Introduction
The non-Hodgkin’s lymphomas constitute a heterogenous group of neoplasms of the lymphoid system that include distinct entities defined by clinical, histologic, immunologic, molecular, and genetic characteristics. Each entity represents clonal expansion of a normal precursor cell. Study of human lymphomas using modern techniques of research immunology and cell biology has contributed immensely to an understanding of both the immune system and neoplastic transformation.

About 53,600 new cases of non-Hodgkin’s lymphomas will be diagnosed in the United States in 1997, and slightly fewer than 50% of patients will die, making this disorder sixth in incidence and mortality among malignancies.1 The incidence of non-Hodgkin’s lymphomas is rising at a rate of 3% to 4% per year, or 50% during the last 15 years, which is one of the largest increases for any cancer group, according to the American Cancer Society.2 This includes not only the increase in AIDS-related lymphomas but also the increase in lymphomas occurring in patients older than 65 years.

Various disease states, such as inherited and acquired immunodeficiency disorders and occupational and environmental exposures, have been associated with the development of non-Hodgkin’s lymphomas.3,4 Considerable progress has occurred in the classification of non-Hodgkin’s lymphomas during the past 15 years. The morphologically oriented Rappaport system, which was introduced almost 50 years ago, allowed for the separation of non-Hodgkin’s lymphomas into two clinically useful categories: those with a favorable prognosis (nodular lymphomas) and those with an unfavorable prognosis (diffuse lymphomas).

The National Cancer Institute-sponsored international Working Formulation (WF) classification introduced in 1982 was meant to be a translation system for other classifications, including the Rappaport and the immunologically oriented Lukes and Collins and Kiel systems.5 The WF categories include low, intermediate, and high-grade lymphoma types, based upon decreasing survival rates, respectively (Table 1). Paradoxically, with the development of effective chemotherapy regimens, the prognosis changed because of the increasing cure rates of patients in the intermediate and unfavorable prognosis categories and the eventual relapse and death of most patients with favorable categories.6

The classification systems mentioned earlier do not include disorders such as chronic lymphocytic leukemia, hairy cell leukemia, plasmacytoma, and mycosis fungoides. In addition, new clinical pathologic entities have been
### Table 1
Comparison of Working Formulation (WF) and Revised European-American Lymphoma (REAL) Classification

| WF Category* | Frequency† (%) | REAL Classification‡ | T-cell Neoplasms |
|--------------|----------------|----------------------|------------------|
| B-cell Neoplasms | T-cell Neoplasms |
| A. Small lymphocytic consistent with CLL Plasmacytoid | 4 | B-cell CLL/SLL/PLL Marginal zone/MALT Mantle cell | T-cell CLL/PLL LGL |
| B. Follicular, predominantly small cleaved cell | 26 | Follicle center, follicular, grade I Mantle zone Marginal zone | |
| C. Follicular, mixed small cleaved and large cell | 9 | Follicle center, follicular, grade II Marginal zone/MALT | |
| D. Follicular, large cell | 4 | Follicle center, follicular, grade III | |
| E. Diffuse, small cleaved cell | 8 | Mantle cell Follicle center, diffuse small cell Marginal zone/MALT | T-cell CLL/PLL LGL |
| F. Diffuse, mixed small and large cell | 7 | Large B-cell lymphoma (rich in T-cells) Follicle center, diffuse small cell Lymphoplasmacytoid Marginal zone/MALT Mantle cell | Peripheral T-cell, unspecified ATL/L Angioimmunoblastic Angiocentric |
| G. Diffuse, large cell | 22 | Diffuse large B-cell lymphoma | Peripheral T-cell, unspecified ATL/L Angioimmunoblastic Angiocentric |
| H. Large cell immunoblastic | 9 | Diffuse large B-cell lymphoma | Peripheral T-cell, unspecified ATL/L Angioimmunoblastic Angiocentric Anaplastic large-cell |
| I. Lymphoblastic | 5 | Precursor B-lymphoblastic | Precursor T-lymphoblastic |
| J. Small noncleaved cell | 6 | Burkitt’s Non-Burkitt’s | Peripheral T-cell, unspecified |
| Burkitt’s | High-grade B-cell, Burkitt’s-like | |

*Categories A–C = low grade (survival 5–10 or more years untreated); D–G = intermediate grade (survival 2–5 years untreated); H–J= high grade (survival 0.5–2.0 years untreated). Categories D–H are also called aggressive lymphomas.

†Frequency in adults in the United States (data from Skarin and Dorfman58).

‡Some disease entities and variant forms have been omitted for clarity. Duplication of some neoplasms is present to allow comparison with WF categories.

ATL/L = adult T-cell lymphoma/leukemia; CLL = chronic lymphocytic leukemia; LGL = large granular lymphocyte leukemia; MALT = mucosa-associated lymphoid tissue; PLL = prolymphocytic leukemia; SLL = small lymphocytic lymphoma.

Modified with permission from Shipp et al4 and Harris et al.7
described recently, coincidental with the wider use of immunochemistry and cytogenetic and molecular analysis. These new entities—including mantle cell, marginal zone (mucosa-associated lymphoid tissue [MALT] and monocytoid B-cell), T-cell–rich B-cell, and anaplastic large-cell lymphomas—share some growth patterns and morphologic features with the classic and common non-Hodgkin’s lymphomas.

