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LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Non-Hodgkin Lymphoma

Rick, non-Hodgkin lymphoma survivor

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Revised **2013**

A Message From John Walter

President and CEO of The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society (LLS) believes we are living at an extraordinary moment. LLS is committed to bringing you the most up-to-date blood cancer information. We know how important it is for you to have an accurate understanding of your diagnosis, treatment and support options. An important part of our mission is bringing you the latest information about advances in treatment for non-Hodgkin lymphoma, so you can work with your healthcare team to determine the best options for the best outcomes. Our vision is that one day the great majority of people who have been diagnosed with non-Hodgkin lymphoma will be cured or will be able to manage their disease with a good quality of life. We hope that the information in this publication will help you along your journey.

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. Since 1954, LLS has been a driving force behind almost every treatment breakthrough for patients with blood cancers, and we have awarded almost $1 billion to fund blood cancer research. Our commitment to pioneering science has contributed to an unprecedented rise in survival rates for people with many different blood cancers. Until there is a cure, LLS will continue to invest in research, patient support programs and services that improve the quality of life for patients and families.

We wish you well.

John Walter
President and CEO

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Acknowledgement

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Introduction

Lymphoma is a general term for a group of blood cancers that start in the lymphatic system. About 54 percent of the blood cancers that occur each year are types of lymphomas. Lymphoma results when a lymphocyte (a type of white blood cell) undergoes a malignant change and multiplies, eventually crowding out healthy cells and creating tumors. These tumors enlarge the lymph nodes and/or grow in other sites that are part of the immune system (for example, the skin and other organs). Lymphocytic leukemia, a blood cancer that also originates in a lymphocyte, is closely related to lymphoma.

There are two major types of lymphoma: Hodgkin lymphoma (see the free LLS publication *Hodgkin Lymphoma*) and non-Hodgkin lymphoma (NHL). More than 60 specific non-Hodgkin lymphoma (NHL) subtypes have been identified. These have been assigned "diagnostic designations" (names) by the World Health Organization (WHO) in its *Classification of Tumors: Tumors of Hematopoietic and Lymphoid Diseases*.

Oncologists (cancer specialists) further characterize the NHL subtypes according to how fast (aggressive) or slow (indolent) the disease progresses. The subtype of NHL (and whether it is the indolent form or the aggressive form) determines appropriate treatment, so getting an accurate diagnosis is very important. Table 1, on page 3, provides a list of some of the NHL subtypes identified as either "aggressive" or "indolent" (the page numbers shown on Table 1 indicate discussions of specific subtypes).

This booklet, intended for patients and their families, covers many NHL subtypes as well as provides detailed information (including diagnosis, staging and treatment) about the more common ones. It also provides a brief description of normal blood and marrow and the lymphatic system, as well as a list of medical terms that will help readers understand information that may be new to them. Some of the medical terms used may be synonyms for other words or phrases used by healthcare professionals. For longer definitions of words or for definitions of words you do not see in this section, visit www.LLS.org/glossary. Check with your doctor if you have questions about how the terms used in this publication apply to you.

Table 1.

Aggressive Subtypes

Rapidly progressing or high-grade NHL—about 60 percent of cases in the United States. Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive NHL.

Page	
25	AIDS-associated Lymphoma*
23	Anaplastic Large Cell Lymphoma
25	Burkitt Lymphoma*
26	Central Nervous System (CNS) Lymphoma
22	Diffuse Large B-Cell Lymphoma
26	Lymphoblastic Lymphoma*
26	Mantle Cell Lymphoma
23	Peripheral T-Cell Lymphoma (most subtypes)
26	Precursor B- and T-cell Lymphoma/Leukemia
29	Transformed Follicular and transformed MALT Lymphoma

** Burkitt lymphoma, AIDS-associated lymphoma and lymphoblastic lymphoma are categorized as "highly aggressive" subtypes.*

Indolent Subtypes

Slowly progressing or low-grade NHL—about 40 percent of cases in the United States. Follicular lymphoma (FL) is the most common type of indolent NHL.

30	Cutaneous T-Cell Lymphoma (Mycosis Fungoides and Sézary Syndrome)
28	Follicular Lymphoma
31	Lymphoplasmacytic Lymphoma and Waldenström Macroglobulinemia
31	Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma
32	Nodal Marginal Zone B-Cell Lymphoma
32	Small Cell Lymphocytic Lymphoma (SLL)/Chronic Lymphocytic Leukemia (CLL)

Table 1. | Some aggressive and indolent NHL subtypes are listed in this table. In addition, certain patients are considered to have "intermediate grade" disease that has a rate of progression between aggressive and indolent. Some cases of indolent NHL "transform" to aggressive NHL.

Here to Help

The information provided in this booklet will be helpful when you talk to your doctor about the tests and treatment you need. We encourage you to take the lead in asking questions and discussing your fears and concerns. These actions will give members of your healthcare team the opportunity to answer your questions, extend emotional support and provide any needed referrals.

A diagnosis of NHL is often a shock to the patient, family members and friends. Denial, depression, hopelessness and fear are some of the reactions people may have. Keep in mind that

- Many people are better able to cope once their treatment plan is established and they can look forward to recovery.
- The outlook for people with NHL is continuing to improve. New approaches to therapy are being studied in clinical trials for patients of all ages and at every stage of treatment.

LLS Has Ways to Help. Treatment for NHL will affect your daily life, at least for a time. During and after treatment, you may want to have friends, family members or caregivers help you get information.

Making treatment choices, paying for medical care, communicating with healthcare providers, family members and friends—these are some of the stressors that go along with a cancer diagnosis. LLS offers free information and patient services for individuals and families touched by blood cancers.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They provide accurate up-to-date disease and treatment information and are available to speak with callers Monday through Friday, 9 a.m. to 6 p.m. ET at (800) 955-4572. You can email infocenter@LLS.org or chat live at www.LLS.org.

Clinical Trials. Our Information Specialists help patients work with their doctors to find out about specific clinical trials. Information Specialists conduct clinical-trial searches for patients, family members and healthcare professionals. You can also use an online clinical-trial search service supported by LLS that offers patients and caregivers immediate access to listings of blood cancer clinical trials. Please visit www.LLS.org/clinicaltrials.

Advocacy and Public Policy. The LLS Office of Public Policy (OPP) enlists volunteers to help advocate for policies and laws to speed the development of new treatments and improve access to quality medical care. Visit www.LLS.org/advocacy to find out more or get involved.

Co-Pay Assistance Program. This program offers assistance for financially eligible patients with certain blood cancer diagnoses to help pay for private or public health insurance premiums and/or co-pay costs for prescription medications. Check www.LLS.org/copay or call (877) 557-2672 to speak to a *Co-Pay Assistance Program Specialist* for eligibility information.

Language Services. Free language services are available when you speak with an Information Specialist. Let your doctor know if you want a professional healthcare interpreter who speaks your native language or uses sign language to be present during your visit. Many times, this is a free service.

Información en Español. LLS has a number of resources available in Spanish for patients, caregivers and healthcare professionals. You can read and download these resources online at www.LLS.org/espanol or order printed copies by mail or phone.

Free Materials. LLS publishes many free education and support materials for patients and healthcare professionals. PDF files can be read online or downloaded. Free print versions can be ordered. Visit www.LLS.org/resourcecenter.

Chapter Programs and Services. LLS chapter offices around the United States and Canada offer support and education. Your chapter can arrange for peer-to-peer support through the *Patti Robinson Kaufmann First Connection Program.* The *Patient Financial Aid* program offers a limited amount of financial aid for qualified patients. Find your chapter by calling (800) 955-4572 or by visiting www.LLS.org/chapterfind.

Other Helpful Organizations. Our website, www.LLS.org/resourcedirectory, offers an extensive list of resources for patients and families about financial assistance, counseling, transportation, summer camps and other needs.

Telephone/Web Education Programs. LLS provides a number of free, live telephone and web education programs presented by experts for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

Children's Concerns. Each family that receives a diagnosis of childhood NHL is thrown into an unfamiliar world of treatment and follow-up care. The child, parents and siblings need support. Remember that help is available. Don't hesitate to ask for assistance for your child, yourself or other family members, even if you are already working with a psychologist, social worker or child life specialist. For practical guidance on how to support your child and other family members, deal with your own concerns, share the news with extended family and friends and make the transition to life after treatment ends, see the free LLS publication *Coping With Childhood Leukemia and Lymphoma*.

Suggestions From Other People Living With Cancer

- Get information about choosing a cancer specialist or treatment center.
- Find out about financial matters: What does your insurance cover? What financial assistance is available to you?
- Learn about the most current tests and treatments for NHL.
- Keep all appointments with the doctor and talk openly about your fears or concerns or any side effects that you experience.
- Talk with family and friends about how you feel and how they can help.
- Contact your doctor if you have fatigue, fever, pain or sleep problems so that any issues can be addressed early on.
- Get medical advice if you have experienced changes in mood, feelings of sadness or depression.

Reach Out. You and your loved ones can reach out for support in several ways. For example:

- LLS offers online Blood Cancer Discussion Boards as well as online chats at www.LLS.org/getinfo.
- Local or Internet support groups and blogs can provide forums for support.
- Patients with cancer often become acquainted with one another, and these friendships provide support.

Information for Veterans. Veterans with certain blood cancers who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information call the Department of Veterans Affairs at (800) 749-8387 or visit www.publichealth.va.gov/exposures/agentorange.

Information for World Trade Center Survivors. People who were involved in the aftermath of the attacks of September 11, 2001, may be eligible for help from the World Trade Center Health Program. These include: responders, workers and volunteers who helped with rescue, recovery and cleanup at the World Trade Center and related sites in New York City; survivors who were in the New York City disaster area, lived, worked or were in school in the area; and responders to the Pentagon and the Shanksville, PA crash who have been diagnosed with a blood cancer. For more information, call the World Trade Center Health Program at (888) 982-4748 or visit www.cdc.gov/wtc/faq.html.

Depression. Treatment for depression has proven benefits for people living with cancer. Depression is an illness that should be treated even when a person is undergoing NHL treatment. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a two-week period.

Contact LLS or ask your healthcare team for guidance and referrals to other sources of help, such as counseling services or community programs. For more information you can contact the National Institute of Mental Health (NIMH) at www.nimh.nih.gov and enter "depression" in the search box at the top of the web page, or call the NIMH toll free at (866) 615-6464.

We'd Like to Hear From You. We hope the information in this booklet helps you. Please tell us what you think at www.LLS.org/publicationfeedback. Click on "LLS Disease & Treatment Publications—Survey for Patients, Family and Friends."

Non-Hodgkin Lymphoma Overview

Non-Hodgkin lymphoma (NHL) is the term used for a diverse group of blood cancers that share a single characteristic—they arise from an injury to the DNA of a lymphocyte parent cell. The damage to the DNA is acquired (occurs after birth) rather than inherited. The altered DNA in one lymphocyte produces a malignant transformation. This transformation results in the uncontrolled and exaggerated growth of the lymphocyte. These lymphocytes and the formed cells have a better-than-normal chance to survive. The accumulation of those cells results in the tumor masses found in the lymph nodes and other sites in the body.

NHL generally develops in the lymph nodes or in lymphatic tissue found in organs such as the stomach, intestines or skin. In some cases NHL involves marrow (spongy tissue in the hollow central cavity of the bones that is the site of blood cell formation) and blood. Lymphoma cells may develop in one or many sites in the body (see *Signs and Symptoms* on page 11).

Table 2 on page 8 lists some of the diagnostic designations for NHL (subtypes), based on the World Health Organization (WHO) Classification of Tumors: Hematopoietic and Lymphoid Diseases. Many doctors use the REAL/WHO (Revised European-American Lymphoma/World Health Organization) classification, which categorizes subtypes by the appearance of the lymphoma cells, the presence of proteins on the surface of the cells and genetic features. Follicular lymphoma and diffuse large B-cell lymphoma are the two most common types and together account for about 53 percent of cases.

The complete WHO classification also includes several types of lymphocytic or lymphoblastic leukemia, but these are not included in Table 2. Lymphocytic or lymphoblastic leukemias and lymphomas are closely related. A cancer that originates in the lymphatic tissue in the marrow is designated "lymphocytic leukemia" or "lymphoblastic leukemia"; the acute and chronic forms of lymphocytic or lymphoblastic leukemia are the two major examples of this type of blood cancer (for more information, see the free LLS publications *Acute Lymphoblastic Leukemia* and *Chronic Lymphocytic Leukemia*). A cancer that begins in a lymph node or other lymphatic structure in the skin, the gastrointestinal tract or another site in the body is called a "lymphoma" (see *Small Cell Lymphocytic Lymphoma (SLL) and Chronic Lymphocytic Leukemia (CLL)* on page 32).

Table 2. Diagnostic Designations for Non-Hodgkin Lymphoma

NHL Subtypes and Frequency

B-Cell Lymphoma

1. Diffuse Large B-Cell Lymphoma (31%)
2. Follicular Lymphoma (22%)
3. Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma (7.5%)
4. Small Cell Lymphocytic Lymphoma–Chronic Lymphocytic Leukemia (7%)
5. Mantle Cell Lymphoma (6%)
6. Mediastinal (Thymic) Large B-Cell Lymphoma (2.4%)
7. Lymphoplasmacytic Lymphoma–Waldenström Macroglobulinemia (less than 2%)
8. Nodal Marginal Zone B-Cell Lymphoma (less than 2%)
9. Splenic Marginal Zone Lymphoma (less than 1%)
10. Extranodal Marginal Zone B-Cell Lymphoma (less than 1%)
11. Intravascular Large B-Cell Lymphoma (less than 1%)
12. Primary Effusion Lymphoma (less than 1%)
13. Burkitt Lymphoma-Burkitt Leukemia (2.5%)
14. Lymphomatoid Granulomatosis (less than 1%)

T-Cell and Natural Killer (NK)-Cell Lymphoma (about 12%)

1. Peripheral T-Cell Lymphoma, not otherwise specified
2. Cutaneous T-Cell Lymphoma (Sézary Syndrome and Mycosis Fungoides)
3. Anaplastic Large Cell Lymphoma
4. Angioimmunoblastic T-Cell Lymphoma
5. NK-Cell Lymphoma

Immunodeficiency-Associated Lymphoproliferative Disorders

The percentages above are approximate; they are provided to give a sense of the relative distribution of NHL subtypes. Immunodeficiency-associated lymphoproliferative disorders account for a very small percentage of total NHL cases.

