The Lymphomas

Hodgkin Lymphoma and Non-Hodgkin Lymphomas

LEUKEMIA | LYMPHOMA | MYELOMA

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Fighting Blood Cancers

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Introduction

This booklet provides information about the lymphomas for patients and their families. A glossary is included at the end of the booklet to help readers understand medical terms that may be new to them. We hope this material is helpful and we welcome comments about its contents. Lymphoma is a general term for a group of cancers that start in the lymphatic system. The lymphomas are divided into two major categories: Hodgkin lymphoma and all other lymphomas, referred to as non-Hodgkin lymphomas (NHL). The lymphomas are a type of blood cancer. Blood cancers include leukemia, lymphoma, myeloma, myelodysplastic syndrome and others. About 56 percent of the blood cancers that occur each year are lymphomas.

The combined projected incidence of Hodgkin lymphoma and non-Hodgkin lymphoma in the United States in 2006 is estimated at 66,670 cases. This includes 7,800 cases of Hodgkin lymphoma, which represents 11.7 percent of all lymphomas, and 58,870 cases of non-Hodgkin lymphomas. (Source: Surveillance, Epidemiology, and End Results [SEER] Program, 2006). There are more than 30 different types of NHL. Nearly 90% of these are types of B-cell lymphomas. There are 14 different types of B-cell lymphomas. About 10 percent of people diagnosed with NHL have a T-cell lymphoma.

Lymphoma results when a lymphocyte (a type of white 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 (e.g., skin, other organs).

Brief descriptions of normal blood and marrow as well as the lymphatic system are provided for background, followed by a detailed description of the lymphomas and their treatment.

Normal Blood and Marrow

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

- Proteins (such as albumin),
- Hormones (such as thyroid hormone),
- Minerals (such as iron),
- Vitamins (such as folate), and
- Antibodies, including those we develop from our vaccinations (such as poliovirus antibodies).

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

- The red cells make up half the volume of the blood. They are filled with hemoglobin, the protein that picks up oxygen in the lungs and delivers oxygen to the cells all around the body.
- The platelets are small cells (one-tenth the size of red cells) that help stop bleeding at the site of an injury in the body. For example, when an individual 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. 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 cells. They are called phagocytes (or eating cells) because they can ingest bacteria or fungi and kill them. Unlike the red cells and platelets, the white cells leave the blood and enter the tissues, where they can ingest invading bacteria or fungi and help combat infection. Eosinophils and basophils are two additional types of white cells. They respond to allergens.
- Most lymphocytes, another type of white cell, are in the lymph nodes, the spleen and lymphatic channels, but some enter the blood. There are three major types of lymphocytes: T cells, B cells and natural killer 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 backbones (vertebrae), hip and shoulder bones, ribs, breastbone, and skull contain marrow that makes blood cells in adults. Blood passes through the marrow and picks up formed red and white cells, and platelets, for circulation.

The process of blood cell formation is called "hematopoiesis." A small group of cells, the stem cells, develops into all the blood cells in the marrow by the process of differentiation (see Figure 1).