In 1994, the International Lymphoma Study Group proposed the revised European-American lymphoma classification (REAL) schema. The REAL classification was based on known disease entities and promoted the concept that a range of morphologic grades and degrees of clinical aggressiveness might be present within each entity. It is a consensus list of about 20 currently recognizable lymphoid neoplasms.

The REAL schema classifies these neoplasms as B-cell, T/natural killer (NK)-cell, and Hodgkin’s disease (Tables 1 and 2). T-cell and B-cell lymphomas are further divided into precursor and peripheral cell types. In this review, Hodgkin’s disease will not be discussed. The REAL classification can be used with the more traditional WF lymphoma categories (Table 1), and a clinically useful REAL schema based upon indolent, aggressive, and highly aggressive lymphoma types has been proposed (Table 2).

Some reservations exist about the clinical practicality and other aspects of the REAL classification. One European cooperative group, however, reclassified cases from the WF schema to the REAL schema and concluded that the latter offers additional information that may allow for design of more appropriate therapies with a better chance of success. Preliminary data analysis from the Southwest Oncology Group shows that the REAL classification allows for improved delineation of histologic risk groups. Full acceptance of the REAL classification of non-Hodgkin’s lymphomas awaits further evaluation of its clinical utility.

Clinical Manifestations

In contrast to patients with Hodgkin’s disease, most patients with non-Hodgkin’s lymphomas present with advanced stage III or IV disease, which often is manifested as generalized adenopathy. In addition, non-Hodgkin’s lymphomas may involve unusual sites, such as epitrochlear or popliteal nodes or Waldeyer’s ring (nasopharynx), resulting in reduced hearing because of eustachian tube obstruction. Sites rarely involved in Hodgkin’s disease but often seen in non-Hodgkin’s lymphomas include skin (solitary or multiple lesions), thyroid, breast, gastrointestinal tract, brain, and ovaries or testes.

Patients with indolent (low-grade) lymphomas have a long history of disease that is slowly progressive over many years, usually without any symptoms. The disease may temporarily regress, the so-called “spontaneous” remission, which
| B-cell Neoplasms | T/NK-cell Neoplasms |
|------------------|---------------------|
| **I. Indolent Chronic Lymphomas (untreated survival measured in years)** |
| Indolent Disseminated Lymphoma/Leukemias |
| B-cell CLL/small lymphocytic lymphoma/prolymphocytic leukemia | T-cell CLL/prolymphocytic leukemia |
| Lymphoplasmacytic lymphoma | Large granular lymphocyte leukemia, T-cell or NK cell type |
| Splenic marginal zone lymphoma/splenic lymphoma with villous lymphocytes | |
| Hairy cell leukemia |
| Plasmacytoma/myeloma |
| **Indolent Extranodal Lymphomas** |
| Extranodal marginal zone/MALT lymphoma | Mycosis fungoides |
| **Indolent Nodal Lymphomas** |
| Nodal marginal zone B-cell lymphoma |
| Follicular center cell lymphoma |
| Mantle cell lymphoma* |
| **II. Aggressive Lymphomas (untreated survival measured in months)** |
| Diffuse large B-cell lymphoma | Anaplastic large-cell lymphoma |
| Peripheral T-cell lymphoma |
| **III. Highly Aggressive/Acute Lymphoma/Leukemias (untreated survival measured in weeks)** |
| Precursor B-lymphoblastic leukemia/lymphoma |
| Burkitt’s and Burkitt’s-like lymphoma |
| Precursor T-lymphoblastic lymphoma/leukemia |
| Adult T-cell lymphoma/leukemia (HTLV I+) |

*Considered an aggressive lymphoma by many authors.
CLL = chronic lymphocytic leukemia; HTLV I+ = positive for human T-cell lymphotropic virus type I; NK = natural killer.
Modified with permission from Shipp et al.⁴ and Harris et al.⁷
is observed in 5% to 15% of cases. Indolent lymphomas also have a propensity to undergo histologic transformation, or conversion to a more aggressive lymphoma, usually of a large-cell type. This occurs in 15% to 30% or more of cases, usually after several years, and is not related to therapy.

Patients with indolent non-Hodgkin’s lymphomas present with three clinical patterns: disseminated disease with circulating malignant cells; primarily nodal disease; and primarily extranodal, slowly progressive disease.

In contrast, aggressive non-Hodgkin’s lymphomas (intermediate and high grade) grow rapidly and may be fatal within months if not treated. B symptoms (unexplained weight loss of more than 10% of body weight, unexplained fever with temperatures more than 38°C, and night sweats) occur mainly in patients with aggressive lymphomas and affect 40% to 50% of patients. The most common aggressive type is diffuse large B-cell lymphoma, which accounts for 60% to 70% of cases. Less common types include anaplastic large-cell lymphoma and peripheral T-cell lymphomas. Clinical features of certain newly recognized lymphomas and primary extranodal lymphomas are noted later in this article.

### Classification and Immunobiology

Current histopathologic classification schemes for non-Hodgkin’s lymphomas are shown in Tables 1 and 2. The WF scheme parallels biologic behavior; that is, categories A to C (low grade) exhibit indolent behavior in the untreated state, with survival of 5 to 10 or more years. Classes D to G (intermediate grade) exhibit more aggressive behavior, with survival of 2 to 5 years, and classes H to J (high grade) exhibit highly aggressive behavior, with survival of less than 6 months to 2 years.