Table 2. | This table is based on information presented in the *World Health Organization Classification of Tumors: Tumors of Hematopoietic and Lymphoid Diseases*. The descriptive parts of the names (e.g., follicular, mantle cell and marginal zone) for some disease subtypes relate to the specific areas of normal lymph nodes (the "follicle," "mantle" and "marginal" zones) where the lymphoma appears to have originated.

Incidence, Causes and Risk Factors

Incidence. About 69,740 cases of non-Hodgkin lymphoma are expected to be diagnosed in the United States in 2013. (Source: Surveillance, Epidemiology, and End Results [SEER] Program; National Cancer Institute, 2013). Most of these (about 85 percent) are comprised of one of 14 different types of NHL that involve lymphocytes called "B cells." The two most common subtypes of NHL, diffuse large B-cell lymphoma and follicular lymphoma, are examples of B-cell lymphomas. The other approximately 15 percent of cases of NHL involve lymphocytes called "T cells" or "natural killer (NK) cells." T-cell lymphoma includes peripheral T-cell lymphoma and cutaneous T-cell lymphoma.

Non-Hodgkin lymphoma occurs in individuals at virtually all ages, but it is uncommon in children. The incidence of NHL increases with age as shown in Figure 1. In the 20- to 24-year age-group, 2.5 cases occur per 100,000 persons. The rate increases almost 20-fold to 44.6 cases per 100,000 individuals by age 60 to 64 years, and over 40-fold to more than 100 cases per 100,000 persons after age 75.

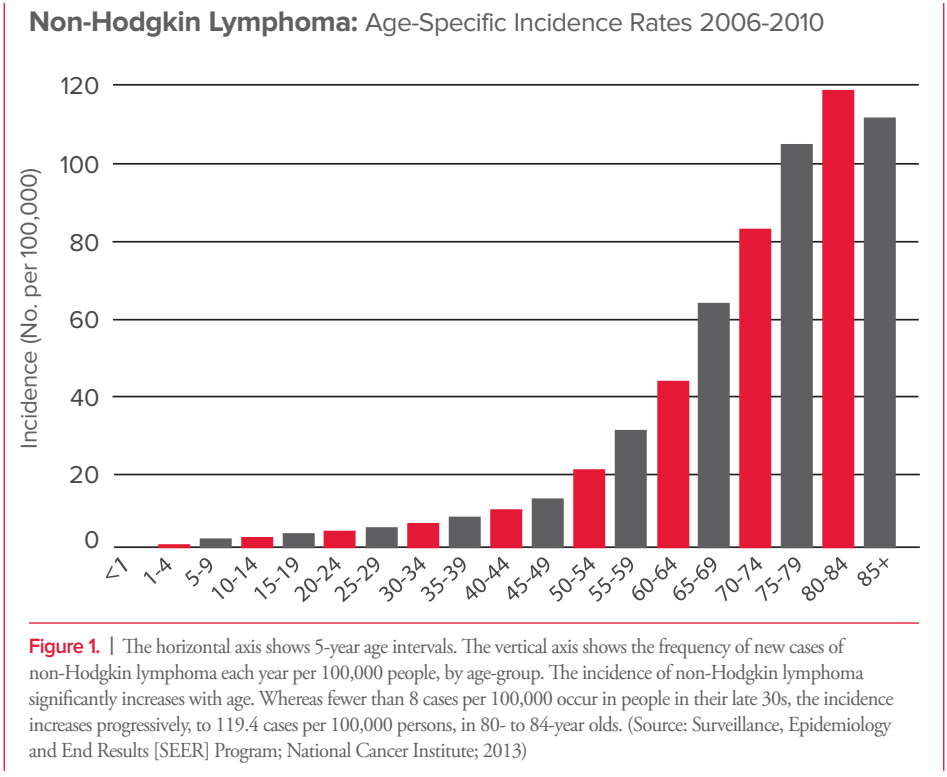


Figure 1. | The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of non-Hodgkin lymphoma each year per 100,000 people, by age-group. The incidence of non-Hodgkin lymphoma significantly increases with age. Whereas fewer than 8 cases per 100,000 occur in people in their late 30s, the incidence increases progressively, to 119.4 cases per 100,000 persons, in 80- to 84-year olds. (Source: Surveillance, Epidemiology and End Results [SEER] Program; National Cancer Institute; 2013)

Causes and Risk Factors. The age-adjusted incidence of NHL rose by more than 89.5 percent from 1975 to 2010, an average annual increase of about 2.6 percent. The reasons for this increase are not certain, and there are probably multiple causes. Since the mid 1980s, the incidence of NHL in individuals with the human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS) has contributed modestly to the overall increase in incidence. However, the increase in the general population began before the spread of HIV. Furthermore, while NHL is between 50 and 100 times more prevalent among people with HIV/AIDS than among uninfected individuals, newer therapies for HIV infection have lowered the incidence of AIDS-related lymphoma.

There is a higher incidence of NHL in farming communities. Studies suggest that specific ingredients in herbicides and pesticides such as organochlorine, organophosphate and phenoxy acid compounds are linked to lymphoma. The number of lymphoma cases caused by such exposures has not been determined. Other studies suggest that pesticides used in agricultural, commercial and home and garden application are associated with cancer risk. More studies are needed.

Exposure to certain viruses and bacteria is associated with NHL. It is thought that infection with a virus or bacterium can lead to intense lymphoid cell proliferation, increasing the probability of a cancer-causing event in a cell. Here are some examples:

- Epstein-Barr virus (EBV) infection—in patients from specific geographic regions—is strongly associated with African Burkitt lymphoma. The role of the virus is unclear, since African Burkitt lymphoma also occurs among people who have not been infected with EBV.
- Epstein-Barr virus infection may play a role in the increased risk of NHL in persons whose immune systems are suppressed as a result of organ transplantation and its associated therapy.
- Human T-lymphotropic virus (HTLV) is associated with a type of T-cell lymphoma in patients from certain geographic regions in southern Japan, the Caribbean, South America and Africa.
- The bacterium *Helicobacter pylori* causes ulcers in the stomach and is associated with the development of mucosa-associated lymphoid tissue (MALT) lymphoma in the stomach wall.

About a dozen inherited syndromes can predispose individuals to later development of NHL. These inherited disorders are uncommon, but the concept of predisposition genes is under study to determine if they play a role in the random occurrence of NHL in otherwise healthy individuals.

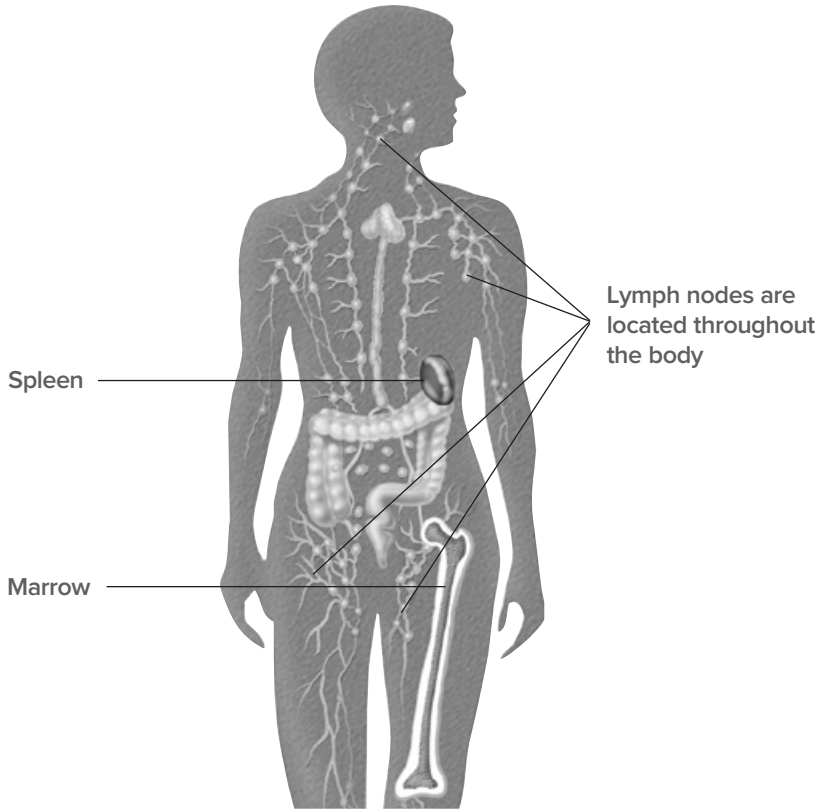
Having autoimmune diseases such as Sjögren's syndrome, lupus, or rheumatoid arthritis, may also increase a person's risk of developing lymphoma. Some of the treatments for these diseases may also be associated with very rare cases of lymphoma.

For more information, contact our Information Specialists at (800) 955-4572 and visit www.LLS.org/resourcedirectory, click on "Blood Cancer: General Information" and then "Disease Registries."

Signs and Symptoms

An enlarged lymph node in the neck, armpit or groin—or less often, a swollen node near the ears, the elbow or in the throat near the tonsils—is sometimes an indication of lymphoma. There are about 600 lymph nodes in the body (see Figure 2).

Non-Hodgkin Lymphoma and the Lymphatic System



The lymphatic system is part of the immune system. The normal immune system helps to protect the body from infection. The marrow, lymph nodes and spleen are some of the parts of the immune system. There are about 600 lymph nodes throughout the body.

Figure 2. | Lymph nodes and other lymphoid tissues that are commonly involved in lymphoma are those around the ears and jaw, in the tonsils and adenoids, in the front and back of the neck, above and below the collar bone, in the armpit, near the elbow, in the chest, in the abdomen, in the pelvis and in the groin. The spleen contains many clusters of lymphocytes that can become malignant and grow, leading to the enlargement of the spleen. The gut-associated (intestinal) lymph tissue may also be the site of lymphoma development.

Keep in mind that enlarged lymph nodes can result from inflammation and are not necessarily a sign of cancer. However, if enlarged lymph nodes are detected during a physical examination or during an imaging test (for example, a chest x-ray) and there is no obvious explanation such as a nearby infection, lymphoma could be the cause.

Occasionally, the disease starts in a site other than the lymph nodes, such as a bone, a lung, the gastrointestinal tract or the skin. In these circumstances, patients may experience symptoms that are associated with that site, such as bone pain, cough, chest pain, abdominal pain, rashes or skin lumps.

Patients may also have fever, excessive sweating (especially noticeable at night), unexplained fatigue, loss of appetite or weight loss. During a medical examination, the doctor may detect an enlarged spleen. Sometimes, a person has no symptoms and the disease may only be discovered during a routine medical examination or while the person is under care for an unrelated condition.

Diagnosis

A diagnosis of NHL is usually made by examining a lymph node biopsy specimen (piece of node taken and studied under the microscope); the examination includes tests called "immunophenotyping" and "cytogenetic analysis." It is important that all patients receive an accurate diagnosis and know their NHL subtype. It is a good idea to have the doctor write down the name of the subtype for the patient.

Lymph Node Biopsy. Making an accurate diagnosis of the specific type of NHL that a patient has can be difficult. Since the subtypes of NHL can be confused with one another, and the prognosis (likely course of a disease), treatment goals and treatment approach may be different, a precise diagnosis is needed. It requires an experienced hematopathologist (a doctor who specializes in interpreting and diagnosing the physical changes caused by diseases of the blood and marrow) to analyze the biopsy slides. Another opinion by a second hematopathologist may be necessary if there is any doubt about the diagnosis, or to confirm the diagnosis in more rare lymphoma cases.

A biopsy (sample of lymph node tissue) of an involved lymph node or other tumor site is needed to confirm the NHL diagnosis and the subtype. A needle biopsy of the lymph node is usually not sufficient to make a firm diagnosis. Generally, the lymph node or part of the lymph node is surgically removed so that the hematopathologist has enough tissue to make a firm diagnosis. Lymph node biopsy tissue can often be removed using a local anesthetic.

Chest or abdominal surgery is occasionally necessary to obtain the biopsy sample needed for diagnosis, and requires general anesthesia. Newer approaches that are less invasive use a tube called a "laparoscope." This allows tissues samples to be taken without major incisions.

Non-Hodgkin lymphoma can involve parts of the body that do not involve lymph nodes. When lymphoma is detected exclusively outside of the lymph nodes, it is called "primary extranodal lymphoma," and the biopsy specimen is taken from the involved tissue, such as the lung or bone.

The biopsy specimen or the tissue is placed on a slide with a preservative and then stained with dyes. The hematopathologist prepares this slide. The slide is examined under a microscope, and cells with lymph node changes are looked at to identify the specific NHL subtype. The distinctive patterns of these cells help the hematopathologist to categorize the subtype.

Examining Lymph Node Biopsy Samples. Several methods may be used, including

- Immunophenotyping, a process that allows the hematopathologist to study the cells obtained at the time of tissue biopsy. Immunophenotyping can provide additional evidence that these cells are lymphoma cells and, further, whether they are B cells, T cells or NK cells.
- Cytogenetic analysis, in which cells are studied to see if chromosomal abnormalities are present. Chromosomal abnormalities can be important in identifying specific subtypes of NHL and choosing the most effective treatment approach.
- Gene expression profiling and microarray analysis identify cancer subtypes and risk factors. These tests help predict how patients will respond to treatment and which patients may be at increased risk to relapse. For example, gene expression profiling is used to identify different forms of diffuse large B-cell lymphoma.

The level of expression of specific proteins made by genes may be a predictor of how well a patient will respond to treatment with specific therapies. These levels can be assessed by polymerase chain reaction (PCR), a technique to expand trace amounts of DNA or RNA so that the specific type of the DNA or RNA can be determined. This method has become useful in detecting a very low concentration of residual lymphoma cells—too few to be seen by using a microscope. The technique can detect the presence of one lymphoma cell among 500,000 to 1 million nonlymphoma cells. The use of PCR requires a specific DNA abnormality or marker, such as an oncogene, in the lymphoma cells.