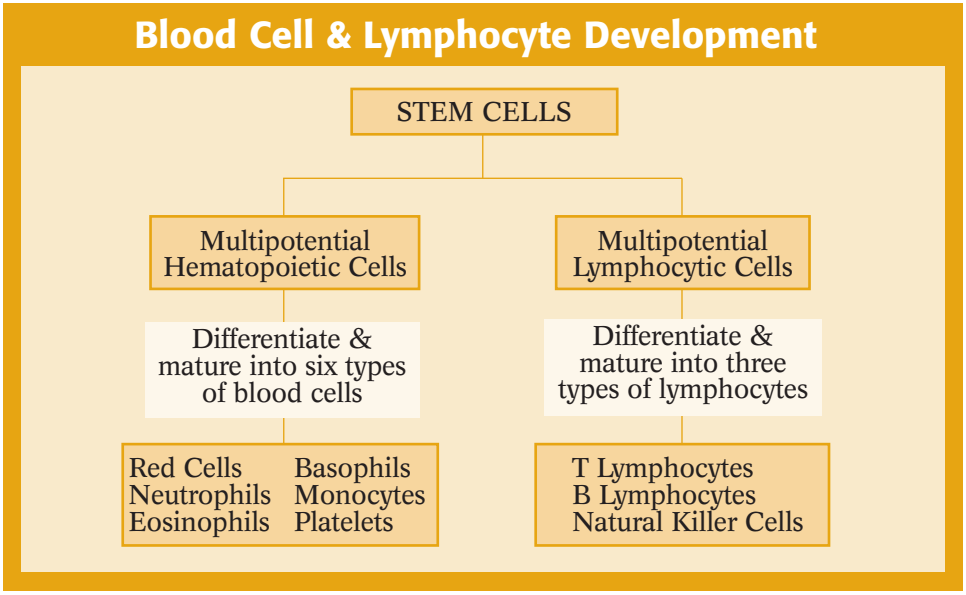

Figure 1. This diagram shows how stem cells develop into functional blood cells (hematopoiesis) and lymphatic cells.

When the fully developed and functional cells are formed, they leave the marrow and enter the blood. In healthy individuals there are enough stem cells to keep producing new blood cells continuously.

Some stem cells enter the blood and circulate. They are present in such small numbers that they cannot be counted or identified in the usual type of blood cell counts. Their presence in the blood is important because they can be collected by a special technique and can be transplanted into a recipient if enough stem cells are harvested from a compatible donor.

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.

In summary, blood cells are made in the marrow. When the cells are formed and functional, they leave the marrow and enter the blood. The red cells and the platelets carry out their respective functions of delivering oxygen and plugging up injured blood vessels throughout the body. The white cells (neutrophils, eosinophils, basophils, monocytes and lymphocytes) enter the tissues (for example, the lungs) to combat infections, such as pneumonia, and perform other immune functions.

The Lymphatic System

The lymphatic system and the blood cell-forming system in the marrow are closely related. Most lymphocytes are in the lymph nodes and other parts of the lymphatic system (see Table 1, page 7), such as the skin, spleen, tonsils and adenoids (special lymph nodes), intestinal lining, and in young people, the thymus. The lymphocytes circulate through channels, called lymphatics, that connect the lymph nodes scattered throughout the body. The lymphatic channels collect into large ducts that empty into a blood vessel. The lymphocytes enter the blood via these ducts. There are three types of lymphocytes. T lymphocytes (T cells) originate in the thymus, hence the designation T. The B lymphocytes (B cells) originate in the bone marrow, although the B comes from the word bursa, an organ in birds that was first found to be the source of B lymphocytes. B lymphocytes make antibodies in response to foreign antigens, especially microbes. Collections of B lymphocytes are present in the marrow.

The T lymphocytes have several functions, including assisting B lymphocytes to make antibodies against invading bacteria, viruses or other microbes. The antibodies attach to the microbe and, in so doing, make it possible for other white cells to recognize the antibody and pull (ingest) it into the cell along with its attached microbe. The cell can then kill and digest the microbe.

The third type of lymphocyte, natural killer (NK) cells, attack virus-infected cells as a natural function without requiring antibody or other mediation. T cells and NK cells have other functions as well and are important elements in studies that are designing immunotherapies to treat lymphoma and other cancers.