A comparison of the WF lymphoma classification with the REAL system is useful for understanding placement of recently described clinical pathologic enti-
ties relative to biologic behavior. The REAL clinical grouping (Table 2) further categorizes indolent lymphomas as disseminated, extranodal, or nodal and separates the highly aggressive, acute lymphomas and leukemias from the more common aggressive lymphomas. The Kiel classification system, popular in Europe, is detailed elsewhere.4

The use of specific monoclonal antibodies directed against cell surface antigens has contributed considerably to the understanding of the immunology of non-Hodgkin’s lymphomas. Use of this method along with molecular biological techniques has shown that most non-Hodgkin’s lymphomas have normal cellular counterparts corresponding to stages in lymphocyte ontogeny. Approximately 85% are of B-cell type, and about 15% are of T-cell type.

The most common B-cell lymphomas are follicular types and diffuse large-cell types. B-cell non-Hodgkin’s lymphomas can be divided into prefollicular center cell type (CD5 positive, CD10 negative), follicular center cell type (CD5 negative, CD10 positive), and postfollicular center cell type (CD5 negative, CD10 negative). T-cell non-Hodgkin’s lymphomas are generally considered to have an immunophenotype corresponding to the post-thymic stage of T-cell development. The exceptions are lymphoblastic lymphomas, which have an immature T-cell phenotype (Table 3).
Many chromosomal and molecular biologic defects have been detected in various non-Hodgkin’s lymphomas, and they often affect genes involved in the control of cell growth. Several chromosomal translocations have been identified, particularly involving sites of immunoglobulin heavy and light chain genes on chromosomes 2, 14, and 22, as discussed below and summarized in Table 3.

Non-Hodgkin’s lymphomas are ideally studied using histologic, immunophenotypic, and cytogenetic/molecular biologic methods, as shown in Table 4. Unfixed or fresh-frozen tissue is required for many of these methods. Assessment by a qualified hematopathologist is recommended.

Monoclonality is confirmed in B-cell lymphomas by demonstration of the restricted expression of a single surface immunoglobulin light chain species in the neoplastic cell population, using immunophenotypic methods. T-cell monoclonality is suggested by the absence of expression of one or more pan-T-cell antigens in the neoplastic cell population (antigen deletion). Monoclonality in B-cell and T-cell non-Hodgkin’s lymphomas may be confirmed by molecular biologic methods that show a clonal immunoglobulin or T-cell receptor gene rearrangement, respectively, in the neoplastic cell population.

### Table 4

| Diagnostic Method                      | Tissue                                      | Results                                      | Comments                      |
|----------------------------------------|---------------------------------------------|----------------------------------------------|-------------------------------|
| Routine histologic study               | Formalin and/or B5 fixed, paraffin embedded | Morphologic classification                   | Traditional                  |
| Immunoperoxidase staining              | Fresh, unfixed tissue (full range of markers); fixed,embedded tissue (subset of markers) | B cell, T cell, tumor subtyping, other tissue types | Technically demanding        |
| Flow cytometry                         | Fresh unfixed tissue, peripheral blood, and bone marrow | B cell, T cell | Rapid |
| Cytogenetics                           | Fresh unfixed tissue, peripheral blood, and bone marrow | Chromosomal translocations and other abnormalities | Technically demanding        |
| Molecular biologic methods (Southern blotting, PCR) | Fresh unfixed tissue, peripheral blood, and bone marrow; fixed tissue in some cases | Gene rearrangements and deletions; subtle alterations | Technically demanding        |
| Electron microscopy                    | Glutaraldehyde-fixed tissue                 | Ultrastructural details                     | Differentiates between NHL and other neoplasms |

NHL = non-Hodgkin’s lymphoma; PCR = polymerase chain reaction.
Histologic Subtypes

**SMALL LYMPHOCYTIC LYMPHOMA**

Small lymphocytic lymphoma, which accounts for approximately 5% of non-Hodgkin’s lymphomas in adults, is an indolent neoplasm that typically presents as a tumor mass without lymphocytosis. Lymph node architecture is diffusely effaced by small, round lymphoid cells with scattered pseudofollicular proliferation centers containing larger nucleolated cells (Fig. 1A and B).

Neoplastic B cells characteristically coexpress the T-cell antigen CD5 and activation antigen CD23. Cytogenetic abnormalities, which include trisomy 12, 14q+, and abnormalities of 13q14, are associated with a poorer prognosis. Small lymphocytic lymphoma is morphologically indistinguishable from chronic lymphocytic leukemia (Fig. 1C). Over time, 10% to 20% of cases of small lymphocytic lymphoma progress to chronic lymphocytic leukemia.11

**LYMPHOPLASMACYTOID LYMPHOMA**

Lymphoplasmacytoid lymphoma, which may present with clinical features of Waldenström’s macroglobulinemia, is another indolent neoplasm of older adults. Consisting of small lymphoid cells with plasmacytic differentiation, it was grouped with small lymphocytic lymphoma in the past (Fig. 1D).

This neoplasm is thought to originate from the postgerminal center B cells that are CD5 negative and have, in contrast to small lymphocytic lymphoma cells, undergone somatic hypermutation of immunoglobulin variable region genes.12 Chromosomal translocation t(9;14) is associated with lymphoplasmacytoid lymphoma.13 This neoplasm, like small lymphocytic lymphoma, may transform to large-cell non-Hodgkin’s lymphoma over time.