Staging

A physical examination, and the findings from imaging tests, computed tomography (CT) scans (also called "diagnostic radiology"), tissue biopsies and blood tests are used to determine the extent of the patient's NHL. This process is called "staging," and the information is used to determine appropriate treatments (chemotherapy, radiation).

Physical Examination and Imaging Tests. The physical exam and imaging tests help the doctor to evaluate

- The location and distribution of lymph node enlargement
- Whether organs other than lymph nodes are involved
- Whether there are very large masses of tumors in one site or another.

Imaging tests include

- X-rays
- Computed tomography (CT) scans of the neck, chest, abdomen and pelvis
- Magnetic resonance imaging (MRI) in select cases
- [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET).

Imaging techniques such as MRI or CT are used in many cancer centers. Patients have CT scans of the neck, chest, abdomen and pelvis—all the areas where lymph nodes are present—to identify areas of disease. The CT scan will also show whether there is involvement of the lungs, liver and other organs—information that will be helpful in staging the disease. In some cases positron emission tomography (PET) scans may assist the doctor in identifying sites of lymphoma in the abdomen, chest or other sites.

FDG-PET scanning differs from x-rays, CT, MRI and ultrasonography, which only provide anatomical images; FDG-PET also measures altered tissue metabolism (activity). This imaging technique relies on a radioactive tracer called "FDG ([18F]-fluorodeoxyglucose)." FDG is a special form of glucose. The radioactive tracer is given intravenously to the patient and enters the cells. Cancer cells have a greater attraction to this glucose than normal cells, so cancer cells trap more of the radioactive tracer; then the local tracer concentration is measured. This technique allows the cancer cells to be separated from normal cells. Using FDG-PET to measure increased FDG uptake in lymphoma cells may provide a very sensitive and relatively rapid assessment of the lymphoma cells' response to therapy.

The use of PET or PET/CT is not a routine part of NHL staging in all cases. PET cannot replace CT or bone marrow biopsy in staging NHL. However, it can provide complementary information. PET is widely used to assess how well a patient responded after therapy is completed, particularly for curable lymphomas.

Blood and Marrow Tests. Patients also have a complete blood count (CBC) that may show

- Anemia (low red blood cell levels)
- Neutropenia (low levels of neutrophils [a type of white blood cell])
- Thrombocytopenia (low platelet levels).

Blood tests are used to

- Determine whether lymphoma cells are present in the blood and if the immunoglobulins made by lymphocytes are deficient or abnormal
- Check indicators of disease severity such as blood protein levels, uric acid levels and erythrocyte sedimentation rate (ESR)
- Assess kidney and liver functions and hepatitis A, hepatitis B and hepatitis C status
- Measure two important biological markers, lactate dehydrogenase (LDH) and beta$_2$-microglobulin, which are helpful prognostic indicators for several NHL subtypes.

Most patients diagnosed with NHL will have a bone marrow biopsy to make sure there is no spread of the disease to the bone marrow and to evaluate the use of specific therapies including radioimmunotherapy. A bone marrow biopsy may not always be required for patients with early-stage disease.

Some of the tests that are done are associated with a specific subtype and are not necessary for all patients with NHL. Examples of specific testing include a

- Full evaluation of the gastrointestinal (GI) tract, including upper and lower endoscopies for patients who have disease involving the GI tract
- Colonoscopy for patients with mantle cell lymphoma (routine colonoscopy is important for all persons beginning at age 50 years, or earlier if there is a family history of colon cancer)
- Spinal tap (lumbar puncture) and/or imaging of the brain or spinal column (may be required for patients with certain subtypes or symptoms that suggest central nervous system involvement).

Stages and Categories of Non-Hodgkin Lymphoma. NHL may be described as

Stage I: Involvement of one lymph node group

Stage II: Involvement of two or more lymph node groups on the same side of the diaphragm (a thin muscle below the lungs)

Stage III: Involvement of lymph node groups on both sides of the diaphragm

Stage IV: Involvement of one or more organs other than the lymph nodes and possible involvement of the lymph nodes (see Figure 3 on page 16).

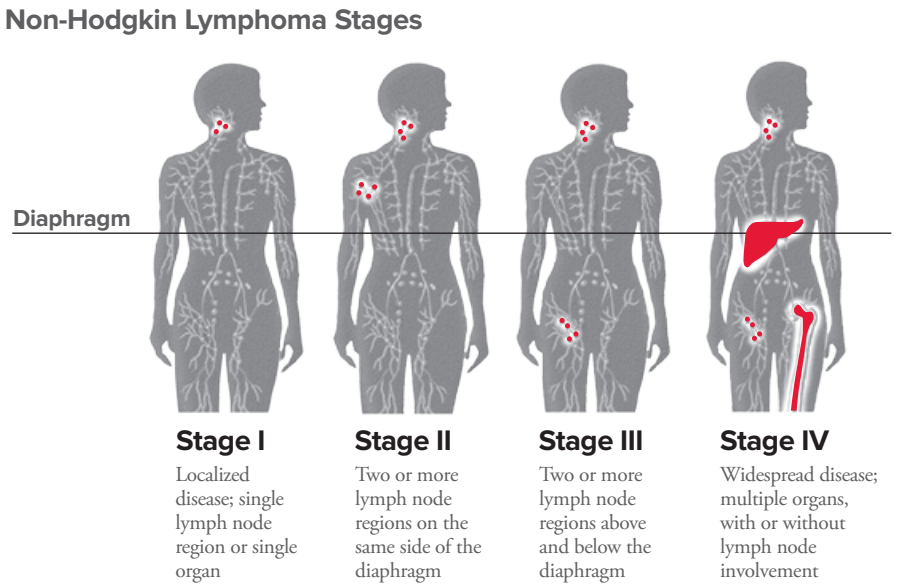


Figure 3. | This illustration shows the location of non-Hodgkin lymphoma in the body for each stage.

Categories A, B, X and E. The four stages of NHL can be divided into categories.

- The A category indicates that patients have not experienced fever, exaggerated sweating and weight loss.
- The B category indicates that patients have fever, excessive sweating and weight loss.
- The X category indicates bulky disease (large masses of lymphocytes).
- The E category indicates areas or an organ involved other than the lymph nodes or has spread to tissues beyond, but near, the major lymphatic areas.

For example, stage IIB indicates that the patient has

- Two lymph node sites near each other with disease involvement (for example, enlarged lymph nodes in the neck and near the collarbone or in the neck and the armpit)
- Fever, excessive sweating and weight loss.

Patients in the B category often require more aggressive treatment.

Keep in mind that "stage IV" does not have the same implications in NHL as it does in some other types of cancer. NHL does not necessarily start at stage I and then spread to stage II and so forth. More than 50 percent of patients with intermediate or aggressive disease and more than 80 percent of patients with indolent types of NHL are diagnosed with stage III or IV disease. A diagnosis of stage IV NHL may be highly curable, depending on the patient's specific subtype of disease.

When all of the diagnostic and staging tests are completed, the doctor will be able to evaluate the information, identify the NHL subtype and determine which areas of the body are involved.

Treatment Overview

The initial therapy and intensity of treatment indicated for a patient are based on the subtype and stage of disease. In general, the goal of treatment is to destroy as many lymphoma cells as possible and to induce a "complete remission"; that is, to eliminate all evidence of disease. Patients who go into remission are sometimes cured of their disease. Treatment can also keep NHL in check for many years, even though imaging or other studies show remaining sites of disease. This situation may be referred to as a "partial remission."

In general, chemotherapy and radiation therapy are the two principal forms of treatment for NHL (See Table 3, below and Table 4, page 18). Although radiation therapy is not often the sole or principal curative therapy, it is an important additional treatment in some cases. Stem cell transplantation and a watch-and-wait strategy are also used to treat some NHL subtypes. Other forms of treatment are emerging, and some are already approved for specific forms of NHL. Many other new therapies are under investigation in clinical trials.

Table 3. Some Drugs Used in the Treatment of Non-Hodgkin Lymphoma

DNA-Damaging Drugs

- bendamustine (Treanda®)
- carboplatin (Paraplatin®)
- carmustine (BCNU, BiCNU®)
- chlorambucil (Leukeran®)
- cisplatin (Platinol®)
- cyclophosphamide (Cytoxan®)
- dacarbazine (DTIC, DTIC-Dome®)
- ifosfamide (Ifex®)
- melphalan (Alkeran®)
- procarbazine (Matulane®)

Antitumor Antibiotics

- doxorubicin (Adriamycin®)
- idarubicin (Idamycin®)
- mitoxantrone (Novantrone®)

Antimetabolites

- cladribine (Leustatin®)
- cytarabine (cytosine arabinoside, ara-C, Cytosar-U®)
- fludarabine (Fludara®)
- gemcitabine (Gemzar®)
- nelarabine (Arranon®)
- methotrexate (Rheumatrex®, Trexall®)
- 6-thioguanine (Thioguanine Tabloid®)

Proteasome Inhibitor Drug

- bortezomib (Velcade®)

DNA Repair Enzyme Inhibitors

- etoposide (Etopophos®, VePesid®, VP-16)

Drugs That Prevent Cells From Dividing by Blocking Mitosis

- paclitaxel (Abraxane®, Onxol®,Taxol®)
- vinblastine (Velban®)
- vincristine (Oncovin®)

Hormones That Can Kill Lymphocytes

- dexamethasone (Decadron®)
- methylprednisolone (Medrol®)
- prednisone

Immunotherapy

- rituximab (Rituxan®)
- yttrium-90-ibritumomab tiuxetan (Zevalin®)

Histone Deacetylase Inhibitor

- vorinostat (Zolinza®)

Retinoid

- bexarotene (Targretin®)

Table 4. Some Examples of Drug Combinations Used to Treat Non-Hodgkin Lymphoma

R-CHOP: rituximab (Rituxan®) plus cyclophosphamide, doxorubicin (hydroxydoxorubicin), Oncovin® (vincristine), prednisone

R- or F-CVP: Rituxan or fludarabine, plus cyclophosphamide, vincristine, prednisone

R-HCVAD: Rituxan, cyclophosphamide, vincristine, Adriamycin® (doxorubicin), dexamethasone, alternating with R-MTXARAC: Rituxan, methotrexate-cytarabine

B-R: Bendamustine, rituximab

DHAP: Dexamethasone, high-dose cytarabine, cisplatin

ICE: Ifosfamide, carboplatin, etoposide

Table 4. | Clinical investigators continue to study the most effective combinations of drugs for treatment of different groups of patients—those with newly diagnosed NHL, with NHL that is not fully responsive to the initial treatment (refractory NHL) or with recurrent NHL (relapsed NHL).

The monoclonal antibody rituximab (Rituxan®) has been an important addition to traditional drug therapy programs and is approved for patients who have

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy
- Nonprogressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP (cyclophosphamide, doxorubicin [hydroxydoxorubicin], Oncovin® [vincristine] and prednisone) or other anthracycline-based chemotherapy regimens
- Advanced follicular, CD20-positive, B-cell NHL as a single-agent maintenance treatment, after response to initial treatment with Rituxan plus chemotherapy (induction treatment).

A recurrence (relapse) of NHL can occur months or years after treatment. In such cases, additional treatment is often successful at restoring a remission. If relapse occurs a long time after initial treatment, sometimes the same or similar agents that were used in the earlier treatment may be effective. In other cases, different approaches may be used.

Factors That Influence Treatment. Each person should discuss treatment options with his or her doctor and ask for help with understanding the benefits and risks of different treatment approaches. The doctor and other members of the oncology team can provide a context for treatment information and discuss specific situations with patients. The most effective treatment plan for a patient with NHL is individualized and depends on

- The subtype of NHL (knowing whether the lymphoma cells are most closely related to T cells, B cells or natural killer [NK] cells gives the doctor important clues as to which treatments should be used)
- The stage and category of the disease (the distribution of lymphoma throughout the body is sometimes important in forming decisions about treatment; see Figure 2, page 11)
- Factors such as fever, drenching night sweats and weight loss of more than 10 percent of body weight, referred to as "B symptoms"
- The presence of lymphoma in areas of the body outside of the lymph nodes (extranodal involvement)
- Other prognostic factors.

The patient's age may be a factor, but older age is no longer a major determinant in treatment for most patients. However, other medical problems, the patient's overall health and the patient's decisions about treatment are all important considerations.

The International Prognostic Index (IPI). The IPI is a scoring system that uses known risk factors to predict overall survival and guide treatment decisions. This information helps doctors to determine appropriate care for patients who have been treated for aggressive lymphomas and predict risk of relapse.

One point is assigned for each of the following risk factors

- Age greater than 60 years
- Stage III or IV disease
- More than one lymph node involved
- Elevated serum lactate dehydrogenase (LDH)
- Level performance status, which is a scale used to evaluate a person's ability to perform daily tasks of living without help.

The number of IPI 'risk factors' a person has defines the IPI risk group to help predict the risk of relapse. Each point represents some increased risk for disease recurrence. The total number of points identifies the following risk groups: low risk (0-1 points); low-intermediate risk (2 points); high-intermediate risk (3 points); high risk (4-5 points). For patients younger than 60 years, the risk categories are slightly different; low risk (0 points); low-intermediate risk (1 point); high-intermediate risk (2 points); high risk (3 points). Patients may want to discuss risk factors with their doctor in order to understand treatment options, including participation in clinical trials.

Pretreatment Considerations. Adults of childbearing age and parents of children diagnosed with NHL should ask their doctor for information about possible long-term and late effects, including effects on fertility (see *Long-Term and Late Effects of Treatment for Non-Hodgkin Lymphoma*, page 35; for more information, see the free LLS publications *Fertility; Long-Term and Late Effects of Treatment in Adults Facts;* and *Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma Facts*).