Parts of the Lymphatic System

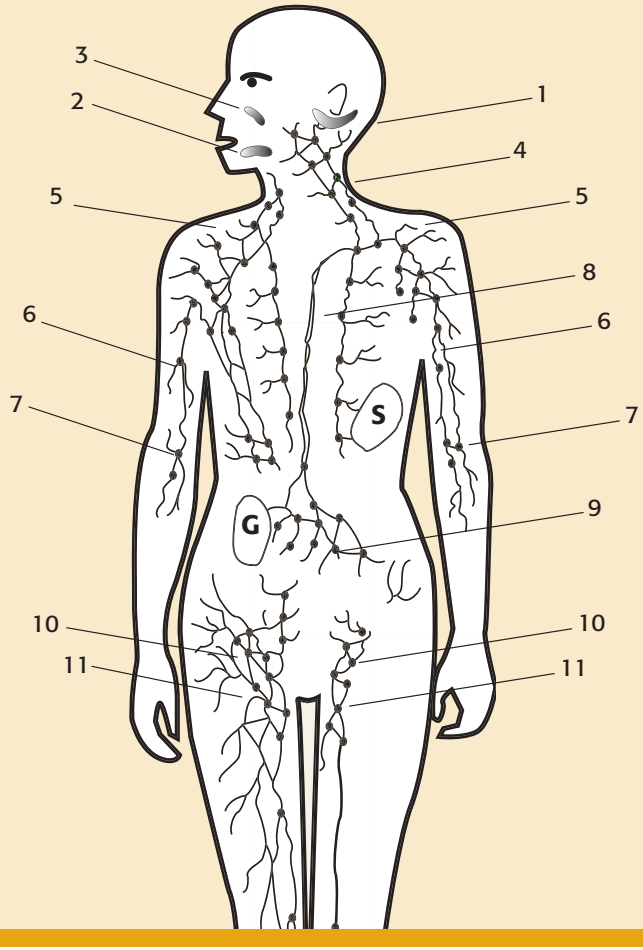

Figure 2. This diagram represents where key lymph nodes are situated throughout the human body. It has been estimated that there are about 600 lymph nodes in the body. The numbers in the diagram denote areas of lymph nodes that frequently are involved in Hodgkin and other lymphomas. These areas of lymph nodes occur around the ears (1) and around the jaw (2). They comprise the tonsils and adenoids (3), are found in the front and back of the neck (4), above and below the collar bone (5), in the armpit (6), near the elbow (7), in the chest (8), in the abdomen (9), in the pelvis (10) and in the groin (11). The spleen (S) contains many clusters of lymphocytes. These clusters may be involved in the malignant process, grow, and lead to involvement and enlargement of the spleen. The gut-associated (intestinal) lymph tissue (G) may also be the site of lymphoma development. Lymphomas are cancers that begin with the malignant transformation of a lymphocyte in the lymphatic system. “Lymph-” indicates that the disease begins in a lymphocyte and “-oma” is a Greek suffix denoting a tumor.

Table 1. Some Parts of the Lymphatic System

Lymph nodes	Gastrointestinal lymph areas
Plasma cells	Tonsils and adenoids
Lymphatic vessels	Natural killer (NK) cells
Spleen	T lymphocytes
Lymphokines	Marrow
B lymphocytes	Immunoglobulins

The Lymphomas

Lymphomas are cancers that begin with the malignant transformation of a lymphocyte in the lymphatic system.

Hodgkin lymphoma and all non-Hodgkin lymphomas result from an injury to the DNA of a lymphocyte. Scientists know that the damage to the DNA is acquired (it occurs after birth) rather than inherited. The change of DNA in one lymphocyte produces a malignant transformation. This results in the uncontrolled and exaggerated growth of the lymphocyte; it gives the malignant lymphocyte and the cells that are formed from its multiplication a survival advantage. The accumulation of these cells results in the tumor masses that are found in the lymph nodes and other sites in the body.

Lymphomas generally start either in lymph nodes or in lymphatic tissue found in organs such as the stomach or intestines. In some cases lymphomas involve marrow and blood. Lymphomas may spread from one site to other parts of the body.

Lymphocytic leukemias are also types of blood cancer. These leukemias begin when there are changes to the cells in the marrow and those cells enter the blood. These cells may also travel to the lymph nodes.

Incidence

Hodgkin lymphoma increases to a peak incidence of over 4 cases per 100,000 persons in their mid 20s. It is slightly more than half that rate in middle-aged people, and increases somewhat in frequency in older individuals.

Hodgkin Lymphoma
Age-Specific Incidence Rates (2000-2003)

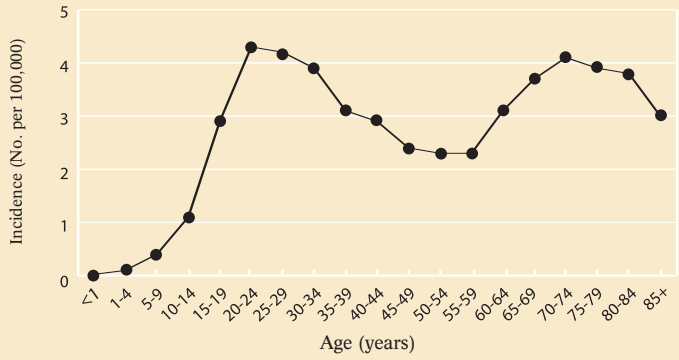

Figure 3. The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of Hodgkin lymphoma each year per 100,000 people, by age-group. (Data from the National Cancer Institute Surveillance, Epidemiology, and End Results [SEER] Program, 2006.)

