adriamycin-containing therapy. Third, grade 3 follicular lymphoma is not the same disease as diffuse large B-cell lymphoma (DLBCL), since it has a higher relapse rate although slightly better overall survival. Finally, pathologists discriminate poorly between follicular lymphoma of grades 1 and 2, but 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 adriamycin-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 biological markers such as BCL2 expression and P53 mutations.

In summary, there was a consensus that follicular lymphoma should be graded, at least into two grades, with what is currently recognized as grade 3 (FLC) being discriminated from lower grade cases. Although there are minor differences in natural history and response to treatment between grades 1 and 2 FL, 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: 0–5 centroblasts/hpf; Grade 2: 6–15 centroblasts/hpf; Grade 3: >15 centroblast/hpf (Table 7). Ten to 20 high power fields, within different follicles, are counted; these are representative follicles, not selected for those with the most numerous large cells).[4]

Should diffuse areas be reported? Several oncologists felt that diffuse areas in all grades of follicular lymphoma do appear to impact on prognosis. There was a consensus that diffuse areas should be reported and quantified according to the recommendations of the REAL classification: predominantly follicular (>75% follicular), follicular and diffuse (25–75% follicular) and predominantly diffuse (>25% follicular). However, it is not clear what the implications of these features would be for treatment. In grade 3

Table 7 Follicular lymphomas and mantle cell: grading and variants

Mantle cell lymphoma
Variant: blastoid
Follicular lymphoma
Grades:
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 residue centrocytes
Variants:
Cutaneous follicle center lymphoma
Diffuse follicle center lymphoma
Grade 1: 0–5 CB/hpf
Grade 2: 6–15 CB/hpf

follicular lymphoma, diffuse areas represent areas of DLBCL and should be reported as such; e.g. 'follicular lymphoma, grade 3/3 (75%) with diffuse large B-cell lymphoma (25%)', not 'follicular lymphoma, grade 3, follicular and diffuse'. The presence of DLBCL in any follicular lymphoma will dictate more aggressive therapy.

SUMMARY: *Follicular lymphoma*

1. Change nomenclature from follicle center lymphoma to 'follicular lymphoma'? YES
2. Should it be graded by the number of large cells? YES
3. Are two grades adequate for clinical practice? YES
   - But three grades will be used to avoid confusion
4. What should be the method of grading? NO CONSENUS
   - Pathologists recommend cell counting method:
   - Grade 1 (1–5 CB/hpf); Grade 2 (6–15 CB/hpf); Grade 3 (>15 CB/hpf)
5. Should diffuse areas be reported? YES
6. How should they be quantified? NO CONSENSUS
   - Pathologists recommend criteria suggested in REAL classification: follicular (>75% follicular), follicular and diffuse (25–75% follicular), predominantly diffuse (<25% follicular)
   - Areas of DLBCL should be classified separately. Example of suggested terminology:
     - Follicular lymphoma, grade 3/3 (75%), with
     - Diffuse large B-cell lymphoma (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 be the terminology 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. Since experience indicates that patients with a component of large-cell lymphoma may not respond to antibiotic therapy, the oncologists were concerned that use of this term may result in cases of extranodal large-cell lymphoma being undertreated. 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 'diffuse large B-cell lymphoma'. Primary large-cell lymphomas of MALT sites should be diagnosed as 'diffuse large B-cell lymphoma', 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 extensively studied. 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 (5–10% with clusters of <20 cells) conferred a slight but significantly worse prognosis compared with cases with <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 NHL classification project indicated that the presence of >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 the data available raised the concern that increased 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 both from MALT lymphoma and from each other. Splenic marginal zone lymphoma (SMZL) appears to be the tissue counterpart of splenic lymphoma with villous lymphocytes (SLVL). Patients are typically older adults with bone marrow and blood involvement and a very 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 appears to have a high rate of early relapse and overall survival similar to or slightly worse than that of follicular lymphoma.

SUMMARY: *Marginal zone lymphomas*

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

B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma

Are B-cell chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) one disease at different stages? As for the precursor neoplasms and Burkitt lymphoma, the committee agreed with the pathologists that B-CLL and SLL are one disease at different stages, not two separate entities, and they should be listed together in the classification (Table 8).