Treatment Setting. Patients may undergo treatments over long periods, but most therapy can be administered in an outpatient setting. Radiation therapy, chemotherapy or immunotherapy can be administered in the outpatient clinic of an oncology center. Short periods of hospitalization are sometimes required. Particularly intensive therapy can cause prolonged or severe decreases in red blood cell, white blood cell and/or platelet counts. Transfusion of appropriate blood products and administration of cytokines (hormones that enhance blood cell production) may be needed. Outpatient treatment is still possible, even in these cases. However, if fever or other signs of infection occur, hospitalization and administration of antibiotics may be necessary. For more information, see the free LLS publication *Blood Transfusion*.

Follow-up Care. Follow-up care is important with both aggressive and indolent forms of NHL because, even if the disease recurs, curative options are still available for many people. Follow-up care needs to be individualized and should be based on several factors, including how the disease initially manifested. Patients who are in remission should continue to be monitored with CT scans or other diagnostic imaging every several months or less frequently as determined by their doctor. They should also be examined regularly by their doctors. Periodic assessment of the patient's state of health, blood cell counts and, if necessary, marrow is important. Over time, the interval between assessments may be lengthened, but assessments should be continued indefinitely.

Treatment Considerations for Children, Adolescents and Young Adults. NHL accounts for an estimated 4 percent of cancers in children younger than 15 years. Burkitt lymphoma is the predominant NHL subtype in children aged 5 through 14 years.

Children and adolescents with NHL should be referred to medical centers that have a specialized pediatric oncology team to ensure that young patients receive optimal treatment, support and follow-up. It is important for young adults and parents of children diagnosed with NHL to talk to members of the oncology team about the stage and the specific subtype of NHL. Doctors use this information about the patient's disease in order to determine the most effective therapy. It is also important to discuss the planned therapy with members of the oncology team to learn about the drugs, potential side effects and long-term effects and the treatment schedule. See *Pretreatment Considerations*, above.

Different treatment strategies may be used for children and for adults with NHL. The choice of therapy for adolescents and young adults can be challenging and is a topic of ongoing research. Pediatric treatment strategies are currently used to treat adults who have certain subtypes of NHL, including Burkitt lymphoma and lymphoblastic lymphoma. Adolescents and young adults should consider being evaluated and treated in a pediatric oncology setting or with a pediatric protocol as part of a clinical trial.

Clinical trials are generally designed to compare potentially more effective therapy with therapy that is currently accepted as standard. One of the main treatment advances in recent times is the ability of doctors to develop treatment plans that limit the amount of therapy required to bring about remission. Our LLS Information Specialists, (800) 955-4572, offer guidance on how patients can work with their doctors to find out if a specific clinical trial is an appropriate treatment option. Information Specialists will conduct individualized clinical-trial searches for patients, family members and healthcare professionals. This service is also available on our website at www.LLS.org/clinicaltrials.

Childhood, adolescent and young adult cancer survivors require close follow-up because cancer therapy side effects may persist or develop months or years after treatment. See the free LLS publication *Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma Facts* for more information.

Treatment–Aggressive Subtypes, Part 1

The information in this section applies to

- Diffuse large B-cell lymphoma (DLBCL)
- Anaplastic large cell lymphoma (ALCL)
- Most peripheral T-cell lymphoma subtypes
- Transformed follicular lymphoma (see *Diffuse Large B-cell Lymphomas* below)
- Transformed MALT lymphoma (see *Diffuse Large B-cell Lymphomas* below).

The goal of treatment for many types of aggressive lymphoma is a cure. Every patient's situation should be evaluated individually by an oncologist who specializes in treating NHL and who will discuss the disease subtype, stage and treatment options with the patient. It is also important to seek treatment at a center with experience in treating NHL.

Treatment for these subtypes starts at the time of diagnosis. Patients with fast-growing NHL are frequently treated with chemotherapy that consists of four or more drugs. In most cases this is the combination therapy called R-CHOP (rituximab [Rituxan®] plus cyclophosphamide [Cytoxan®], doxorubicin [hydroxydoxorubicin], Oncovin® [vincristine] and prednisone). This intensive, multidrug chemotherapy can be very effective for aggressive lymphoma, and cures can be achieved.

Diffuse Large B-Cell Lymphomas (DLBCL). This is the most common NHL subtype and represents about 30 percent of cases of NHL diagnosed in the United States. With DLBCL, the lymphoma cells are spread diffusely throughout the lymph node, disrupting normal lymph node structure in a uniform pattern. DLBCL development usually starts in lymph nodes in the neck or abdomen and is characterized by masses of large B cells (lymphocytes). It is often widespread in the body and includes

- Tumor masses composed of large B lymphocytes
- Extranodal involvement (tumor masses outside the lymph nodes in other sites of the body)
- Fever and drenching night sweats.

DLBCL may be the initial diagnosis, or an indolent lymphoma, such as a small B-cell lymphoma or a follicular lymphoma, may have transformed and become a DLBCL. It most commonly occurs in middle-aged and older persons. Most cases have no known cause. Gene expression profiling has been used to define groups of patients who may have different responses to therapy or who may have a different clinical behavior based on the number and types of genes that are more

active or less active in the tumor sample. To date, gene expression profiling studies have distinguished three molecular subtypes of DLBCL called "germinal center B-cell-like" (GCB), "activated B-cell-like" (ABC), and "primary mediastinal B-cell lymphoma" (PMBL). These distinct DLBCL subtypes arise due to specific genetic changes.

According to some studies, treatment outcomes for DLBCL patients who appear to have the GCB type were significantly better than treatment outcomes for patients who have the ABC subtype. A number of clinical trials are under way to investigate whether using novel approaches to therapy will improve treatment outcomes for patients who do not have the GCB subtype. For more information, talk to your doctor or contact an Information Specialist.

DLBCL is frequently treated with chemotherapy made up of four or more drugs. A common combination is cyclophosphamide (Cytoxan®), doxorubicin (hydroxydoxorubicin), vincristine (Oncovin®), and prednisone with rituximab (Rituxan®) (R-CHOP). Rituxan is indicated for previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens. This combination can be very effective; about 50 to 60 percent of patients with DLBCL are cured with this treatment regimen. At this time, there is no standard maintenance treatment for DLBCL. Studies are ongoing to see if maintenance treatment is an appropriate option for patients. If you are interested in participating in a clinical trial, talk to your doctor or an Information Specialist.

If you want to read about follicular lymphoma or transformed follicular lymphoma, please see page 29 for additional information.

If you want to read about transformed MALT lymphoma, please see page 31 for additional information.

Anaplastic Large Cell Lymphoma (ALCL). This subtype usually starts in lymph nodes and can spread to the skin, but it can also begin in the skin. Treatment with chemotherapy or radiation therapy is often successful, especially if the tumor cells contain a protein called "ALK-1." Brentuximab vedotin (Adcetris®), given by injection, is FDA-approved for the treatment of patients with systemic ALCL after failure of at least one prior multi-agent chemotherapy regimen. About 80 percent of patients with this subtype are cured. This disease is more common in young people.

Peripheral T-Cell Lymphoma. This aggressive subtype is one of the most difficult types of lymphoma to treat. Currently, it is mostly treated like DLBCL. Studies are under way to try to develop new treatment approaches, and patients are encouraged to seek out these trials. Subtypes include extranodal T-cell or natural killer cell (NK-cell) lymphoma; nasal type lymphoma, which often involves the upper airway passages, such as the nose and nasopharynx, but also invades the skin and gastrointestinal tract; enteropathy-type T-cell lymphoma, which can occur in people

who are sensitive to gluten; and subcutaneous panniculitis-like T-cell lymphoma, which invades the deepest layers of the skin and causes nodules to form under the skin. Many new drugs are under study for treatment of T-cell lymphoma.

Pralatrexate (Folotyn®) has been approved for patients with relapsed or refractory peripheral T-cell lymphoma. In addition, romidepsin (Istodax®) was approved by the FDA for the treatment of peripheral T-cell lymphoma patients who have received at least one prior therapy. For more information about peripheral T-cell lymphomas, including treatment options, see the free LLS publication *Peripheral T-Cell Lymphoma Facts*.

Examples of Specific Approaches to Therapy for Aggressive Subtypes. For early-stage disease, treatment includes the combination chemotherapy CHOP (cyclophosphamide [Cytoxan®], doxorubicin [hydroxydoxorubicin], Oncovin® and prednisone) with rituximab (Rituxan®) and/or involved-field radiation therapy. The standard of care for advanced-stage disease is R-CHOP. The number of chemotherapy cycles used depends upon stage and extent of disease. If the lymphoma is in the bone marrow, nasal sinuses or testicles, or if it is near the spinal cord, it may spread to the central nervous system. Therefore, chemotherapy may be given into the spinal fluid. Patients with high-risk disease based on prognostic factors may benefit from more aggressive initial treatment and should discuss clinical-trial options with their doctors. An elevated beta$_2$-microglobulin level, a high serum lactate dehydrogenase (LDH) level, expression of survivin (a protein that inhibits cell death), expression of cyclin D3, *p53* gene mutation and certain other factors are associated with higher risk for relapse after standard therapy. Imaging with FDG-PET may be used to assess response after therapy and determine if there is a need for more aggressive therapy. Relapse is more common in the first two to three years after diagnosis but is rare four years after diagnosis.

When many lymphoma cells are killed simultaneously by therapy, the amount of uric acid (a breakdown product of cells that enters the blood and is excreted in the urine) increases and can interfere with heart and kidney function. Patients with a high level of uric acid may be given the drug allopurinol (Zyloprim®) to minimize the buildup of uric acid in the blood. Allopurinol is taken by mouth. Another drug, rasburicase (Elitek®), given as a single intravenous dose, can rapidly lower an elevated uric acid level.

Refractory or Relapsed Disease. In some patients, NHL does not respond to initial treatment. This is called "refractory" disease. There are other patients who have a return of their lymphoma after achieving a remission. This is referred to as "relapsed" disease.

Most patients with refractory or relapsed disease receive second-line therapy, in some cases followed by allogeneic or autologous stem cell transplantation. Second-line regimens may include ifosfamide, carboplatin, and etoposide (ICE),

sometimes with the addition of Rituxan (RICE); dexamethasone, cytarabine and cisplatin (DHAP); or etoposide, methylprednisolone, high-dose cytarabine and cisplatin (ESHAP), sometimes with the addition of Rituxan (R-ESHAP).

Autologous stem cell transplantation after high-dose chemotherapy may be an option for some patients with lymphoma who have relapsed after R-CHOP chemotherapy. Autologous stem cell transplantation permits more patients and older patients with relapse of their disease to receive intensive chemotherapy and rescue of their marrow function by infusion of stem cells. It may not be as effective in treating the disease as allogeneic transplantation. However, allogeneic transplant is not used as often, is highly more toxic and is considered a last option. If an autologous transplant is not an option, because of either older age or medical complications, then treatment in clinical trials can be explored.

Treatment–Aggressive Subtypes, Part 2

The information in this section applies to

- Acquired immunodeficiency syndrome (AIDS)-associated lymphoma
- Burkitt lymphoma
- Central nervous system (CNS) lymphoma
- Mantle cell lymphoma
- Precursor B- and T-cell lymphoma/leukemia

AIDS-associated Lymphoma. The types of NHL that are most often seen in people with AIDS are diffuse large B-cell lymphoma, Burkitt lymphoma and primary central nervous system (CNS) lymphoma. Treatment outcomes are affected by how well the patient with AIDS is responding to treatment and managing the effects of chemotherapy on blood counts. The number of people developing AIDS-associated NHL has decreased in the last several years because of improved HIV treatment.

Burkitt Lymphoma. This aggressive B-cell subtype represents about 2.5 percent of NHL cases, usually appears as abdominal masses of lymphoma cells and is not uniformly associated with the Epstein-Barr virus. It may involve the marrow, blood, CNS and other organs. More than half of those treated can be cured with current therapies.

Burkitt lymphoma was first brought to wide attention by Dennis Burkitt, MD, FRS, a surgeon working in equatorial Africa. There, the disease usually appears in children as a mass in a facial bone, especially the jaw, and signs of the Epstein-Barr virus are usually found in the lymphoma cells along with an abnormality of chromosome 8. In Africa, both the chromosomal abnormality and viral infection are thought to play a causal role in the onset of Burkitt lymphoma. Burkitt lymphoma occurs far less frequently in other parts of the world. Highly aggressive

chemotherapy is used to treat this type of NHL, often requiring admission to the hospital. Commonly used agents include prednisone, cyclophosphamide, vincristine, cytarabine, doxorubicin and methotrexate.

Central Nervous System (CNS) Lymphoma. Primary central nervous system lymphoma forms in the brain and/or the spinal cord. It occurs most often as a feature of AIDS-associated lymphoma, but may be related to other NHL subtypes. Secondary CNS lymphoma starts with lymphoma in other parts of the body and then spreads to the brain and/or the spinal cord.

Both primary and secondary CNS lymphomas are uncommon. Treatment options depend on the stage, location of the disease within the central nervous system, whether the disease has just been diagnosed or has recurred and the patient's age and general health. Treatment may consist of standard therapy or treatment that is being studied in a clinical trial. Standard treatment may include chemotherapy, glucocorticoid drugs and/or radiation therapy. Immunotherapy and high-dose chemotherapy with stem cell transplantation are examples of treatments for CNS lymphoma that are being studied in clinical trials.

Mantle Cell Lymphoma. Mantle cell lymphoma represents about 6 percent of NHL cases. The malignant cells originate from a lymphocyte in the mantle zone of a lymph node. This subtype usually occurs in people over 50 years of age and is found four times more frequently in men than it is in women. The disease is usually already widespread at diagnosis, involving lymph nodes, the marrow and sometimes the liver, intestines and spleen. For more information about mantle cell lymphoma, including treatment options, see the free LLS publication *Mantle Cell Lymphoma Facts*.