Non-Hodgkin Lymphomas
Age-Specific Incidence Rates (2000-2003)

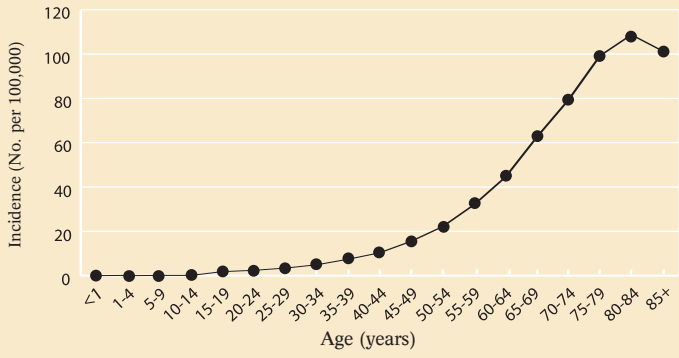

Figure 4. The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of non-Hodgkin lymphomas each year per 100,000 people, by age-group. (Data from the National Cancer Institute Surveillance, Epidemiology, and End Results [SEER] Program, 2006.) Although lymphoma occurs in individuals at virtually all ages, it is very uncommon in those under age 10 and increases significantly with age. Whereas fewer than 8 cases per 100,000 occur in people in their late 30s, the incidence increases progressively, to 108.7 cases per 100,000 persons, in 80-84 year-olds.

The incidence of non-Hodgkin lymphomas increase with age, as shown in Figure 4, page 8. About 2.4 cases per 100,000 persons occur in 20-year-old individuals. The rate increases more than 18 times, to over 44 cases per 100,000 individuals by age 60, and over 40-fold, to nearly 100 cases per 100,000 persons, after age 75.

Causes and Risk Factors

Hodgkin Lymphoma Most cases of Hodgkin lymphoma occur in people who do not have identifiable risk factors, and most people with presumptive risk factors do not get the disease. The causes of the disease are uncertain. To illustrate:

- Many studies of environmental, especially occupational, linkages have been conducted, with unclear results.
- Epstein-Barr virus has been associated with nearly half of cases. However, this virus has not been conclusively established as a cause of Hodgkin lymphoma.
- People infected with human T-cell lymphocytotropic virus (HTLV) or human immunodeficiency virus (HIV) also have an increased probability of developing Hodgkin lymphoma.
- There are occasional cases of familial clustering, as with many cancers.
- There is an increase in incidence of Hodgkin lymphoma in siblings of patients with the disease.

Non-Hodgkin Lymphomas The annual incidence of non-Hodgkin lymphomas has nearly doubled over the last 55 years. The reasons for this increase are not certain, and there are probably multiple causes. The increase began before the spread of HIV within the population. Since the mid 1980s, the incidence of lymphoma in individuals infected with HIV, has contributed modestly to the increase in lymphoma incidence. For this population, the incidence of lymphoma is between 50 and 100 times the incidence rate expected in uninfected individuals. On the other hand, newer therapy for HIV infection has lowered the incidence of acquired immune deficiency syndrome (AIDS)-related lymphoma.

There is an increase in the incidence of non-Hodgkin lymphomas in farming communities. Studies point to specific ingredients – such as organochlorine, organophosphate and phenoxyacid compounds – in herbicides and pesticides as being associated with lymphoma. However, the number of lymphoma cases caused by such exposures has not been determined.

Exposure to certain viruses and bacteria is associated with lymphoma. For example:

- In specific geographical regions, infection with Epstein-Barr virus is strongly associated with African Burkitt lymphoma. The precise role of the Epstein-Barr virus is unclear since this disease can occur in its absence. Also, the specific cancer-causing event is a translocation of chromosomes or other type of gene mutation. It is thought that the virus or bacterium can lead to intense lymphoid cell proliferation, which increases the probability of a cancer-causing event in a cell.
- Epstein-Barr virus infection may play a role in the increased risk of non-Hodgkin lymphomas in persons with immune suppression as a result of organ transplantation and its therapy.
- HTLV is associated with a type of T-cell lymphoma in 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 lymphatic tissue (MALT) lymphoma in the stomach wall.