Are cases of B-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-CLL; the committee felt that the available data do not support calling it a different disease and that further study was needed to determine whether plasmacytoid differentiation was 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.

Table 8 B-cell neoplasms, predominantly disseminated/leukemic types, variants

B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
Variant: with monoclonal gammopathy/plasmacytoid differentiation
Hairy cell leukemia
Variant: hairy cell leukemia variant

SUMMARY: *B-CLL/SLL*
1. Are B-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 (MCL) 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 text of the classification, so that variant cases will be recognized as MCL for diagnosis and graded similarly for research studies (Table 7).

SUMMARY: *Mantle cell lymphoma*
Should it 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 MCL 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 Clinical Advisory Committee that neither biological 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 them. Nonetheless, neither reliable pathological or biological criteria for subclassification nor distinctive therapies that can be recommended for

Table 9 Diffuse large B-cell lymphoma, morphologic variants and subtypes

Diffuse large B-cell lymphoma, morphologic variants:
• Centroblastic
• Immunoblastic
• T-cell/histiocyte-rich
• Lymphomatoid granulomatosis type
• Anaplastic large B-cell
• Plasmablastic
Diffuse large B-cell lymphoma, subtypes:
Mediastinal (thymic) large B-cell lymphoma
Primary effusion lymphoma
Intravascular large B-cell lymphoma

clinical practice are available at this time. For these reasons, the committee felt 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' lymphoma be a subtype of DLBCL, a subtype of Burkitt lymphoma, or a distinct category? What should be 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. There are abundant data indicating that, in children, cases classified as Burkitt-like (or non-Burkitt) behave identically to Burkitt 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 NHL study, Burkitt-like was a non-reproducible category, with only about 50% agreement among the pathologists; the major areas of overlap were DLBCL and Burkitt lymphoma. The oncologists urged that the category of Burkitt-like lymphoma be reserved for tumors that should be treated 'like Burkitt lymphoma' – that is, very high-grade tumors. The committee concluded that Burkitt-like lymphoma should be listed as a morphologic variant of Burkitt lymphoma in the WHO classification. The term 'atypical Burkitt lymphoma' was proposed for this variant; however, the Steering Committee subsequently decided that the term Burkitt-like was preferable, since the relationship to Burkitt lymphoma is not known in all cases. Thus, the category of Burkitt lymphoma will include classic Burkitt lymphoma and a variant – Burkitt-like lymphoma. In addition, three sub-categories – endemic, non-endemic, and immunodeficiency-associated – were proposed to reflect the major clinical and genetic subtypes of this disease.

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 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 lymphoma should be the presence of the 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 cases in which cytogenetic analysis is not available should not be diagnosed as Burkitt lymphoma or Burkitt-like lymphoma without a Ki-67 fraction close to 100%. Thus, the definition of Burkitt-like lymphoma is a lymphoma that morphologically resembles Burkitt lymphoma, but has more pleomorphism or large cells than classical Burkitt lymphoma, and has a proliferation fraction of $>99\%$ (Table 10).

Table 10 Burkitt lymphoma, morphologic variants and subtypes

Burkitt lymphoma, morphologic variants:
Burkitt-like
With plasmacytoid differentiation (AIDS-associated)
Burkitt lymphoma, subtypes (clinical and genetic)
Endemic
Sporadic
Immunodeficiency-associated

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 lymphoma; most of which have a very indolent clinical course. One category — marginal zone/MALT lymphoma — is easily recognized by pathologists as a low-grade lymphoma. However, the other major category, called 'cutaneous follicle center lymphoma' in the recently-proposed EORTC classification, 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 (Table 7). 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 EORTC study. There is concern that if its distinctive histologic and clinical features are not recognized by both pathologists and oncologists, these patients will be overtreated with aggressive chemotherapy (Table 7).