Precursor B- and T-Cell Lymphoma/Leukemia. Precursor B- and T-cell lymphoblastic lymphoma or leukemia are rare, aggressive diseases that can develop in either B cells or T cells. Disease that is predominantly in the marrow is described as "leukemia," whereas disease that is predominantly in tissue outside of the marrow is described as "lymphoma." Most cases of acute lymphoblastic leukemia arise in B cells, and most cases of lymphoblastic lymphoma arise in T cells. Acute lymphoblastic leukemia diagnosis and treatment is described in detail in the free LLS publication *Acute Lymphoblastic Leukemia*. Treatment for newly diagnosed patients with precursor T-cell lymphoblastic lymphoma or leukemia is aggressive chemotherapy and radiation. Nelarabine (Arranon®) is FDA-approved for the treatment of patients with T-cell lymphoblastic lymphoma or T-cell lymphoblastic leukemia whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

Patients who are diagnosed with precursor T-cell lymphoblastic lymphoma or leukemia are encouraged to speak to their doctors or contact an LLS Information Specialist to learn about clinical trials that may be available.

Treatment–Indolent Subtypes

The information in this section applies to

- Follicular lymphoma
- Cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome)
- Lymphoplasmacytic lymphoma and Waldenström macroglobulinemia
- Marginal zone lymphoma
- Small cell lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL).

The management of indolent lymphoma subtypes at initial diagnosis ranges from observation with careful monitoring (sometimes called "watch and wait") to aggressive therapy. Appropriate management for any given patient is highly individual and depends on factors that include the patient's

- Prognostic factors
- Stage of disease
- Age and other medical conditions.

Most cases of indolent B-cell lymphoma such as follicular lymphoma and small cell lymphocytic lymphoma are chronic illnesses that should be treated when indicated. Current data suggest that there is no initial treatment that fundamentally alters patients' survival rates. In indolent lymphoma, deferring initial treatment is often a very appropriate treatment option.

The Watch-and-Wait Approach. Many doctors consider observation (watch and wait) to be an active form of therapy, involving careful monitoring and follow-up. Patients need to discuss the potential benefits of the watch-and-wait approach versus initiating chemotherapy and/or other therapies. Studies comparing watching and waiting to initial therapy have shown no survival advantage in the group of patients who were treated at diagnosis, compared to those who were observed. Studies are ongoing, and one trial showed that treating with rituximab (Rituxan®) increased the time until a patient needed chemotherapy compared to watch and wait. However, no major difference in quality of life was observed, and the overall survival was the same. More studies need to be done to confirm this data.

There are patients with indolent lymphoma who need aggressive initial therapy. However, patients with no symptoms and a small volume of disease frequently can be observed over long periods of time. Some studies indicate that watching and waiting allows about half of the patients to defer their treatment for at least three years. Some patients who have been in watch-and-wait mode for more than 10 years have never needed treatment. In most cases, treatment is begun at the time of diagnosis for patients with widespread disease. However, a watch-and-wait approach may be indicated for patients with widespread disease at initial diagnosis if their therapy options are not curative and if they are not burdened by their disease,

or do not meet other indications for treatment. Some patients may remain stable for years and thus avoid the side effects of unnecessary therapy. Therapy should be started for a patient who shows signs of lymphoma progression, such as newly involved or enlarging lymph nodes, bone or other organ involvement or a decrease in blood cell formation that causes low red blood cell, white blood cell or platelet counts. The specific decision to treat follicular lymphoma is made collaboratively by the oncologist and patient. Each case is evaluated individually and approaches vary between patients.

Treatment Options. When patients with indolent lymphoma are treated, it is often with one to five drugs, radiation, radioimmunotherapy or a clinical trial. Rituxan® has been an important addition to traditional drug therapy programs. It is approved to treat diffuse large B-cell lymphoma as well as indolent lymphoma patients with

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy
- Nonprogressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy
- Advanced follicular, CD20-positive, B-cell NHL as a single-agent maintenance treatment, after response to initial treatment with Rituxan plus chemotherapy (induction treatment).

Slow-growing lymphoma often comes back after treatment, and new drug combinations may be required later. A series of remissions lasting a number of years often occurs, and patients can continue their usual activities for very long periods of time. Patients with low-grade lymphoma whose disease continues to progress after receiving other forms of treatment may benefit from autologous stem cell transplantation.

Follicular Lymphoma (FL). In follicular lymphoma the abnormal smaller B-cell lymphoma cells are grouped in clusters or follicles throughout the lymph node. This is the second most frequent type of lymphoma, accounting for about 20 percent of cases of NHL. FL cells often have a specific chromosome abnormality (a translocation between parts of chromosomes 14 and 18) that causes the overexpression of a gene, *BCL-2*, and makes the cells resistant to therapy. However, treatment may keep the disease in check for many years, even when tests show that disease remains in some parts of the body. FL has a relatively high rate of transforming into a more aggressive disease.

Follicular Lymphoma Treatment. Stage I or stage II FL may be treated with

- Radiation therapy
- Chemotherapy/Rituxan followed by radiation therapy
- Watch and wait (patients with less advanced disease can be observed with periodic examinations and imaging tests).

Some patients with FL who respond to treatment may be followed without any need for further therapy. However, periodic observation continues to be important to identify patients who need additional treatment.

For patients with stage II FL with large lymph nodes, stage III or IV FL, or advanced-stage relapsed FL, treatment will be based on symptoms, the amount of disease and the patient's choices.

A FL patient who requires treatment may want to consider taking part in a clinical trial.

Other treatment options include

- Radiation to lymph nodes that are causing symptoms, or to a large localized mass, if one is present
- Chemotherapy drugs in combination with Rituxan. These may be single drugs such as, cyclophosphamide, chlorambucil or bendamustine (Treanda®), or combinations of drugs such as cyclophosphamide, vincristine, and prednisone (CVP)
- A radioactive monoclonal antibody, such as yttrium-90-ibritumomab tiuxetan (Zevalin®). Zevalin is a radioimmunotherapeutic agent that is approved for relapsed or refractory CD20-positive, low-grade, follicular or transformed B-cell lymphoma and for previously untreated follicular NHL patients who achieve a partial or complete response to first-line chemotherapy
- Stem cell transplantation for some patients (see the free LLS publication *Blood and Marrow Stem Cell Transplantation*)
- Observation without any specific treatment (watch and wait)
- Maintenance Rituxan after completion of initial therapy with either Rituxan alone or Rituxan in combination with chemotherapy. This involves a single dose of Rituxan administered on a prescribed schedule (generally every 2-3 months). Rituxan maintenance may last for two years.

Transformed Follicular Lymphoma (FL). FL has a relatively high rate of transforming into an aggressive large B-cell lymphoma. Patients with transformed FL appear to benefit from high-dose therapies along with autologous stem cell transplantation. (See *Diffuse Large B-cell Lymphomas*, page 22.)

A clinical trial may be a good option for patients with disease that transforms after several different treatment approaches have been tried. Other options include

- Chemotherapy with or without Rituxan®
- Treatment with a radioimmunotherapeutic monoclonal antibody, such as Zevalin®
- Radiation therapy
- Supportive care.

For FL that is in a single area and transforms early in treatment, combination chemotherapy with Rituxan, or combination chemotherapy with Rituxan and radiation therapy, are two possible treatment approaches.

Treatment for transformed FL may include autologous stem cell transplantation within a clinical trial. When an autologous stem cell transplant is an option, stem cells should be collected before treatment with radioimmunotherapy.

The Follicular Lymphoma International Prognostic Index (FLIPI). The FLIPI is a scoring system used to predict which patients with follicular lymphoma may be at higher risk for disease recurrence. This information helps doctors to determine appropriate care for patients who have been treated for FL. One point is assigned for each of the following risk factors (also known by the acronym NoLASH): more than four lymph **No**des involved; elevated serum **L**actate dehydrogenase (LDH) level; **A**ge greater than 60 years; **S**tage III or IV disease; and low **H**emoglobin concentration (less than 12 g/dL). Each point represents some increased risk for disease recurrence. The total number of points identifies the following risk groups: low risk (0-1 points); intermediate risk (2 points); high risk (3-5 points). Patients may want to discuss risk factors with their doctor in order to understand treatment options, including participation in clinical trials.

Cutaneous T-Cell Lymphoma (Mycosis Fungoides and Sézary Syndrome). This NHL subtype principally involves the skin and lymph nodes; in advanced disease, other organs are also involved. The lymphoma originates in a T cell. The disease may come and go for many years and may be difficult to diagnose with certainty in its early phases, even with a skin biopsy. It may be referred to as "mycosis fungoides" when there is prominent skin involvement. The malignant lymphocytes can enter the blood and, in sufficient number, can mimic some features of chronic lymphocytic leukemia. The lymphocytes that accumulate in the blood have, on close inspection, characteristic folding of their nuclei. When the disease has these features it may be called "Sézary syndrome." Both mycosis fungoides and Sézary syndrome are now usually referred to as "cutaneous T-cell lymphoma."

Therapy for cutaneous T-cell lymphoma depends on the nature of the skin lesions and whether disease is present in the lymph nodes. Topical therapies are among the approaches used to treat the skin lesions. These include drugs applied directly to the skin and two different forms of therapy based on exposing skin lesions to light—ultraviolet light therapy and electron beam therapy. Ultraviolet light is used in conjunction with psoralen and is often referred to as PUVA (psoralen and ultraviolet A) therapy. If there is widespread involvement of lymph nodes and other sites, single- or multidrug chemotherapy or photopheresis can be used depending on the objective of therapy and the rate of disease progression.

For more information about cutaneous T-cell lymphoma, see the free LLS publication *Cutaneous T-Cell Lymphoma Facts*.

Lymphoplasmacytic Lymphoma and Waldenström Macroglobulinemia. Lymphoplasmacytic lymphoma and Waldenström macroglobulinemia are closely related, slow-growing types of lymphoma that originate in a B-lymphocyte precursor.

In lymphoplasmacytic lymphoma, the lymph nodes are more involved than in Waldenström macroglobulinemia. Both disorders show malignant lymphoplasmacytic cells in the marrow and spleen. Lymphoplasmacytic lymphoma is usually diagnosed by lymph node biopsy, while Waldenström macroglobulinemia is diagnosed by marrow examination. These two types of lymphoma account for less than 2 percent of NHL cases. The malignant lymphoplasmacytic cells in both disorders secrete an abnormal protein, monoclonal immunoglobulin M (IgM). If the monoclonal IgM levels in the blood become elevated enough, patients experience increased blood viscosity, inadequate blood flow, and symptoms and signs of limited blood flow (for example, headache, visual blurring, mental confusion). This is referred to as "hyperviscosity syndrome," which may require urgent intervention.

Hyperviscosity syndrome can be treated by plasmapheresis (a process in which plasma is separated from whole blood and the rest is returned to the patient) to reverse acute symptoms and signs, but long-term control requires a reduction in the mass of lymphoma cells that make the protein. One option is to take a watch-and-wait approach, followed by multidrug chemotherapy and a monoclonal antibody, if indicated. If the disease appears to be progressive, therapy may be administered at the time of diagnosis. Progressed disease may also involve the lungs, the gastrointestinal tract and other organs.

For more information about Waldenström macroglobulinemia, see the free LLS publication *Waldenström Macroglobulinemia Facts*.

Marginal Zone Lymphoma. This indolent B-cell lymphoma subtype may be extranodal (disease outside of the lymph nodes) or nodal (disease within the lymph nodes). The disease tends to remain localized. Marginal zone lymphomas include

- Mucosa-associated lymphoid tissue (MALT) lymphoma, which affects sites outside the lymph nodes such as the gastrointestinal tract, eyes, thyroid gland, salivary glands, lungs or skin, and represents about 7.5 percent of NHL cases. Patients with MALT lymphoma may have a history of autoimmune disease. A higher incidence of MALT lymphoma involving the stomach is seen in patients who have been infected with the bacterium *Helicobacter pylori* (*H. pylori*). Bacteria have also been implicated in other forms of MALT lymphoma. Treatment often includes potent combinations of antibiotics, which both eradicate the *H. pylori* infection and cause the lymphoma to regress. Many patients with *H. pylori* have been cured of MALT lymphoma without radiation or chemotherapy.
- Transformed MALT lymphoma is an aggressive lymphoma and is uncommon. For this small subset of patients, MALT lymphoma can transform into diffuse large B-cell lymphoma (DLBCL). These patients have shown to benefit from treatments used for DLBCL. See *Diffuse Large B-cell Lymphomas* on page 22.

- Nodal marginal zone B-cell lymphomas, also known as "monocytoid B-cell lymphomas," which may be found in the spleen and blood. This form of NHL is uncommon, accounting for less than 2 percent of NHL cases, and is generally treated like follicular lymphoma. See *Follicular Lymphoma Treatment* on page 28.

- Splenic marginal zone lymphoma (SMZL), an indolent lymphoma, is diagnosed in less than 1 percent of all NHL patients. SMZL typically affects patients older than 50 years. One of the first signs of SMZL is an enlarged spleen; however, symptoms can be slow to develop. Category B symptoms (see page 16) are not common, but patients may experience fatigue. The bone marrow and blood are often involved.

  To diagnose this type of lymphoma, a doctor will order a CT scan, bone marrow biopsy and additional blood tests. SMZL has been associated with hepatitis C infection. Treatment for hepatitis C with interferon (alone or in combination with ribavirin), may result in a remission of the patient's lymphoma. If the patient does not have hepatitis C or any symptoms, the first treatment is observation and follow-up, often called "watch and wait." See *The Watch and Wait Approach* on page 27.

  When treatment is needed, it is usually because of an enlarged spleen that is causing symptoms or low white blood cell counts. Symptoms of an enlarged spleen include being unable to eat a large meal and/or having a feeling of discomfort, fullness or pain on the upper left side of the abdomen. If the patient has an enlarged spleen, removal of the spleen (splenectomy) is the preferred treatment for SMZL.

  For patients who cannot have surgery, chemotherapy and/or rituximab (Rituxan®) may be considered. Some of the chemotherapy combinations used include CVP (cyclophosphamide [Cytoxan®], vincristine [Oncovin®] and prednisone) or CHOP (cyclophosphamide [Cytoxan], doxorubicin [hydroxydoxorubicin], Oncovin [vincristine] and prednisone). Fludarabine (Fludara®) alone or in combination with cyclophosphamide may also be used with Rituxan.

  Rituxan alone may be the treatment of choice for older patients and for patients who have impaired kidney function.

  Clinical trials are currently researching new treatment approaches for SMZL. Speak to your doctor or an LLS Information Specialist to find out more about clinical trials.