About a dozen inherited syndromes can predispose individuals to later development of non-Hodgkin lymphomas. These inherited disorders are rare, but the concept of predisposition genes is under study to determine if they play a role in the sporadic occurrence of lymphoma in otherwise healthy individuals.

Classification of Lymphomas

Hodgkin and Non-Hodgkin Lymphomas The lymphomas are divided into two major categories: Hodgkin lymphoma and all other lymphomas, called non-Hodgkin lymphomas.

Hodgkin lymphoma was named after Thomas Hodgkin who described several such cases in 1832. These cases were accepted as representation of a new malignant condition involving lymph nodes. About 40 years later the concept of other lymphomas (originally called lymphosarcoma), distinct from Hodgkin lymphoma, was proposed by Virchow, Cohnheim and Billroth, three medical giants of the late 19th century.

Hodgkin lymphoma has continued to receive special recognition by the World Health Organization (WHO), which influences disease classification throughout the world. The disease was called Hodgkin's disease for about 170 years. The name was

officially changed to Hodgkin lymphoma when it became evident that the disease begins in a lymphocyte – and this cell of origin was not identified with certainty until the late 20th century.

Lymphoma and Lymphocytic Leukemias There are close disease pathologies and biological connections between these two types of malignancies, both of which begin in a lymphocyte. When the disease begins in the lymphatic tissue in the marrow, the designation is lymphocytic leukemia; acute and chronic lymphocytic leukemia (ALL and CLL) are the two major examples, although there are subtypes of each. When the disease begins in a lymph node or other lymphatic structure in the skin, gastrointestinal tract or other sites in the body, the disease is called a lymphoma.

World Health Organization Classification of Lymphomas Table 2 lists the various subtypes of non-Hodgkin and Hodgkin lymphomas. The WHO classification includes several types of lymphocytic leukemias as well. These have been omitted in Table 2 but many are included in the Society patient booklets on acute and chronic lymphocytic leukemia. Follicular and large B-cell lymphomas are the two most prevalent types, and together account for about 50 percent of cases.

Hodgkin Lymphoma

Symptoms and Signs

The most common early sign of Hodgkin lymphoma is a painless swelling of lymph nodes in the neck, upper chest, interior of the chest, armpit, abdomen or groin. Involvement of lymph nodes in other locations may occur, but less frequently. Other symptoms include fever; sweating, especially at night; weight loss and itching. Patients may experience pain in the lymph nodes after drinking alcohol, an uncommon but specific finding in Hodgkin lymphoma. The spleen may be enlarged.

When a patient's medical history and physical examination lead to suspicion of Hodgkin lymphoma, the physician may order an imaging test (see the discussion on imaging, page 13). The test may reveal enlarged lymph nodes in the chest or abdomen or both. Tumor masses can occur outside the lymph nodes in lung, bone or other body tissue.

Table 2. Diagnostic Designations of the Lymphomas

I. Types and Frequencies of Non-Hodgkin Lymphomas

A) B-Cell Lymphomas

1. Diffuse Large B-Cell Lymphoma (31%)
2. Follicular Lymphoma (22%)
3. Mucosa-Associated Lymphatic 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 (<2%)
8. Nodal Marginal Zone B-Cell Lymphoma (<2%)
9. Splenic Marginal Zone Lymphoma (<1%)
10. Extranodal Marginal Zone B-Cell Lymphoma (<1%)
11. Intravascular Large B-Cell Lymphoma (<1%)
12. Primary Effusion Lymphoma (<1%)
13. Burkitt Lymphoma-Burkitt Leukemia (2.5%)
14. Lymphomatoid Granulomatosis (<1%)

B) T-Cell and NK-Cell Lymphomas (~12%)

