do not bear the characteristic cell surface molecules of B or T cells, and their immunoglobulin or TCR genes have not undergone rearrangement. Morphologically, the cells are large, with abundant cytoplasm containing azurophilic granules, and they are often called *large granular lymphocytes*. Functionally, they are part of the innate immune system, responding nonspecifically to a wide range of pathogens without requiring prior antigenic exposure.

NEOPLASIA OF LYMPHOID ORIGIN

Malignant transformation of lymphocytes leads to a diverse array of neoplasms of lymphoid origin, including tumors that arise from T cells, B cells, or NK cells. Lymphoid malignancies usually involve lymphoid tissues, but they can arise in or spread to any site. The major clinical groupings of lymphoid malignancies include non-Hodgkin's lymphomas (NHLs), Hodgkin's lymphoma, lymphoid leukemias, and plasma cell dyscrasias.

Non-Hodgkin's Lymphomas

Definition and Epidemiology

The NHLs comprise a heterogeneous group of lymphoid malignancies that have different histologic appearances, cells of origin and immunophenotypes, molecular biologic factors, clinical features, prognoses, and outcomes with therapy. According to the Surveillance, Epidemiology, and End Results (SEER) database, the NHLs are the seventh most common cancer type, with 70000 cases occurring in 2013 and 19,000 patients succumbing to these diseases. The NHLs occur at a median age of 66 and are more common in men and in whites. The rate of NHLs increased slowly between 2000 and 2010 by 0.5% per year, but the annual death rate declined during the same time period.

Pathology

In view of the heterogeneity of NHLs, classification systems have been devised to identify specific pathologic subtypes that correlate with distinct clinical entities. These systems have evolved steadily over the past 50 years as correlations between histopathologic and biologic behavior have emerged. Pathologic classification schemes have attempted to correlate malignant NHL subtypes with normal cellular counterparts. The World Health Organization (WHO) classification (Table 49-1) is the most current and incorporates morphologic features, immunophenotype, and cytogenetic characteristics to describe NHL subtypes. The most common NHLs encountered in the United States are diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, small lymphocytic lymphoma or leukemia (i.e., chronic lymphocytic leukemia [CLL]), and mantle cell lymphoma.

The cause of most NHLs is unknown. In most patients with NHL, no apparent genetic predisposition or epidemiologic or environmental factor can be identified. Many of the NHL subtypes carry pathognomonic chromosomal translocations that often involve an immunoglobulin locus (or TCR locus in T-cell–derived NHLs) and an oncogene or growth regulatory gene. The cause of these aberrant chromosomal rearrangements is unknown.

Patients with congenital immunodeficiency syndromes or autoimmune disorders are at increased risk for NHL. Oncogenic human viruses play a causal role in some of the less common NHL variants. Epstein-Barr virus (EBV) is associated with several biologically aggressive NHLs, including acquired immunodeficiency syndrome (AIDS)–related diffuse, aggressive lymphomas, the lymphoproliferative disorders that arise in patients who are immunosuppressed after organ transplantation, and the form of Burkitt's lymphoma that is endemic in Africa. Human T-cell lymphotropic virus type 1 (HTLV-1) is causally linked with adult T-cell leukemia/lymphoma, which is endemic in areas of Japan and the Caribbean basin. The human herpesvirus 8 (HHV-8) of Kaposi's sarcoma has been implicated in a variant of diffuse, aggressive NHL that arises in serosal cavities and is encountered almost exclusively in patients infected with human immunodeficiency virus (HIV).

Several indolent lymphomas have been linked to infectious agents that appear to indirectly promote lymphomagenesis through chronic antigen stimulation, resulting in B-lymphocyte proliferation. *Helicobacter pylori* infection is linked to gastric MALT lymphomas in this manner, and eradication of infection

TABLE 49-1 WORLD HEALTH ORGANIZATION CLASSIFICATION OF LYMPHOID NEOPLASMS*

B-CELL NEOPLASMS
Precursor B-cell neoplasm
Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)
Mature (peripheral) B-cell neoplasms
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma (± villous lymphocytes)
Splenic B-cell lymphoma/leukemia, unclassifiable
Hairy cell leukemia
Plasma cell myeloma/plasmacytoma
Extranodal marginal zone B-cell lymphoma of MALT type
Nodal marginal zone B-cell lymphoma of MALT type
Primary cutaneous follicle center lymphoma
Follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal large B-cell lymphoma
Primary effusion lymphoma
Burkitt's lymphoma/Burkitt cell leukemia
T-CELL AND NK-CELL NEOPLASMS
Precursor T-cell neoplasm
Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)
Mature (peripheral) T-cell neoplasms
T-cell prolymphocytic leukemia
T-cell granular lymphocytic leukemia
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia (HTLV-1 positive)
Extranodal NK-cell or T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic gamma-delta T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides/Sézary syndrome
Anaplastic large cell lymphoma, T-cell/null cell, primary cutaneous type
Peripheral T-cell lymphoma, not otherwise characterized
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, T-cell/null cell, primary systemic type

HTLV-1, Human T-cell leukemia virus type 1; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

*Only major categories are included, and common entities are shown in bold type. B-cell and T-cell/NK-cell neoplasms are grouped according to major clinical presentations: predominantly disseminated or leukemic, primary extranodal, and predominantly nodal.