Small Cell Lymphocytic Lymphoma (SLL) and Chronic Lymphocytic Leukemia (CLL). Small cell lymphocytic lymphoma and chronic lymphocytic leukemia are highly similar subtypes with regard to

- Incidence (median age of patients is 65 years)
- Signs and symptoms (usually widespread enlarged lymph nodes [lymphadenopathy] and slight marrow and blood involvement)

- Disease progression (may be very slow)
- Treatment.

SLL primarily involves lymph nodes or lymphoid tissue and represents about 7 percent of NHL cases. CLL is primarily a disease of the blood and marrow, but CLL cells may travel to the lymph nodes.

Bendamustine (Treanda®) is a chemotherapy agent that was approved by the FDA for the treatment of patients with CLL and for patients with indolent B-cell NHL who have progressed during or within six months of treatment with rituximab (Rituxan) or a Rituxan-containing regimen.

Localized SLL is an uncommon disease. Radiation alone to the specific site is a treatment option that should be discussed with the doctor.

For more information about CLL, see the free LLS publication *Chronic Lymphocytic Leukemia*.

Side Effects of Treatment for Non-Hodgkin Lymphoma

The side effects of treatment for lymphoma depend on the intensity and type of treatment (such as the location of the radiation therapy), the age of the patient, and coexisting medical conditions (for example, diabetes mellitus and chronic renal disease). In addition, certain drugs have a tendency to affect certain tissues (for example, the tendency of vincristine to affect nerve tissue).

In recent years, new drugs and other therapies have increased doctors' ability to control side effects that are troubling for many patients, such as nausea and vomiting. When side effects do occur, most are short-lived and resolve when therapy is completed. The benefit of treatment, with its goal of remission (and, in some cases, cure) largely outweighs the risks, discomfort and unpleasantness. For more information, see the free LLS publication *Understanding Side Effects of Drug Therapy*.

Suppressed Blood Cell Formation. Decreases in blood cell counts may occur in patients treated with chemotherapy. Blood transfusions may be necessary for some patients with low blood cell counts. If decreases in white blood cell counts are severe and continue over extended periods of time, infection may develop and require antibiotic treatment. Sometimes, chemotherapy dosages or the time between chemotherapy cycles must be altered to allow the patient's blood counts to recover from the effects of treatment. Sometimes, a granulocyte-colony stimulating factor is used to support the release of white blood cells from the bone marrow into the blood stream. This is a subcutaneous injection given to increase the white blood cells that help prevent infection.

Oral and Gastrointestinal Effects. Treatment for lymphoma may cause mouth sores, nausea, vomiting, diarrhea, constipation, bladder irritation and blood in the urine. However, the medications available to prevent nausea and vomiting are quite effective causing these to occur infrequently.

Other Effects. Therapy can induce extreme fatigue, fever, cough, lung function impairment, cardiac function impairment, and allergies ranging from mild to severe. Patients may also experience rashes, hair loss, weakness, nerve function impairment ranging from tingling sensations to (infrequently) more serious impairment of function, and other effects. These diverse effects depend on the drugs and dosages used and on the individual patient's susceptibility. For example, vincristine (Oncovin®) can cause nerve damage called "neuropathy." Initially, the patient experiences numbness and tingling in the fingertips and toes. The sensation might come and go, but if it continues, it may become permanent. Then, in general, the treatment options are limited. Therefore, it is important that the patient be monitored for these side effects between each cycle of chemotherapy that includes vincristine. If the neuropathy becomes severe, the dosing of vincristine may need to be adjusted.

NHL patients are advised to receive certain vaccinations once they have finished their treatment, including vaccinations for pneumococcal pneumonia and influenza. There are two types of pneumococcal vaccines available for adults: a pneumococcal polysaccharide vaccine (PPSV23) and a pneumococcal conjugate vaccine (PCV13). Immunizations using live organisms or with high viral loads, such as the herpes zoster or shingles vaccine, should not be administered. Your doctor can give you more information.

Children may experience side effects of treatment both in the short- and long-term that can affect learning. For more information, see the free LLS publication *Learning & Living With Cancer: Advocating for your child's educational needs*.

Long-Term and Late Effects of Treatment for Non-Hodgkin Lymphoma

Long-term effects of cancer therapy are medical problems that persist for months or years after treatment ends. Treatment-related fatigue and fertility issues are examples of possible long-term effects. Late effects are medical problems that do not develop or become apparent until years after treatment ends. Two examples of late effects are heart disease and second cancers.

Long-term and late effects range from mild to severe. Various factors can influence the risk, including the type and duration of treatment, the patient's age at time of treatment, gender and overall health. Many survivors of NHL do not develop significant long-term or late effects of treatment. However, it is important for all adult patients and for parents of children who will be treated for NHL to discuss possible long-term and late effects with members of the treatment team so that the proper planning, evaluation and follow-up care can take place.

For more information, see the free LLS publications *Fertility*; *Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma Facts;* and *Long-Term and Late Effects of Treatment in Adults Facts*.

Research and Clinical Trials

New approaches under study in clinical trials for NHL treatment, many of which are being supported by LLS research programs, hold the promise of increasing the rate of remission and finding a cure for NHL.

Clinical Trials. Every new drug or treatment regimen goes through a series of studies called "clinical trials" before it becomes part of standard therapy. Clinical trials are carefully designed and rigorously reviewed by expert clinicians and researchers to ensure as much safety and scientific accuracy as possible. Participation in a carefully conducted clinical trial may be the best available therapy. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, at (800) 955-4572, can offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. Information Specialists will conduct individualized clinical-trial searches for patients, family members and healthcare professionals. This service is also available at www.LLS.org/clinicaltrials.

Research Approaches. There are clinical trials for newly diagnosed patients and for patients with relapsed or refractory disease. A number of approaches are under study in clinical trials for the treatment of patients with NHL.

Agents Under Study. The following are examples of specific agents under study.

- The chemotherapy agent bendamustine (Treanda®), approved for chronic lymphocytic leukemia (CLL) and relapsed indolent NHL, is being studied in newly diagnosed mantle cell lymphoma, with rituximab (Rituxan®) and lenalidomide (Revlimid®).
- Bortezomib (Velcade®), a drug called a "proteasome inhibitor" that is approved to treat patients with mantle cell lymphoma who have received at least one prior therapy, is now being investigated for effectiveness as part of initial treatment for mantle cell lymphoma. Researchers are also exploring the use of Velcade in combination with other agents such as Treanda and lenalidomide (Revlimid®).
- Agents called "histone deacetylase (HDAC) inhibitors" are a class of drugs that address "epigenetic" changes in the DNA. One HDAC inhibitor, vorinostat (Zolinza®), which controls how DNA is regulated, is approved for treatment of patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following treatment with two systemic therapies. This agent is now being studied to treat T-cell and B-cell lymphoma both alone and in combination with other drugs.
- The immunomodulatory drug Revlimid is being studied as treatment for diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma and chronic lymphocytic leukemia (CLL).
- The monoclonal antibody therapy yttrium-90-ibritumomab tiuxetan (Zevalin®) has been approved for relapsed low-grade lymphoma and for previously untreated follicular NHL patients who achieve a partial or complete response to first-line chemotherapy. The effectiveness of this agent is now being studied in the retreatment of lymphoma, as therapy for newly diagnosed indolent lymphoma, as therapy for aggressive forms of NHL in combination with or following other drug regimens and as part of high-dose therapy programs along with autologous stem cell transplantation.
- Ofatumumab (Arzerra®) is a monoclonal antibody approved for relapsed CLL and is now being studied in clinical trials in various combinations for the treatment of chronic lymphocytic leukemia, diffuse large B-cell lymphoma and follicular lymphoma.
- Pralatrexate (Folotyn®), approved for various T-cell lymphoma subtypes, is being studied in combination with other chemotherapy drugs. Pralatrexate is a type of chemotherapy that disrupts processes in cells that are required for cell replication.
- There are several other drugs under investigation that target B cell receptor signaling pathways inside the lymphoma cells. Some of these drugs include
  - Everolimus, an mTOR inhibitor, is being studied in combination with other treatments for previously treated NHL.

- Ibrutinib (Imbruvica™), a BTK inhibitor that is being studied in previously treated CLL/SLL and mantle cell lymphoma patients.
- Idelalisib, an oral PI3K delta inhibitor, which is being studied for the treatment of patients with indolent NHL that is refractory to Rituxan and to an alkylating agent containing chemotherapy. This drug is being developed as both a single agent and in combination with other therapy.
- Temsirolimus, an mTOR inhibitor, is currently being studied in combination with other treatments for previously treated NHL.

Gene Expression Profiling (GEP) and Tissue Microarrays (TMAs). These are tools that help us better understand the biology of lymphoma. GEP and TMAs help us characterize lymphoma more carefully. As an example, certain biomarkers in tumor cells are associated with a greater or lesser response to therapy and can serve as predictors indicating whether someone will relapse from therapy or whether their disease will behave either more or less aggressively. Some of the most important of these biomarkers are gene based. A tool used to analyze the activity of genes is called a "microarray."

Microenvironment. There is increasing focus on looking at the tumor microenvironment; that is, the cells that are associated with the tumor, rather than the tumor itself. In follicular lymphoma, certain cells that are actually found next to the tumor cells have been shown to predict a better or worse outcome.

Reduced-Intensity Stem Cell Transplantation (Nonmyeloablative Allogeneic Transplantation). Clinical trials are under way to determine the usefulness of this approach in older and sicker patients for many blood cancers, including some NHL subtypes. As a result, transplantation may be an option for patients aged 60 to 70 years. Patients being conditioned for a reduced-intensity transplant receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. Immunosuppressive drugs are used to prevent rejection of the graft (the donor immune cells), allowing the engrafted immune cells to attack the recipient's disease. The effectiveness of reduced-intensity transplantation is due to the graft-versus-lymphoma effect of the donor's lymphocytes rather than to high doses of chemotherapy.

Vaccines. Scientists are developing vaccines that stimulate the immune system to combat and suppress lymphoma cell growth. Unlike classic vaccines, they do not prevent the disease; but if used during remission, they stimulate the immune system to attack the residual lymphoma cells and prevent them from causing a relapse.

We encourage you to contact an Information Specialist and visit www.LLS.org/clinicaltrials for more information about specific treatments under study in clinical trials.

Normal Blood and Marrow and the Lymphatic System

Blood and Marrow. Blood is composed of plasma and cells suspended in plasma. Plasma is largely made up of water in which many chemicals are dissolved. These chemicals include

- Proteins
  - Albumin, the most common protein in blood
  - Blood-clotting proteins, made by the liver
  - Erythropoietin, a protein made by the kidneys that stimulates red cell production
  - Immunoglobulins, antibodies made by plasma cells in response to infections including those we develop from our vaccinations (such as poliovirus antibodies, which are made by normal plasma cells in the bone marrow)
- Hormones (such as thyroid hormone and cortisol)
- Minerals (such as iron and magnesium)
- Vitamins (such as folate and vitamin B_{12})
- Electrolytes (such as calcium, potassium and sodium)
- Antibodies, which are made by plasma cells.

The cells suspended in plasma include red blood cells, platelets and white blood cells (neutrophils, monocytes, eosinophils, basophils, and lymphocytes).

- The red blood cells make up a little less than half the volume of the blood. They are filled with hemoglobin, the protein that picks up oxygen in the lungs and delivers it to the cells all around the body; hemoglobin then picks up carbon dioxide from the body's cells and delivers it back to the lungs, where it is removed when we exhale.
- The platelets are small cells (one-tenth the size of red blood cells) that help stop bleeding at the site of an injury in the body. For example, when a person has a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of the vessel, clump together, and plug up the bleeding site with the help of blood-clotting proteins such as fibrin, and electrolytes such as calcium. Later, a firm clot forms. The vessel wall then heals at the site of the clot and returns to its normal state.

- The neutrophils and monocytes are white blood cells. They are called "phagocytes" (eating cells) because they can ingest bacteria or fungi and kill them. Unlike the red blood cells and platelets, the monocytes can leave the blood and enter the tissue, where they can attack the invading organisms and help combat infection. Eosinophils and basophils are types of white blood cells that respond to allergens or parasites.
- Most lymphocytes, another type of white blood cell, are found in the lymph nodes, the spleen and the lymphatic channels, but some enter the blood. There are three major types of lymphocytes: T lymphocytes (T cells), B lymphocytes (B cells) and natural killer (NK) cells. These cells are a key part of the immune system.

Marrow is a spongy tissue where blood cell development takes place. It occupies the central cavity of bones. In newborns, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have functioning marrow. The spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull contain the marrow that makes blood cells in adults. The process of blood cell formation is called "hematopoiesis." A small group of cells, the stem cells, develop into all the blood cells in the marrow by the process of differentiation (see Figure 4).

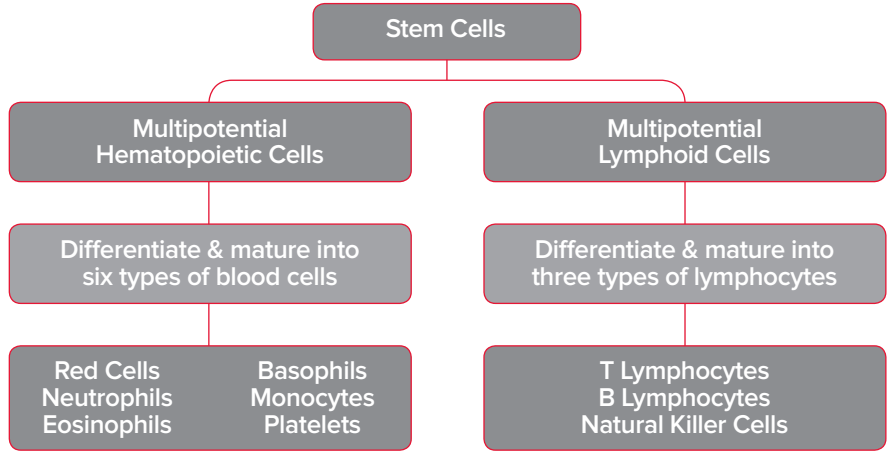


Figure 4. | **Stem cells** develop into blood cells (hematopoiesis) and lymphoid cells.