**MARGINAL ZONE LYMPHOMA**

Marginal zone lymphoma is a provisional classification that encompasses a group of low-grade B-cell neoplasms thought to originate in CD5/10/23-negative marginal zone cells of spleen, mucosa-associated lymphoid tissue, and lymph nodes.7 Neoplastic cells have more cytoplasm than do small lymphocytic lymphoma cells and may have a monocytoid appearance; *monocytoid B-cell lymphoma* is another term for the nodal form of this entity (Fig. 2). In the splenic form, neoplastic cells may have villous...
projections, in which instance the entity has been called splenic lymphoma with villous lymphocytes. Tumor behavior is indolent, and localized extranodal tumors (for example, in the gastrointestinal tract or lung) may be cured by surgical excision. Trisomy 3 is associated with marginal zone lymphoma; chromosome translocation t(11;18) has been reported in extranodal cases.

MANTLE CELL LYMPHOMA

Mantle cell lymphoma, an entity first described in the mid-1970s, accounts for approximately 5% of non-Hodgkin’s lymphoma in adults. It is composed of small lymphoid cells with irregular to occasionally cleaved nuclei that occur in a nodular (mantle zone) or diffuse form, typically in older adults (Fig. 3). The entity was previously classified as an intermediate (between well differentiated and poorly differentiated) lymphocytic lymphoma.

Neoplastic cells are thought to originate in CD5-positive B cells of the mantle zone of lymphoid follicles; in contrast to the cells of small lymphocytic lymphoma, these are CD23 negative. Mantle cell lymphoma cells express elevated levels of cyclin D1, a cell cycle regulatory protein usually associated with chromosomal translocation t(11;14). Cyclin D1 is thought to con-
tribute to lymphoma genesis by shortening the G1 phase of the cell cycle in neoplastic cells. Prognosis is poorer than in the other small-cell non-Hodgkin’s lymphomas, which are indolent, and poorer than in aggressive large-cell types. Median survival is 3 to 4 years.14

**FOLLICULAR CENTER CELL LYMPHOMA**

Follicular center cell lymphoma, which accounts for approximately 35% of non-Hodgkin’s lymphomas in adults, consists of a variable mixture of small lymphoid cells with cleaved nuclei and large cells that have round, oval, or irregular nuclei with distinct nucleoli, resulting in small cleaved cell, mixed small and large cell, and large-cell subtypes (Fig. 4).

These tumors of CD5-negative, CD10-positive B cells usually originate in lymph nodes. Neoplastic cells express increased levels of bcl-2, an anti-apoptosis protein associated with chromosomal translocation t(14;18) and thought to contribute to lymphoma genesis. As many as 50% of follicular center cell lymphomas progress to diffuse large-cell lymphoma over time.

**DIFFUSE LARGE B-CELL LYMPHOMA**

Diffuse large B-cell lymphoma, an aggressive neoplasm, accounts for approximately 30% of non-Hodgkin’s lymphomas in adults and 25% in children. Neoplastic cells have the appearance of large follicular center cell lymphoma cells or an immunoblastic or anaplastic appearance (Fig. 5). Approximately 20% to 30% of cases exhibit the chromosomal translocation t(14;18) noted earlier, and approximately 30% exhibit gene rearrangements at the 3q27 locus involving the bcl-6 gene. The latter are associated with extranodal involvement and favorable clinical features.15

**SMALL NONCLEAVED CELL LYMPHOMA**

Small noncleaved cell lymphomas form a group of highly aggressive neoplasms that includes Burkitt’s and non-Burkitt’s types. These lymphomas account for 5% or less of non-Hodgkin’s lymphomas in adults but approximately 35% of non-Hodgkin’s lymphomas in children. Small noncleaved cell lymphoma often presents as an abdominal or head and neck mass in children.
Neoplastic B cells are small to intermediate in size and have one to three distinct nucleoli (Fig. 6). Often, many mitotic figures and necrotic cells are present, as expected in a high-grade neoplasm.

Burkitt’s type small noncleaved cell lymphoma is associated with translocations t(8;14), t(2;8), and t(8;22) involving the c-myc oncogene, which, like cyclin D1, is thought to affect progression through the G2 phase of the cell cycle.16 Non-Burkitt’s type (or Burkitt’s-like) small noncleaved cell lymphoma is not associated with c-myc translocations; rather, it is associated with bcl-2 translocations in 30% of cases.17 Small noncleaved cell lymphoma is morphologically indistinguishable from B-cell acute lymphoblastic leukemia, the L3 subtype of acute lymphoblastic leukemia.

LYMPHOBLASTIC LYMPHOMA

Lymphoblastic lymphoma, another highly aggressive non-Hodgkin’s lymphoma, is uncommon in adults. It accounts for approximately 30% of pediatric non-Hodgkin’s lymphomas, however, typically presenting as a mediastinal mass. Most cases are precursor T-cell type, expressing several phenotypic markers of immature T cells, including terminal deoxynucleotidyl transferase (TdT). A few cases are precursor B-cell type (Fig. 7).

Lymphoblastic lymphoma is associated with several chromosomal translocations and other rearrangements involving T-cell receptor genes and transcription factor genes, such as TAL1, which may be rearranged in 25% of cases of lymphoblastic lymphoma and T-cell acute lymphoblastic lymphoma.16

PERIPHERAL T-CELL LYMPHOMAS

Peripheral T-cell lymphomas form a heterogeneous group of neoplasms that account for 10% to 15% of non-Hodgkin’s lymphomas in adults and children (Fig. 8). Angioimmunoblastic T-cell lymphoma is a common specific subtype.