1. Extranodal T-Cell or Natural Killer (NK) Cell Lymphoma
2. Cutaneous T-Cell Lymphoma (Sézary Syndrome and Mycosis Fungoides)
3. Anaplastic Large Cell Lymphoma
4. Angioimmunoblastic T-Cell Lymphoma

C) Immunodeficiency-Associated Lymphoproliferative Disorders

II. Hodgkin Lymphoma (Specially Designated Types of B-Cell Lymphomas)

1. Nodular Lymphocytic Predominance Type
2. Classical Type
3. Nodular Sclerosis Type
4. Mixed Cellularity Type
5. Lymphocytic-Rich Classical Type
6. Lymphocyte-Depleted Type

This table is slightly modified from information presented in the *World Health Organization Classification of Tumors: Tumors of Hematopoietic and Lymphoid Tissues*. The percentages above for non-Hodgkin lymphoma (NHL) subtypes A and B 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.

The combined projected incidence of Hodgkin and NHL's in the U.S. in 2006 is estimated at 66,670 cases. Hodgkin lymphoma accounts for about 7,800 or 11.7% of all lymphoma cases.

Diagnosis

The steps taken in determining the presence and extent of Hodgkin lymphoma are important for diagnosis and for assessing the treatment approach. The diagnosis of Hodgkin lymphoma requires the biopsy of an involved lymph node or other tumor site. A pathologist prepares a slide from the biopsy specimen and evaluates the cells using a microscope. See page 23 for information about the biopsy procedure. Several patterns of lymph node changes are characteristic and diagnostic of Hodgkin lymphoma. The changes can be categorized into several patterns as seen under the microscope, and these determine the subtype of Hodgkin lymphoma (see Table 2, page 12).

In some cases, the use of immunophenotyping or immunostaining can help distinguish Hodgkin lymphoma from other types of lymphomas or other lymph node reactions that are not cancerous. The physician looks for the presence of special cells to confirm the diagnosis. These cells are called Reed-Sternberg cells in recognition of the two physicians who first described them. Other related cells are referred to as Hodgkin cells.

The diagnosis of Hodgkin lymphoma can be difficult. Diagnosis often requires experienced pathologists (physicians who specialize in interpreting and diagnosing the physical changes caused by disease in the body) to analyze the biopsy slides.

Staging

"Staging" is the term used for determining the extent of the disease. This is done once the diagnosis is confirmed. Staging provides very important information to the physician who is planning treatment. In addition to a physical examination, the physician can use imaging tests to determine the extent of the disease. These tests help the physician to evaluate:

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

In most cases, these procedures will include computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen. Gallium scans are another technique used to identify lymph nodes involved in lymphoma. Positron emission tomography (PET) is a very sensitive technique that can be used to identify tissue abnormalities and increasingly is being used to measure the response of lymphoma sites to therapy. Today, it is unusual to require a procedure referred to as a staging

laparotomy, which is a surgical procedure to inspect and biopsy the lymph nodes in the abdomen and the liver, and remove the spleen. The information gathered from imaging studies permits the patient's disease to be assigned to a particular stage of involvement:

Stage I
Apparent involvement of a single lymph node region or a single organ, such as bone.

Stage II
Involvement of two or three lymph node regions that are close to each other, for example, all in the neck and chest, or all in the abdomen.

Stage III
Involvement of several lymph node regions in the neck, chest and abdomen.

Stage IV
Widespread involvement of lymph nodes and other organs, such as lungs, liver and bone.

A and B categories The four stages of Hodgkin lymphoma can be divided into A and B categories.

- The A category indicates the absence of fever, exaggerated sweating and weight loss.
- Patients who experience fever, excessive sweating and weight loss are in the B category. For example, stage IIB indicates that the patient has:
    1. Two lymph node sites near each other with disease involvement (e.g., enlarged lymph nodes in the neck and near the collarbone, or in the neck and the armpit), and
    2. Fever, excessive sweating and weight loss.

Blood cell counts, bone marrow examination, and blood tests that can detect liver involvement and the severity of the disease also are useful in assessing the approach to treatment.

Patients belonging to the B category (presence of symptoms) often require a more aggressive treatment approach. The extent of disease and the presence of symptoms determine whether radiation therapy, chemotherapy or both are recommended for treatment (see Table 3, page 15).