In healthy individuals, there are enough stem cells to keep producing new blood cells continuously. Blood passes through the marrow and picks up the fully developed and functional red and white blood cells and platelets for circulation in the blood.

Some stem cells enter the blood and circulate. They are present in such small numbers that they cannot be counted or identified by standard blood count tests. Their presence in the blood is important because they can be collected by a special technique. There are also methods to induce more stem cells to leave their home in the marrow and circulate in the blood, allowing a greater stem cell collection to occur. If enough stem cells are harvested from a compatible donor, they can be transplanted into a recipient.

Stem cell circulation, from marrow to blood and back, also occurs in the fetus. After birth, placental and umbilical cord blood can be collected, stored and used as a source of stem cells for transplantation.

The Lymphatic System. The marrow is really two organs in one. The first is the blood cell-forming organ. The second is the lymphocyte-forming organ and is a part of the immune system.

The marrow produces three main types of lymphocytes. They are

- B lymphocytes (B cells), which make antibodies in response to foreign substances (antigens), especially microbes
- T lymphocytes (T cells), which mature in the thymus. The T lymphocytes have several functions, including assisting B lymphocytes to make antibodies against invading bacteria, viruses or other microbes. The antibody attaches to the microbe, making it possible for other white blood cells to recognize the antibody and pull it into the cell along with its attached microbe (ingest it). The white cell then kills and digests the microbe
- Natural killer (NK) cells, which attack virus-infected cells without requiring antibody or other mediation. T cells and NK cells have other functions as well and are important elements in research efforts to design immunotherapies to treat lymphoma and other cancers.

The lymphocytes circulate through channels called “lymphatics,” which connect the lymph nodes to each other throughout the body. The lymphatic channels collect into large ducts that empty into blood vessels. Lymphocytes enter the blood via these ducts. Most lymphocytes are found in the lymph nodes and other parts of the lymphatic system such as the skin; spleen; tonsils and adenoids (special lymph nodes); intestinal lining; and, in young people, the thymus.

Medical Terms

For longer definitions of words or for definitions of words you do not see in this section, visit **www.LLS.org/glossary**.

Allogeneic Stem Cell Transplantation. A treatment that uses donor stem cells to restore a patient's marrow and blood cells. Allogeneic transplantation, an investigational therapy, may be considered in the treatment of indolent NHL, particularly for younger patients whose disease behaves more aggressively than the average indolent lymphoma. A type of allogeneic transplant called a "reduced-intensity" or "nonmyeloablative" transplant is under study. It uses lower doses of conditioning therapy and may be safer, especially for older patients. For more information, see the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

Anemia. A decrease in the number of red blood cells and, therefore, the hemoglobin concentration of the blood. This results in a diminished ability of the blood to carry oxygen. Severe anemia can cause a pale complexion, weakness, fatigue and shortness of breath on exertion.

Antibodies. Proteins released by plasma cells (derived from B lymphocytes) that recognize and bind to specific foreign substances called "antigens." Antibodies coat, mark for destruction or inactivate foreign particles such as bacteria, viruses or harmful toxins.

Antigen. A foreign substance, usually a protein, that stimulates an immune response when it is ingested, inhaled or comes into contact with the skin or mucous membranes. Examples of antigens are bacteria, viruses or allergens. Antigens stimulate plasma cells to produce antibodies.

Antioncogene. See Tumor Suppressor Gene.

Apheresis. The process of removing certain components of a donor's blood and returning the unneeded parts to the donor. The process, also called "hemapheresis," uses continuous circulation of blood from a donor through a specialized machine and then back to the donor. Apheresis makes it possible to remove desired elements from large volumes of blood. Platelets, red blood cells, white blood cells and plasma can be removed separately.

Autologous Stem Cell Transplantation. A treatment that uses a patient's own stem cells to delay the progression of certain blood cancers. The autologous transplantation process takes place after the patient achieves a complete response (remission), or a good partial response, to induction drug therapy. For diffuse large b-cell lymphoma, mantle cell lymphoma, and follicular lymphoma, an autologous transplant in first remission may be a good treatment option. For more information, see the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

***BCL-2* Gene Rearrangement.** Rearrangement in the *BCL-2* gene that occurs in B cells and is present in many cases of follicular lymphoma, diffuse large B-cell lymphoma and other cancers.

Biopsy. A procedure to obtain tissue for diagnosis. In many cases, a special needle can be used to obtain the tissue. In some cases, a larger piece of tissue may be surgically removed. Since the appearance of a lymph node is important in categorizing the type of lymphoma that may be present, surgical removal of an entire, swollen lymph node or nodes may be necessary (lymph node biopsy).

Bone Marrow. A spongy tissue in the hollow central cavity of the bones that is the site of blood cell formation. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. In these sites, the marrow is filled with fat cells. When marrow cells have matured into blood cells, they enter the blood that passes through the marrow and are carried throughout the body.

Bone Marrow Aspiration. A test to examine marrow cells to detect cell abnormalities. A marrow sample is usually taken from the patient's hip bone. After medication is given to numb the skin, the liquid sample is removed using a special needle inserted through the bone into the bone marrow.

Bone Marrow Biopsy. A test to examine marrow cells to detect cell abnormalities. This test differs from a bone marrow aspiration in that a small amount of bone filled with marrow is removed, usually from the hip (pelvic) bone. After medication is given to numb the skin, a special hollow biopsy needle is used to remove a core of bone containing marrow. Bone marrow aspiration and bone marrow biopsy may be done in the doctor's office or in a hospital. The two tests are almost always done together.

Bone Marrow Transplantation. See Allogeneic Stem Cell Transplantation; Autologous Stem Cell Transplantation.

Central Line (Indwelling Catheter). A special tubing inserted into a large vein in the upper chest. The central line, sometimes referred to as an "indwelling catheter," is tunneled under the skin of the chest to keep it firmly in place. The external end of the catheter can be used to administer medications, fluids or blood products or to withdraw blood samples. See Port.

Chemotherapy. The use of chemicals (drugs or medications) to kill malignant cells. Numerous chemicals have been developed for this purpose, and most act to injure the DNA of the cancer cells. When the DNA is injured, the cells cannot grow or survive.

Chromosome. Threadlike structures within cells that carry genes in a linear order. Human cells have 23 pairs of chromosomes: chromosome pairs 1 to 22 and one pair of sex chromosomes (X for females and Y for males). See Translocation.

Clonal. The designation for a population of cells derived from a single transformed parent cell. Virtually all cancers are derived from a single cell with an injury (mutation) to its DNA and thus are monoclonal. Leukemia, lymphoma and myeloma are examples of clonal cancers; that is, cancers derived from a single abnormal cell.

Cluster Designation (CD). A term used with a number to identify a specific molecule on the surface of an immune cell. It is commonly used in its abbreviated form, for example, "CD20" (the target of the monoclonal antibody therapy rituximab [Rituxan®]) and "CD52" (the target of the monoclonal antibody therapy alemtuzumab [Campath®]).

Colony-Stimulating Factor. See Growth Factor.

Computed Tomography (CT) Scan. A technique for imaging body tissues and organs. X-ray transmissions are converted to detailed images using a computer to synthesize x-ray data. The images are displayed as a cross-section of the body at any level from the head to the feet. A CT scan of the chest, abdomen or pelvis permits detection of an enlarged lymph node, liver or spleen. A CT scan can be used to measure the size of these and other structures during and after treatment.

CT Scan. See Computed Tomography Scan.

Cytogenetic Analysis. The process of analyzing the number and size of the chromosomes of cells. It detects chromosome alterations and in some cases, may identify the actual genes that have been affected. These findings help healthcare professionals diagnose specific types of blood cancers, determine treatment approaches and monitor the response to treatment. The individual who prepares and examines the chromosomes and interprets the results is called a "cytogeneticist."

Differentiation. The process by which stem cells give rise to functional cells of a single blood cell line. Differentiation of stem cells forms the red blood cells, platelets and white blood cells (neutrophils, monocytes, eosinophils, basophils and lymphocytes). See Hematopoiesis.

DNA. The genetic material in the cell. Deoxyribonucleic acid is the scientific name for DNA, which is made up of a sugar-phosphate backbone with ladderlike "steps" composed of purines and pyrimidines (building blocks of nucleic acids). The sequence of the purines and pyrimidines in the DNA is responsible for passing genetic information to new cells during the process of cell division; for passing genetic information from one generation to the next during reproduction; and for providing the instructions for building proteins, which in turn carry out the major functions of a cell. A mutation is generally a change in or loss of the sequence of the purines or pyrimidines of the DNA. Mutations can lead to cell death, to changes in the way a cell functions or, in some cases, to cancer.

DNA-Gene Chip. See Microarray.

Eosinophil. A type of white blood cell that participates in allergic reactions and helps fight certain parasitic infections.

Epigenetic Change. Any change that alters gene activity without changing the DNA sequence. While epigenetic changes are natural and essential to many of the body's functions, certain epigenetic changes can cause major adverse health effects, including cancer.

Erythrocytes. See Red Blood Cells.

Erythrocyte Sedimentation Rate. See Sedimentation Rate.

Extranodal Lymphoma. Lymphoma that has spread outside the lymph nodes to the organs—the thyroid, lungs, liver, bones, stomach or central nervous system. Doctors adjust their therapeutic approach if organs outside of lymph nodes are involved. If the brain, liver or bones are involved, for example, the treatment approach is likely to target these areas. If lymphoma is found in any of the organs but not in lymph nodes or multiple lymphatic sites, the disease is called a "solitary extranodal lymphoma."

FISH. See Fluorescence In Situ Hybridization.

Flow Cytometry. A test that permits the identification of specific cell types within a sample of cells. The test may be used to examine blood cells, marrow cells or cells from a biopsy. One use of flow cytometry is to determine whether a sample of cells is composed of T cells or B cells. This permits the doctor to determine if the leukemia or lymphoma is of the B- or T-cell type.

Fluorescence In Situ Hybridization (FISH). A technique for studying chromosomes in tissue using DNA probes tagged with fluorescent molecules that emit light of different wavelengths (and in different colors). The probes match to the chromosomes within the cells, and the chromosomes fluoresce in color.

G-CSF (Granulocyte-Colony Stimulating Factor). See Growth Factor.

Gene Expression Profiling. A research method that uses microarray analysis to identify a combination of genes that are turned off or on in response to a specific condition. A set of genes in a blood or tissue sample can be used to monitor the levels of thousands of genes at once.

GM-CSF (Granulocyte-Macrophage Colony Stimulating Factor). See Growth Factor.

Granulocyte. A type of white blood cell that has a large number of granules in the cell body. Neutrophils, eosinophils and basophils are types of granulocytes.

Growth Factor. A chemical used to stimulate the production of neutrophils and shorten the period of low neutrophil counts in the blood after chemotherapy. Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage

colony stimulating factor (GM-CSF) are examples of growth factors that are made commercially. GM-CSF can also stimulate monocytes.

Hemapheresis. See Apheresis.

Hematologist. A doctor who specializes in the treatment of blood cell diseases. This person is either an internist who treats adults or a pediatrician who treats children.

Hematopathologist. See Pathologist.

Hematopoiesis. The process of blood cell development in the marrow. The most undeveloped cells in the marrow are stem cells. They start the process of blood cell development. The stem cells begin to develop into young or immature blood cells such as red blood cells or white blood cells of various types. This process is called "differentiation." The young or immature blood cells then further develop into fully functional blood cells. This process is called "maturation."

The mature cells leave the marrow, enter the blood and circulate throughout the body. Hematopoiesis is a continuous process that is active normally throughout life. When the marrow is invaded with cancer cells, the constant demand for new blood cells cannot be met, resulting in a severe deficiency in blood cell counts.

HLA. The abbreviation for "human leukocyte antigen(s)." These antigens are proteins on the surface of most tissue cells, and they give an individual his or her unique tissue type. HLA factors are inherited from mother and father, and the greatest chance of having the same HLA type is between siblings. On average, one in four siblings is expected to share the same HLA type. The testing for HLA antigens is referred to as "tissue typing."

Immunophenotyping. A method that uses the reaction of antibodies with cell antigens to determine a specific type of cell in a sample of blood cells, marrow cells or lymph node cells. The antibodies react with specific antigens on the cell. A tag is attached to an antibody so that it can be detected. The tag can be identified by the laboratory equipment used for the test. As cells carrying their array of antigens are tagged with specific antibodies, they can be identified.

Immunotherapy. The term for several treatment approaches used by doctors to harness the body's immune system to treat lymphoma and other diseases. These therapies include monoclonal antibody therapy, radioimmunotherapy and vaccine therapy.

Monoclonal antibodies are proteins made in the laboratory that either react with or attach to antigens on the target cells. The antibodies are used therapeutically in three ways: as "naked" antibodies (monoclonal antibodies), as antibodies to which radioactive isotopes are attached (radioimmunotherapy), and as antibodies to which toxins are attached (immunotoxins). For more information, see the free LLS publication *Immunotherapy Facts*.

Indwelling Catheter. See Central Line.

Intrathecal. Designation for the space between the covering or lining of the central nervous system (CNS) and the brain or spinal cord. That lining is called the "meninges." In some situations, drugs have to be administered directly into the spinal canal when cancer cells are present in the meninges. This procedure is called "intrathecal therapy."

Lactate Dehydrogenase (LDH). An enzyme present in all normal and abnormal cells. It is released from cells into the blood and is present in normal amounts in the liquid portion of blood (the plasma). When blood is collected and allowed to clot, the fluid portion is called the "serum." Many chemicals are measured in the serum, including LDH. Normal serum contains low levels of LDH. The level may be elevated in many diseases, such as hepatitis and various cancers. The LDH is often elevated in lymphoma and lymphocytic leukemias. Changes in LDH are nonspecific, but when LDH is elevated in the presence of lymphocytic cancers, the change may reflect the extent of the tumor and the rapidity of tumor growth. LDH monitoring is used in some cases along with other measures to plan the intensity of therapy for lymphoma. Burkitt lymphoma and other types of aggressive lymphoma are often associated with marked elevations in serum LDH. Also known as lactic acid dehydrogenase.