Peripheral T-cell lymphomas are aggressive neoplasms, often presenting as stage IV disease.18 Patients may have B symptoms, hepatosplenomegaly, pulmonary and skin lesions, eosinophilia and Coombs-positive hemolytic anemia, and various infections, which may be fatal. The immunophenotype varies but includes expression of several pan-T-cell antigens with frequent absence of expression of one or more of these antigens.19 T-cell receptor genes exhibit clonal rearrangements.

In children, a significant number of cases of large-cell lymphoma are T-cell type with an associated chromosomal translocation t(2;5) thought to affect cell growth and differentiation.16 This translocation is associated with CD30-positive anaplastic large-cell lymphoma, a specific subtype of peripheral T-cell lymphoma, and with nonanaplastic lymphomas (Fig. 5B). About 20% of cases of anaplastic large-cell lymphoma express B-cell markers, and 5% lack evidence of T-cell or B-cell origin.

The malignant cells are large, with bizarre, irregularly shaped or polylobated nuclei that have abundant basophilic cytoplasm. Because of the involvement of
sinusoidal areas of lymph nodes and a cohesive growth pattern, a mistaken diagnosis of metastatic carcinoma may be made. Also, the large cells with prominent nucleoli may suggest Reed-Sternberg cells. Clinically, patients with anaplastic large-cell lymphoma may present with cutaneous lesions and a protracted course or generalized stage IV disease with an aggressive illness.\textsuperscript{20}

**EXTRANODAL LYMPHOMAS**

Almost 25\% of non-Hodgkin’s lymphomas primarily involve extranodal sites. Most are diffuse large B-cell lymphomas (55\% of gastric and intestinal; more than 90\% of bone, central nervous system, and eye; 20\% of ocular adnexa; and less than 15\% of skin lymphomas).\textsuperscript{7}

Mucosa-associated lymphoid tissue lymphomas often primarily involve the stomach (40\%), intestine (20\%), and ocular adnexae (30\%); lung, breast, and thyroid are uncommon sites. Primary extranodal follicular lymphomas are often seen in ocular adnexae (40\%) and skin (less than 15\%) but are rare in the gastrointestinal tract, bone, and central nervous system. Extranodal Burkitt’s and Burkitt’s-like lymphomas occur mainly in the stomach, intestine, bone, and bone marrow.

### Bone marrow biopsy is indicated in most patients because bone marrow involvement is highly likely in non-Hodgkin’s lymphoma.

**Clinical Evaluation and Staging**

Clinical evaluation begins with a detailed history and physical examination. The presence or absence of B symptoms must be determined. Particular attention must be paid to the presence of any skin lesions

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**Table 5**

**Staging Evaluation of Non-Hodgkin’s Lymphomas**

| Required Studies |
|------------------|
| Standard blood studies |
| Complete blood count, differential blood count, blood smear examination |
| LDH and β₂-microglobulin levels |
| Liver function tests |
| Renal function tests |
| Serum electrolyte, calcium, and uric acid levels |
| Bilateral bone marrow biopsies and aspirates |
| Radiologic studies |
| Chest film (posteroanterior and lateral) |
| CT scan of the thorax if chest symptoms are present or chest film is abnormal |
| CT scan of the abdomen and pelvis |
| Gallium-67 scan (in intermediate-grade and high-grade lymphomas) |
| Additional Studies in Selected Cases |
| CT or MR imaging of the head and spine for cranial/spinal symptoms |
| Upper and lower gastrointestinal tract contrast studies or ultrasound for abdominal complaints |
| Bone imaging or plain bone radiographs for skeletal complaints |
| MR imaging to detect bone marrow involvement |
| Spinal fluid analysis for suspected meningeal lymphoma |

LDH = lactate dehydrogenase.
or adenopathy and evaluation of Waldeyer’s ring. The size of the liver and spleen should be noted.

Routine blood counts and blood chemistry studies are necessary, particularly the lactate dehydrogenase (LDH) level, which is a prognostic parameter (Table 5). The peripheral blood smear should be carefully examined for any abnormal lymphoid cells, which often are seen in indolent B-cell lymphomas, as well as in highly aggressive B-cell and T-cell types.

Analysis of peripheral blood by flow cytometry may reveal clonal excess that is diagnostic of circulating lymphoma cells even when the differential leukocyte count is normal. Detection of small numbers of malignant cells in the peripheral blood by polymerase chain reaction techniques is useful in research studies but usually not clinically practical.

Bone marrow biopsy is indicated in most patients because in non-Hodgkin’s lymphomas the likelihood of marrow involvement, which may not be associated with any cytopenia, is high. In some large-cell lymphomas, bone marrow involvement is characterized by the presence of discordant smaller lymphoid cells of the same lineage. Immunophenotypic analysis by flow cytometry of bone

Fig. 9. CT scan of the chest shows a large anterior mediastinal mass in a 25-year-old man with stage IIA diffuse large B-cell lymphoma who presented with superior vena cava syndrome. The trachea is compressed by the tumor mass.