Table 3. Special Considerations in the Treatment of Hodgkin Lymphoma

Enlarged chest nodes or abdominal lymph nodes
Enlarged spleen
Large number of lymph node groups affected
Specific organs (e.g., lungs, liver, bone) involved
Severe anemia
Patient's age and health (e.g., coexisting diabetes mellitus, coronary insufficiency, kidney disease, etc.)

Treatment for Hodgkin Lymphoma

The goal of treatment is to cure the patient. Chemotherapy or a combination of chemotherapy and radiation can result in cures. Over 75 percent of all patients diagnosed with Hodgkin lymphoma can be cured by current treatment approaches. The cure rate is higher, approaching 90 percent, in younger patients.

Chemotherapy and "involved" field radiation is the usual approach in most cases today. This use of radiation targets only the obvious lymphoma masses, and chemotherapy is used to kill neighboring lymphoma cells. "Extended" field radiation therapy alone was the first curative approach to the disease. This approach treated both the involved areas and neighboring, apparently uninvolved, areas on the presumption that disease had probably spread to those neighboring areas but could not be detected by the imaging available in the late 1960s.

Chemotherapy usually involves at least four drugs used simultaneously. Drugs are dissolved in fluids and given to the patient via an indwelling catheter. The catheter is sometimes called a central line, a port or a Port-a-cath®.

Radiation involves the use of special machines that produce high-energy rays capable of killing the lymphoma cells. Shielding uninvolved organs such as the lungs or liver may minimize side effects. In addition, continuous improvements in the devices that deliver radiation permit more precise targeting of treatment areas.

If the disease is widespread and associated with signs such as fever, drenching night sweats, or weight loss, chemotherapy may be used alone. If a patient's condition falls between these extremes, decisions regarding the use of either radiation therapy and/or chemotherapy are made according to each patient's needs.

Radiation can be added to chemotherapy to shrink large lymphoma tumor masses. The term "bulky" disease is used to describe such masses of lymphoma tissue, often found among nearby lymph nodes

Treatment Setting Most of the therapy can be administered in an outpatient setting. Radiation therapy and chemotherapy can be administered in the outpatient clinic of an oncology center. Sometimes, short periods of hospitalization are required. If therapy is particularly intensive, it may result in prolonged or severe decreases in red cell, white cell and/or platelet counts. Transfusion of appropriate blood products and administration of cytokines (hormones that enhance blood cell production) may be needed. Even in these cases, outpatient treatment may still be feasible.

Course and Outcome The effectiveness of therapy depends upon the age of the patient and the extent (stage) of the disease. Many patients are cured after initial treatment. For the smaller number of patients who may have a recurrence of disease or a relapse, re-treatment with chemotherapy is often successful. These patients may be cured or have very prolonged disease-free periods after their second treatment regimen. Occasionally, in patients with evidence of progressive disease, use of autologous blood or marrow stem cell infusion allows for intensive chemotherapy, which can induce remission and a long-term, disease-free interval.

One of the important features of Hodgkin lymphoma is a decrease in the immune system's function. The cells of the immune system, especially the T lymphocytes, do not react normally. This situation can make patients susceptible to certain types of infection. Herpes zoster (shingles) is an example of a viral disease that occurs with increased frequency in patients with Hodgkin lymphoma. The effects of chemotherapy and radiation therapy can enhance susceptibility to infection since these treatments add to the suppression of immune cell function. Removal of the spleen, now performed less often, also contributes to the risk of severe infections. However, when patients are cured, their immune function may improve. In addition, improvement in the treatment of Hodgkin lymphoma, increased awareness of the risk of infectious diseases, and the availability of better antimicrobial therapy has made infectious complications less of a medical problem for patients.

Information about side effects of treatment for Hodgkin lymphoma begins on page 34.

Non-Hodgkin Lymphomas

Terms Used to Describe Non-Hodgkin Lymphomas

B-Cell Lymphomas A lymphoma subtype that is composed of malignant B lymphocytes. B cells received their name from the B in bursa, an organ in birds, first discovered to be the source of B lymphocytes. In humans, the lymphatic areas of the marrow and intestines are thought to be the source of B lymphocytes.