Leukocytes. See White Blood Cells.

Leukopenia. A decrease below normal in the concentration of blood leukocytes (white blood cells).

Lymphadenopathy. Enlargement of lymph nodes.

Lymphatic System. The system comprising the lymph nodes, the thymus gland (in the first several decades of life), the lymphatic channels, the lymphatic tissue of the marrow, the gastrointestinal tract, the skin and the spleen, and the T, B and natural killer (NK) lymphocytes contained in these sites.

Lymph Nodes. Bean-sized structures that contain large numbers of lymphocytes and are connected with each other by small channels called "lymphatics." These nodes are distributed throughout the body. In patients with lymphoma and some types of lymphocytic leukemia, the malignant lymphocytes grow and the lymph nodes may become enlarged. This enlargement of lymph nodes can be seen, felt or measured by computed tomography (CT) scan or magnetic resonance imaging (MRI), depending on the degree of enlargement and the location.

Lymphocyte. A type of white blood cell that is the essential cell type in the body's immune system. There are three major types of lymphocytes: B lymphocytes, which produce antibodies to help combat infectious agents like bacteria, viruses and fungi; T lymphocytes, which have several functions, including assisting B lymphocytes to make antibodies; and natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

Macrophage. See Monocyte/Macrophage.

Magnetic Resonance Imaging (MRI). A testing technique that provides detailed images of body structures. It differs from the CT scan in that the patient is not exposed to x-rays. Signals are generated in the tissues in response to a magnetic field produced by a specialized instrument and are converted by computer into images of body structures. Healthcare professionals use MRI to measure the size, or a change in size, of organs such as the lymph nodes, liver and spleen or tumor masses.

Marrow. See Bone Marrow.

Maturation. See Hematopoiesis.

Meninges. See Intrathecal.

Microarray. A two-dimensional grid of molecules (often but not always DNA genes or gene fragment spots), usually arranged on a glass slide or silicone wafer. A typical microarray (also called "DNA-gene chip") contains 10,000 to 200,000 microscopic DNA spots. Scientists use a microarray to study gene expression and to learn which genes are expressed or not expressed under given circumstances. See Gene Expression Profiling.

Monoclonal. See Clonal.

Monoclonal Antibody Therapy. See Immunotherapy.

Monocyte/Macrophage. A type of white blood cell that represents about 5 to 10 percent of the cells in normal human blood. The monocyte and the neutrophil are the two major microbe-eating and microbe-killing cells in the blood. When monocytes leave the blood and enter the tissue, they are converted to macrophages. The macrophage is the monocyte-in-action: It can combat infection in the tissues, ingest dead cells (in this function it is called a "scavenger cell") and assist lymphocytes in their immune functions.

MRI. See Magnetic Resonance Imaging.

Mutation. An alteration in a gene that results from a change to a part of the stretch of DNA that represents the gene. A "germ cell mutation" is present in the egg or the sperm and can be transmitted from parent to offspring. A "somatic mutation" occurs in a specific tissue cell and can result in the growth of that cell into a tumor. Most cancers start after a somatic mutation. In leukemia, lymphoma or myeloma, a primitive marrow (blood-forming) or lymph node cell undergoes a somatic mutation or mutations that lead to the formation of a tumor. If a mutation results from a major abnormality of chromosomes such as a translocation, it can be detected by cytogenetic examination. Sometimes the alteration in the gene is more subtle and requires more sensitive tests to identify the oncogene.

Neutropenia. A decrease below normal in the concentration of neutrophils, a type of white blood cell.

Neutrophil. The principal phagocyte (microbe-eating cell) in the blood. The neutrophil is the main cell that combats infections. Patients with certain blood cancers or patients who have undergone chemotherapy often do not have sufficient quantities of neutrophils circulating in their bloodstream. A severe deficiency of neutrophils increases the patient's susceptibility to infection.

Nonmyeloablative Stem Cell Transplantation. See Reduced-Intensity Stem Cell Transplantation.

Oncogene. A mutated gene that is the cause of a cancer. Several subtypes of acute myeloid leukemia, acute lymphoblastic leukemia, lymphoma, and nearly all cases of chronic myeloid leukemia are associated with an oncogene.

Oncologist. A doctor who diagnoses and treats patients with cancer. Oncologists are usually internists who undergo additional specialized training to treat adults with cancer (or pediatricians, who treat children). Radiation oncologists specialize in the use of radiation to treat cancer, and surgical oncologists specialize in the use of surgical procedures to diagnose and treat cancer. These doctors cooperate and collaborate to provide the best treatment plan (surgery, radiation therapy, chemotherapy or immunotherapy) for the patient.

Pathologist. A doctor who identifies disease by studying tissues under a microscope. A hematopathologist is a type of pathologist who studies diseases of blood cells by looking at peripheral blood smears, bone marrow aspirates and biopsies, lymph nodes and other tissues and uses his or her expertise to identify diseases such as NHL. In addition to the microscope, a hematopathologist also uses laboratory values, flow cytometry and molecular diagnostic tests to make the most accurate diagnosis. The hematopathologist works closely with the hematologist or oncologist who sees the patient and decides on the best treatment based upon the diagnosis.

Percutaneously Inserted Central Venous Catheter (PICC or PIC Line). A long, thin, flexible tube that is inserted into the body and can be left in place for weeks or even months for administration of medications, fluids and nutrition. It can also be used to obtain blood samples. The PICC eliminates the need for standard intravenous (IV) administration.

Phagocytes. Cells that protect the body from infection by eating and killing microorganisms such as bacteria and fungi. The two principal phagocytes are neutrophils and monocytes. They leave the blood and enter tissues in which an infection has developed. Chemotherapy and radiation can cause a severe decrease in the concentrations of these cells which makes patients more susceptible to infection. Treatment may suppress blood cell production in the marrow, resulting in deficiencies of these phagocytic cells.

PICC or PIC line. See Percutaneously Inserted Central Venous Catheter.

Platelets. Small blood cells (about one-tenth the volume of red blood cells) that

stick to the site of blood vessel injury, aggregate and then seal off the injured blood vessel to stop bleeding. "Thrombocyte" is a synonym for platelet and is often used as the prefix in terms describing disorders of platelets, such as thrombocytopenia (too few) or thrombocythemia (too many).

Polymerase Chain Reaction (PCR). A technique to expand trace amounts of DNA or RNA so that the specific type of the DNA or RNA can be studied or determined. This technique has become useful in detecting a very low concentration of residual lymphoma cells, too few to be seen using a microscope. PCR can detect the presence of one lymphoma cell among 500,000 to1 million nonlymphoma cells. PCR requires a specific DNA (or RNA) abnormality or marker, like an oncogene, in the lymphoma cells in order to be used for identifying residual abnormal cells.

Port. A small device used with a central line (catheter) to access a vein. The port is placed under the skin of the chest. After the site heals, no dressings or any special home care is required. To give medicines or nutrition or to take blood samples, the doctor or nurse inserts a needle through the skin into the port. A numbing cream can be put on the skin before the port is used.

Positron Emission Tomography (PET) Scan. A procedure used to image lymphoma masses. In this technique, glucose, a type of sugar, is labeled with a positron particle emitting a radioisotope such as fluorine-18. The utilization of sugar is greater in lymphoma cells than in normal tissue, and the isotope thus becomes concentrated in areas of lymphoma. The location of the lymphoma sites in the body can be identified by scanning for intense positron particle emission. PET is combined with CT to establish the precise location of lymphoma masses; compared to other imaging procedures, PET can detect much smaller lymphoma masses. In some cases, successfully treated lymphoma may convert to fibrous tissue that looks like a mass in imaging studies, perhaps leading the doctor to think that the mass was not successfully treated. Since lymphoma tissue is not fibrous and scars (primarily fibrous) do not take up the fluorine-18-labeled sugar, PET can distinguish residual lymphoma from healed scar tissue. PET is increasingly used for both staging of lymphoma and assessing response.

Radiation Therapy. The use of x-rays and other forms of radiation in treatment. Radiation therapy may be useful in the treatment of localized lymphoma. Few cases of non-Hodgkin lymphoma are treated solely with radiation therapy because lymphoma cells are likely to be spread widely throughout the body. Radiation therapy can be an important adjunct to therapy when there are particularly large masses of lymphoma in a localized area or when local large lymph nodes are compressing or invading normal organs or structures and chemotherapy cannot control the problem.

Radioimmunotherapy. See Immunotherapy.

Recurrence/Relapse. The return of a disease after it has been in remission

following treatment.

Red Blood Cells. Blood cells (erythrocytes) that carry hemoglobin, which binds oxygen and carries it to the tissues of the body. The red blood cells make up about 40 to 45 percent of the volume of the blood in healthy individuals.

Reduced-Intensity Stem Cell Transplantation. A form of allogeneic transplantation. In reduced-intensity transplantation (also called "nonmyeloablative stem cell transplantation"), patients receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. For more information about all types of stem cell transplantation, see the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

Remission. A disappearance of evidence of a disease, usually as a result of treatment. The terms "complete" and "partial" are used to modify the term "remission." Complete remission means that all evidence of the disease is gone. Partial remission means that the disease is markedly improved by treatment, but residual evidence of the disease is present. Long-term benefit usually requires a complete remission, especially in progressive lymphomas.

RNA. Abbreviation for ribonucleic acid, a molecule in cells that carries out DNA's instructions for making proteins.

Sedimentation Rate. A blood test that measures how quickly red blood cells (erythrocytes) settle in a test tube in one hour. A sedimentation rate test is done to find out if inflammation is present in the body, to check on the progress of a disease or to see how well a treatment is working. This test is also called a "sed rate" or "erythrocyte sedimentation rate (ESR)."

Serum. See Lactate Dehydrogenase (LDH).

Solitary Extranodal Lymphoma. See Extranodal Lymphoma.

Spleen. An organ located in the left upper portion of the abdomen just under the left side of the diaphragm. It contains clusters of lymphocytes and also filters old or worn-out cells from the blood. It is often affected in lymphocytic leukemias and lymphomas. Enlargement of the spleen is called "splenomegaly." Surgical removal of the spleen is known as "splenectomy."

Stem Cells. Primitive cells in marrow that are essential to the formation of red blood cells, white blood cells and platelets. Stem cells are largely found in the marrow, but some leave the marrow and circulate in the blood. Using special techniques, the stem cells in blood can be collected, preserved by freezing and later thawed and used for stem cell therapy. See Hematopoiesis.

Thrombocyte. See Platelets.

Thrombocythemia. An increase above normal in the concentration of platelets in the blood.

Thrombocytopenia. A decrease below normal in the concentration of platelets in the blood.

Toxin. A naturally derived substance that is poisonous to cells. A toxin can be attached to antibodies that then attach to cancer cells. The toxin may kill the cancer cells.

Translocation. An abnormality of chromosomes in marrow or lymph node cells that occurs when a piece of one chromosome breaks off and attaches to the end of another chromosome. In a balanced translocation, genetic material is exchanged between two different chromosomes with no gain or loss of genetic information. When a translocation takes place, the gene at which the break occurs is altered. This is one form of somatic mutation that may transform the gene into an oncogene (cancer-causing gene). See Mutation.

Tumor Suppressor Gene. A gene that acts to prevent cell growth. If a mutation occurs that "turns off" this gene and causes loss of function, it may make the individual more susceptible to the development of cancer in the tissue in which the mutation occurred. Another term for tumor suppressor gene is "antioncogene."

White Blood Cells. Any of the five major types of infection-fighting white cells in the blood: neutrophils, eosinophils, basophils, monocytes and lymphocytes. White cells are also called "leukocytes."

More Information

Free LLS publications include

Blood and Marrow Stem Cell Transplantation
Blood Transfusion
Cutaneous T-Cell Lymphoma Facts
Fertility
Immunotherapy Facts
Long-Term and Late Effects of Treatment in Adults
Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma
Mantle Cell Lymphoma Facts
Peripheral T-Cell Lymphoma Facts
Understanding Clinical Trials for Blood Cancers
Understanding Side Effects of Drug Therapy
Waldenström Macroglobulinemia Facts

Visit "Suggested Reading" at www.LLS.org/resourcecenter to see a list of helpful books on a wide range of topics.

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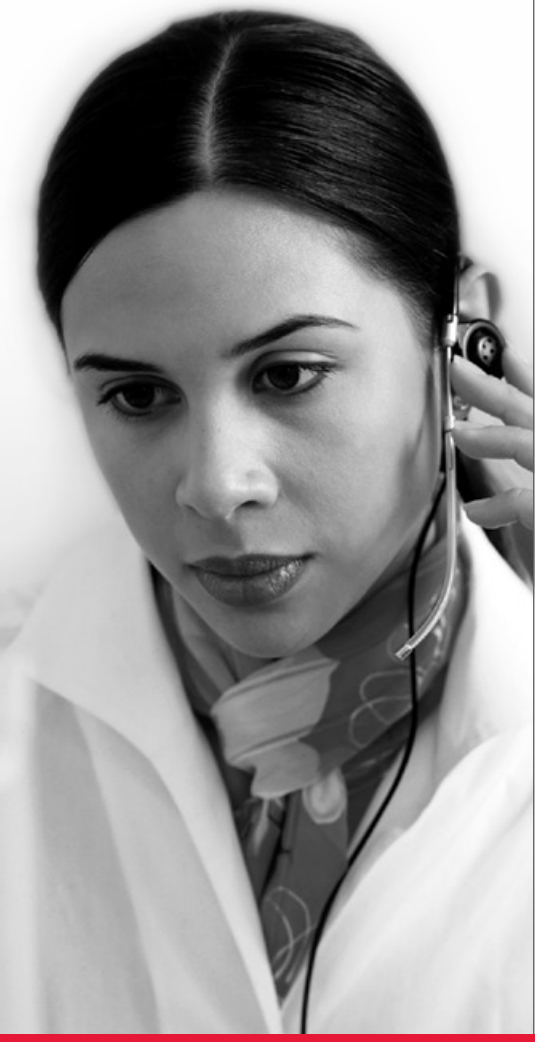

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