Fig. 10. (A) CT scan shows mesenteric and retroperitoneal adenopathy in a 58-year-old man with stage IVA small lymphocytic lymphoma. (B) Repeat CT scan 16 months after initiation of chemotherapy shows regression of all adenopathy, confirming a complete remission. A benign cyst of the right kidney is present. Reproduced with permission from Skarin and Dorfman.

Fig. 11. Gallium-67 scan of the same patient shown in Fig. 9 shows marked uptake in the mediastinal tumor mass. Repeat study after complete remission from combination chemotherapy showed no uptake of gallium-67.
marrow, blood, body fluid, or lymphoid or splenic tissue samples detects the presence of abnormal cells and identifies lymphoma subtypes. Bone marrow involvement also may be detected by magnetic resonance (MR) imaging.

Radiographic staging studies include lateral and posteroanterior chest films. If findings are abnormal or symptoms are present, a computed tomography (CT) scan of the chest should be done to define any enlarged mediastinal or hilar nodes and parenchymal lesions (Fig. 9). Abdominal and pelvic CT scans also are important to determine involvement of organs, soft tissues, or lymph nodes (Fig. 10). Upper or lower gastrointestinal series are indicated in patients with gastrointestinal symptoms in conjunction with appropriate endoscopic studies.

In patients with central nervous system symptoms, the brain is evaluated by CT scan with contrast or MR imaging using gadolinium. In patients with neurologic symptoms and those at risk of central nervous system involvement (e.g., those with aggressive and highly aggressive lymphomas, particularly with invasion of the blood, bone marrow, bone, orbit, nasal sinuses, or testes), examination of the spinal fluid for malignant cells may be indicated.

Routine bone imaging is not done, but in patients with skeletal symptoms, a nucleide scan or selected CT or MR imaging studies may be important in the differential diagnosis.

Gallium-67 scans are valuable in the staging of non-Hodgkin’s lymphomas, particularly aggressive and highly aggressive types, because correlation can be made with CT imaging. In some cases, disease sites not visualized by CT scan may be detected. Gallium uptake also correlates with disease activity and thus is useful as an indicator of response and prognosis. Uptake of gallium-67 occurs in only about 50% of indolent lymphomas.
but in most aggressive and highly aggressive types (Fig. 11).

The Ann Arbor staging system originally designed for Hodgkin’s disease is traditionally used for non-Hodgkin’s lymphomas. The schema is based on the number of lymph node sites, disease above or below the diaphragm, involvement of extranodal sites, and the presence or absence of systemic symptoms (Table 6). Unlike Hodgkin’s disease, which spreads to contiguous lymph node groups, non-Hodgkin’s lymphoma spreads unpredictably, and most patients present with stage III or IV disease. The Ann Arbor staging system is therefore less predictable in defining prognosis and survival.

Several clinical and laboratory features of non-Hodgkin’s lymphoma have been identified that more accurately predict disease outcome. They can be divided into three categories: the lymphoma’s growth rate and invasive potential (LDH and β₂-microglobulin levels, stage, size of mass, number of nodal and extranodal sites of disease, marrow involvement), the patient’s response to the lymphoma (B symptoms and performance status), and the patient’s ability to tolerate intensive therapy (age, performance status, and marrow involvement).

### Prognostic Factors

A prognostic index has been developed by the International Non-Hodgkin’s Lymphomas Prognostic Factors Project based on data from 2,031 patients with aggressive (intermediate- and high-grade) lymphomas treated with regimens containing doxorubicin. The model used the following risk factors: age (younger than 60 years versus older than 60 years), LDH level (lower than normal versus higher than normal), performance status (0 or 1 versus 2 to 4), stage (I or II versus III or IV), and extranodal involvement (less than one site versus more than one site).

Four risk groups were identified with predicted 5-year survival rates of 73%, 51%, 43%, and 26%, according to increasing number of adverse risk factors: none or one, two, three, and four or five, respectively. Patients older than 60 years were found to have complete remissions similar to those of patients younger than 60 years, but the duration was shorter with resultant poorer survival. Analysis of patients younger than 60 years revealed three clinical features that were independently associated with survival: stage, LDH level, and performance status.

The importance of the prognostic index is that good-risk (low relapse rate) patients can be identified for standard therapy and poor-risk (high relapse rate) patients can be identified for new research protocols to improve the cure rate. In addition, treatment results among institutions and cooperative groups can be compared because standardized prognostic factors are used. The prognostic factor models have been tested in indolent lymphomas and have proved useful in predicting relapse from complete remission and survival.

Recent studies have documented the importance of gallium-67 uptake in lymphomas as a useful prognostic indicator.
With conventional chemotherapy, only 25% of patients who were gallium-positive midway through therapy had durable responses, whereas 70% of those who were gallium-negative remained free of disease. With use of high-dose combination chemotherapy in aggressive lymphomas, only 14% of those who were gallium-positive midway through treatment obtained durable remission. In comparison, 91% of those who became gallium-negative remained disease free.

Other prognostic factors have been described recently that reflect cellular and molecular features of lymphomas. They include tumor cell proliferation markers, immunophenotype, adhesion molecule expression, and karyotypic abnormalities. It is likely that these newly identified biologic variables will replace clinical surrogate features in new prognostic factor models in the future.

### Treatment

The following is a general discussion of treatment. Detailed management plans and therapy for uncommon non-Hodgkin’s lymphomas, recently described subtypes, and HIV-related lymphomas can be found in standard oncology textbooks.