The consensus of the committee was that separate classifications of lymphomas at specific extranodal sites were 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 will be

Table 11 Plasma cell disorders: Subtypes and variants

Monoclonal gammopathy of undetermined significance (MGUS)
Plasma cell myeloma variants:
• Indolent myeloma
• Smoldering myeloma
• Osteosclerotic myeloma (POEMS syndrome)
• Plasma cell leukemia
• Non-secretory myeloma
Plasmacytoma variants:
• Solitary plasmacytoma of bone
• Extramedullary plasmacytoma

Table 12 Immunosecretory disorders (clinical manifestations of diverse lymphoid neoplasms)

Clinical syndrome	Underlying neoplasm
Waldenstrom's macroglobulinemia	Lymphoplasmacytic lymphoma
Heavy chain diseases (HCD)	
• gamma HCD	Lymphoplasmacytic lymphoma
• alpha HCD	Extranodal marginal zone lymphoma (immunoproliferative small intestinal disorder)
• Mu HCD	B-cell chronic lymphocytic leukemia
Immunoglobulin deposition diseases:	
• Systemic light chain disease	Plasma cell myeloma, monoclonal gammopathy
• Primary amyloidosis	Plasma cell myeloma, monoclonal gammopathy

described in the text 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 text describing each lymphoma subtype.

SUMMARY: *Large B-cell lymphoma and Burkitt-like lymphoma*

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' be a subtype of large B-cell lymphoma? NO
   - Burkitt-like lymphoma will be considered a variant of Burkitt lymphoma
   - Major criteria:
     1. Morphology intermediate between Burkitt lymphoma and large-cell lymphoma
     2. t(8;14)(q24;q32) and variants, c-MYC rearrangement, or
     3. proliferation fraction (Ki-67) > 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 non-immunosuppressed patients, but have some distinctive features in immune deficient patients. For example, in HIV+ patients, primary CNS lymphoma is always EBV+, in contrast to sporadic CNS lymphoma. Hodgkin disease 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 appear to be distinctive. A recently described plasmablastic lymphoma is distinctive, and its relationship to myeloma remains to be determined.

The polymorphic post-transplant lymphoproliferative disorders (PTLD) appear to be a unique form of lymphoproliferation that do 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 both in the text and in a table. In addition, the pathologists felt that a separate classification of PTLD would be useful, because of their distinctive biological and clinical features (Table 3).

SUMMARY: *Lymphomas in immunodeficiency states*
Do we need a separate classification? NO

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

Peripheral T/NK-cell neoplasms

Are clinical syndromes integral to the definition of T/NK-cell neoplasms? Many distinct T- and/or NK-cell diseases have a range of 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 ($\alpha\beta$ *vs* $\gamma\delta$) or T *vs* NK lineage are not sufficient to define distinct disease entities. To a greater extent than is appreciated for B-cell neoplasms,

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

Table 14 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 (ALCL)T/null cell type, variants
• Lymphohistiocytic
• Small cell

it appears that clinical syndromes, and particularly location (nodal *vs* extranodal and specific extranodal sites) are important in determining the biological behavior of the disease. The committee agreed that clinical syndromes appear 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? Based on the available data, there appears to be no immediate justification for, or clear criteria for, recognizing cytologic subtypes within this broad category. 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.

SUMMARY: *Peripheral T/NK-cell lymphomas*
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 (ALCL)

Should cutaneous and systemic ALCL be considered one disease or two? What should be the terminology for the cutaneous type? There is evidence that most cases of ALCL of T-cell type presenting with disease localized to the skin are a different disease from systemic ALCL: the clinical course is indolent, they lack the t(2;5)(p23;q35) and are ALK protein negative and appear to form a spectrum with lymphomatoid papulosis. Although some members of the committee felt 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 felt 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 (Table 15).

In conclusion, the committee agreed that the entity, primary cutaneous ALCL, should be included in the list of neoplasms, and a discussion of 'CD30+ cutaneous lymphoproliferative diseases' should be included in the text with a discussion of lymphomatoid papulosis and borderline lesions. Because of the difficulty in predicting by 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).

Table 15 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 CD-30 positive T-cell lymphoproliferative disorders
• Lymphomatoid papulosis (type A and B)*
• Primary cutaneous ALCL
• Borderline lesions

*Not considered a neoplasm

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 t(2;5)(p23;q35), the question was raised whether this can be used as the defining criterion for ALCL. Clinically, cases with the t(2;5) and/or ALK positivity appear 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 appear 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.