#### Indolent Lymphomas

Indolent nodal lymphomas are localized in only 10% to 15% of cases. In patients with stage I or II disease, however, regional radiotherapy results in long-term control with rates of freedom from relapse of 44% to 47% at 10 years and survival rates of 75% for selected patients younger than 60 years.

Treatment of advanced stage III or IV indolent lymphomas varies from the Stanford “watch-and-wait” approach to use of single alkylating agents, combination chemotherapy regimens with two to four drugs, and high-dose therapy with bone marrow transplant reinfusion. In a recent French study, patients with follicular lymphoma and a low tumor burden were randomized to receive chlorambucil, interferon, or no initial treatment. No differences were present in progression-free or overall survival with a median follow-up of 5 years.

Many chromosomal and molecular biologic defects, often affecting genes involved in control of cell growth, have been detected in various non-Hodgkin’s lymphomas.

The choice of treatment must consider many factors, including age, symptoms, extent of disease, comorbid disease, and follow-up. Several clinical research protocols have addressed potential curative therapy through the use of high-dose bone marrow transplant regimens in high-risk stage III and IV patients induced initially into complete or nearly complete remission.

Results of a prospective study in previously untreated patients at Dana-Farber Cancer Institute show a projected disease-free survival of 63% and overall survival of 89% at 3 years. Patients whose bone marrow, based on polymerase chain reaction, was negative for \( bcl-2 \) (a molecular marker for lymphoma cells) after purging had a significantly longer freedom from relapse.
Although long remissions can be achieved with intensive treatment, significant improvement in the cure rate requires additional innovative approaches with new agents or regimens. For example, a powerful method of killing residual lymphoma cells using anti-B-4-blocked ricin monoclonal antibody is under investigation.\textsuperscript{34}

Three new purine nucleoside analogs have been approved by the US Food and Drug Administration (FDA) for use in indolent lymphoproliferative disorders: 2-fluoro-ara-AMP (fludarabine), 2-deoxycoformycin (2-DCF, pentostatin), and 2-chlorodeoxyadenosine (2-CdA). These structurally similar analogs of adenosine differ in their interaction with adenosine deaminase, which degrades purine and deoxypurine nucleotides.

Fludarabine results in complete remission in 15% to 40% of patients with indolent lymphomas (the rate is higher in previously untreated cases) and 10% to 70% of patients with chronic lymphocytic leukemia.\textsuperscript{35} 2-DCF results in durable complete remission rates of 64% to 89% in hairy cell leukemia after 3 to 6 months of therapy. Major toxicities include myelosuppression and immunosuppression. The drug appears superior to interferon or splenectomy in management of hairy cell leukemia.\textsuperscript{35} Both 2-DCF and 2-CdA are active in indolent lymphomas, Waldenström’s macroglobulinemia, and cutaneous T-cell lymphomas.

The role of these new agents, including cross-resistance and combination with standard drugs in lymphoproliferative disorders, awaits the results of phase II and III studies.\textsuperscript{36}

**AGGRESSIVE LYMPHOMAS**

Management of apparently localized stage I or II aggressive lymphomas (using diffuse large B-cell lymphoma as a common example) consists of combination chemotherapy with or without regional radiotherapy.

In patients with low-risk (non-bulky) disease, the Vancouver group found that three cycles of CHOP (cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone) followed by involved field irradiation resulted in a 5-year projected disease-free survival of 84%.\textsuperscript{37}

A randomized Southwest Oncology Group trial that compared three cycles of CHOP plus radiation therapy with eight cycles of CHOP alone reported superior results with the combined modality arm.\textsuperscript{38} Excess cardiotoxicity occurred in patients receiving eight courses of CHOP. It is possible that four to six cycles of CHOP alone may be equivalent to three cycles plus radiation therapy, particularly in some subgroups. Results of an Eastern Cooperative Oncology Group trial randomizing patients to radiation therapy or no radiation therapy after chemotherapy appeared to show a slight benefit of regional radiation therapy.\textsuperscript{39} Longer follow-up and detailed analysis are required before firm conclusions can be made.

In patients with advanced stage III or IV aggressive lymphomas, a series of combination chemotherapy programs has been evaluated during the past 20 years consisting of first-, second-, and third-generation regimens.\textsuperscript{5}

A randomized Intergroup study was undertaken to determine whether the new programs using six or more drugs were more effective than the standard four-drug CHOP first-generation regimen. Final analysis showed similar results from CHOP, m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone), MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin), and ProMACE-CytaBOM (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, nitrogen mustard, vincristine, procarbazine, cytarabine, bleomycin), with 6-year overall survival rates of 33%, 36%, 32%, and 34%, respectively.\textsuperscript{40} Although CHOP was found to be less toxic than the
other regimens (fatal reactions were 1% versus 3% to 6%), the cure rate of less than 40% in unselected patients underscores the need for development of more effective treatment strategies.

Use of the international prognostic index allows for identification of good-risk patients who may have a predictive 5-year survival of more than 70% compared with poor-risk patients, who clearly need new treatment. A prospective Cancer and Leukemia Group B study is under way in previously untreated poor-prognosis patients using high-dose CHOP with granulocyte-colony stimulating factor support. Results from the pilot study using the concept of dose intensity show a complete remission rate of 86%, with 69% of all patients disease free at a median follow-up time of 20 months.41

Another approach to increase the cure rate is consolidation high-dose therapy with bone marrow or stem-cell support in poor-prognosis patients who have achieved a first complete remission. Encouraging results have been reported in a randomized French study comparing consolidation high-dose cyclophosphamide (6 g/m²), carmustine (300 mg/m²), etoposide (1 g/m²), and autologous bone marrow transplant (ABMT) versus additional conventional dose therapy with ifosfamide, etoposide, cytarabine, and doxorubicin.42,43

Although low- and intermediate-risk patients had similar outcomes, those with high-intermediate/high-risk features had increased disease-free survival and overall survival with use of high-dose therapy (57% versus 36% disease-free survival, \( P = 0.01 \), and 65% versus 52% overall survival, \( P = 0.06 \)). Other randomized trials are under evaluation.

For patients who do not achieve complete remission or subsequently relapse, new agents and regimens have been used with some success, but overall survival is eventually poor. Salvage regimens generally use drugs such as cisplatin, etoposide, cytarabine, and ifosfamide, which were not used in the first-line induction program.44

Another approach, designed to overcome drug resistance, consists of continuous infusion of natural products (etoposide, vincristine, doxorubicin) rather than bolus injections.45 The infusion regimen called EPOCH (etoposide, vincristine, cyclophosphamide, and doxorubicin) resulted in an impressive but brief response rate (42% complete remission and 35% partial remission).

High-dose therapy has also been used with some success in several pilot studies. A multi-institutional study of patients with intermediate-grade and high-grade lymphoma in first or second relapse used two cycles of DHAP (dex-amethasone, high-dose cytarabine, cis-platin) followed by randomization to receive either high-dose chemotherapy and radiation therapy with ABMT or further DHAP plus radiation therapy.46 At 5 years, the rate of event-free survival was 46% in the transplantation group compared with 12% in the group without ABMT (\( P = 0.001 \)), and the overall survival rates were 53% and 32%,

**Patients with highly aggressive lymphomas usually present with advanced disease and are treated with intensive pediatric leukemia–like regimens, including central nervous system prophylaxis.**
respectively (P = 0.038). These data support high-dose therapy with ABMT in suitable patients, particularly those with sensitive relapse.

**Highly Aggressive Lymphomas**

Patients with highly aggressive lymphomas (Burkitt’s and Burkitt’s-like lymphomas and lymphoblastic lymphoma) usually present with advanced disease. They are treated with intensive pediatric leukemia–like regimens, including central nervous system prophylaxis. These lymphomas have a high predilection for involving the skin, bone marrow, and central nervous system and for developing a leukemic phase.

In a multi-institutional study from the NCI, improved results were achieved both in adults younger than 60 years and in children with Burkitt’s and Burkitt’s-

like lymphomas who were treated with identical intensive chemotherapy regimens. The regimen uses cyclophosphamide, doxorubicin, prednisone, vincristine, high-dose methotrexate, and intrathecal methotrexate. In high-risk patients, ifosfamide, etoposide, and high-dose cytarabine are added. Cure rates of more than 80% have been predicted. A French multidrug study noted similar results except in patients who had stage IV Burkitt’s lymphoma with a leukemic phase; these patients had a 3-year survival of 57%.

Lymphoblastic lymphomas are mainly of early T-cell origin and occur in adolescents and young adults. Patients have been treated with pediatric acute lymphoblastic leukemia–like regimens. Early studies showed that those with high risk (stage IV disease and bone marrow or central nervous system involvement or initial elevated LDH level) had a poor prognosis, with only 20% predicted to survive beyond 5 years. However, among low-risk patients (those without the previously described features), survival was more than 90%.

Because the poor results in high-risk patients are partly the result of relapse after an initial complete remission, the role of high-dose therapy with or without total body irradiation plus autologous or allogeneic bone marrow support is under investigation.

**Future Directions**

Continued research in the fields of molecular epidemiology, cell biology, and molecular genetics may better define the mechanisms of lymphoma genesis and determine various risk factors in human study populations worldwide. For example, it has been shown that the incidence of non-Hodgkin’s lymphoma subtypes varies among different countries.

New treatment regimens are being evaluated with promising novel agents such as the taxanes (e.g., paclitaxel), topoisomerase I inhibitors (e.g., CPT-11 and topotecan), signal transduction modulators (e.g., bryostatin), and multidrug resistance modulators (e.g., PSC 833, a nonimmunosuppressive cyclosporine). Applications of biotherapy are promising with development of humanized monoclonal antibodies such as the anti-CD20 antibody IDEC-C2B8, radiolabeled anti-CD20, and specific T-cell–mediated immunotherapy. Results of bcl-2...
antisense therapy are encouraging.55

Advances in peripheral blood progenitor cell (stem cell) technologies will permit ex vivo expansion of targeted populations of hematopoietic cells for reducing and shortening myelosuppression after high-dose chemotherapy and will also allow for specific gene therapy.66 For example, one goal is to insert the multidrug resistance gene into highly purified CD34-positive cells to protect them from chemotherapy. Closed gene transformation systems are being developed.

Finally, improved prognostic factor index categories will become available that will permit selection of patients at risk of failure from standard treatment programs so that new, innovative, and intensive therapies can be used to improve the cure rate. For example, prognostic importance has been placed on cellular and biologic markers such as circulating IL-6 levels, tumor cell surface CD44 expression, bcl-6 rearrangements, Ki-67 expression, and overexpression of the bcl-2 protein.57

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