SUMMARY: *Anaplastic large cell lymphoma*
1. Is cutaneous ALCL different from systemic ALCL? Probably YES, but
   - distinction between them is not always straightforward and cutaneous type is not always indolent
2. Should lymphomatoid papulosis appear in the list of lymphoid neoplasms? NO
   - should be discussed in the text 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 disease (HD)

Grading of nodular sclerosis HD: should it be required for clinical use?

Data on the clinical impact of grading nodular sclerosis Hodgkin disease (NSHD) according to the British National Lymphoma Investigation (BNLI) criteria (Grade 1 = few RS cells; Grade 2 = many RS 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: Hodgkin disease or Hodgkin lymphoma?

Because it is now clear that Hodgkin disease 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 lymphoma. Opinion of the committee was divided on this score, with some feeling 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 (LRCHD): is it a 'real' subtype?

Very little clinical data exist on this subtype, proposed as 'provisional' in the REAL classification. The committee agreed that it was important to separate these cases from nodular lymphocyte predominance Hodgkin disease (NLPHD) for clinical purposes and that it would be valuable to separate them from other types of classical HD for clinical research purposes.

Anaplastic large cell lymphoma, Hodgkin like: is it real?

The pathologists proposed to drop this provisional category from the REAL classification, believing that there is probably no true biological borderline between Hodgkin disease (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 NSHD may have increased numbers of malignant cells and therefore resemble ALCL. However, this resemblance does not indicate a biological 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 Hodgkin disease and ALCL, expression of CD15 with or without B-cell antigens favors HD, whereas absence of CD15 and expression of T-cell antigens or ALK protein favor ALCL. Detection of T-cell receptor gene or NPM/ALK rearrangement would confirm T-cell lymphoma, and absence of rearrangements would favor Hodgkin disease. Cases that cannot be resolved by a combination of morphology, immunophenotype 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.

SUMMARY: *Hodgkin disease*

1. Should grading of NS 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 Hodgkin disease to lymphoma? NO CONSENSUS
   - Proposal: allow both (Hodgkin disease/Hodgkin 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 non-experts 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 favoring one comprehensive list with common entities highlighted

SUMMARY: *Clinical groupings of lymphoid neoplasms*

1. Are clinical groupings necessary or useful? NO

2. Should common entities be highlighted? 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 the pathology report. Suggested categories and terminology for unclassifiable cases are listed in Table 16.

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

Conclusions

The committee concluded that the approach to the classification of hematologic malignancies proposed by the ILSG 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.

The WHO Classification. *Steering Committee*. ES Jaffe, NL Harris, J Diebold, G Flandrin, H-K Muller-Hermelink, J Vardiman. *Emeritus Consultants*: C Berard, K Lennert. *Committee Chairs:* R Brunning, D Catovsky, A Feller, T Grogan, NL Harris, D Knowles, H Stein, E Ralfkiaer, J Vardiman, R Warnke. *Committee members:* PM Banks, R Bartl, J Bennett, F Berger, B Borisch, JKC Chan, WC CHan, G Delsol, WT Dura, B Favara, KM Foucar, G Frizzera, K Gatter, A Georgii, DR Head, M Imbert, PG Isaacson, M Kikuchi, R Kyle, R Mann, E Matutes, E Montserrat, BN Nathwani, G Pallesen, M Paulli, RV Pierre, S Pileri, MA Piris, S Poppema, M Raphael, J Said, SH Swerdlow, B Van Camp, LM Weiss, DH Wright.

The Clinical Advisory Committee. *Chairs:* CD Bloomfield, TA Lister. *Clinical Advisory Committee Members:* JO Armitage, G Brittinger, AK Burnett, GP Canellos, F Cavalli, B Coiffier, J Connors, VT DeVita, Jr., V Diehl, E Estey, B Falini, RI Fisher, C Gisselbrecht, JM Goldman, W Hiddemann, D Hoeltzer, RT Hoppe, SJ Horning, JC Kluin-Nelemans, A Levine, DL Longo, I Magrath, SB Murphy, R Ohno, C-H Pui, KR Rai, S Rosenburg, JM Rowe, AH Sarris, MA Shipp, DR Willemze, W Wilson, RA Zittoun. *Invited Pathologists:* CD Baroni, C DeWolf-Peeters, N Hurwitz, J Jancar, PM Kluin, R Langholm, L Peterson, D Weisenburger, CL Willman.

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