T-Cell Lymphomas The malignant cells in these lymphomas have features that originate from T lymphocytes, as determined by immunophenotyping or analysis with special molecular diagnostic studies.

The four major types of T-cell lymphomas are peripheral T-cell lymphoma, T-cell lymphoblastic lymphoma, cutaneous T-cell lymphoma and adult T-cell lymphoma. These lymphomas are composed of malignant cells that are T cell in type. T cells received their name from the T in thymus, an organ in the chest that shrinks and disappears as people grow into adulthood. It is the source of T lymphocytes.

Extranodal Lymphomas At the time of diagnosis, lymphoma can already be localized to virtually any organ in the body. For example, in addition to the lymph nodes, extranodal sites – the thyroid, lung, liver, bone, stomach and the central nervous system (CNS, brain and/or spinal column) – may have lymphoma involvement. Disease that is present in any of these sites – the thyroid, lung, bone, stomach and others – may result in symptoms or signs that lead to a biopsy that reveals the lymphoma. If a careful search does not uncover lymphoma in lymph nodes or multiple lymphatic sites, this situation is referred to as solitary extranodal lymphoma.

In contrast, extranodal sites may be involved as a feature of generalized lymphoma. Thus, the lung, liver, bone, and the CNS may have lymphoma involvement as well as lymph nodes.

Central Nervous System Lymphomas This term applies to the presence of lymphoma:

1) Only in the brain or spinal column (primary CNS lymphoma); this type is more often seen as a feature of AIDS-related lymphoma that follows human immunodeficiency virus infection; or

2) In the brain or spinal column as well as in other locations (secondary CNS lymphoma); the secondary type is usually a feature of aggressive lymphomas such as Burkitt lymphoma.

Treatment for both types can include radiation therapy and chemotherapy using drugs and dosages that can penetrate the CNS.

High-Grade (Aggressive) Lymphomas The general term applied to several subtypes of lymphoma that progress relatively rapidly if untreated; these subtypes include:

- AIDS-associated lymphoma,
- Anaplastic large cell lymphoma,
- Burkitt lymphoma,
- Diffuse large B-cell lymphoma, and
- Lymphoblastic lymphoma.

Although these represent more rapidly progressive lymphomas, some of the high-grade or aggressive lymphomas also respond very well to combinations of drugs used in treatment protocols, which can result in cures.

Low-Grade (Indolent) Lymphomas This term encompasses several subtypes of lymphomas whose rate of progression is, on average, relatively slow. Usually, the lymphoma cells have features of B lymphocytes. Typical subtypes included in this designation are small cell lymphocyte lymphoma and follicular lymphoma.

Diffuse Lymphomas These subtypes of lymphoma have a uniform pattern of disruption of normal lymph node architecture (structure), as seen in a lymph node biopsy. When the biopsy specimen is examined under the microscope, the lymphoma cells are spread diffusely throughout the lymph node.

Follicular Lymphomas This term is used to describe the subtype of lymphoma in which the lymphoma cells are grouped in clusters or follicles. This pattern is distinct from diffuse lymphomas. There is more information about follicular lymphoma in the next section.

Most Common Subtypes of B-Cell Non-Hodgkin Lymphomas

Descriptions of some types of non-Hodgkin lymphomas are given below. Nearly 90 percent of non-Hodgkin lymphomas are one of 14 different types of B-cell lymphomas. Table 2 (page 12) shows the frequency of these and other types of lymphomas.

The names for some disease subtypes relate to the appearance of the lymphoma cells as compared to normal lymphocytes in a lymph node. "Follicle," "mantle" and "marginal" zones are names for specific areas of normal lymph nodes; these names have been used to describe lymphomas that appear to originate in a cell residing in those areas (e.g., follicular, mantle cell and marginal zone lymphomas).

Diffuse Large B-Cell Lymphomas This form of lymphoma is the most common in the Western world. It usually starts in lymph nodes in the neck or abdomen. It is an aggressive type of lymphoma that is characterized by a number of features. These include:

- The presence of large B lymphocytes composing the tumor masses,
- A relatively high frequency of widespread involvement,
- Fever and sweating, and
- Extranodal involvement.

Gene expression studies of the lymphoma cells indicate that this subtype has at least three distinct genetic patterns. Clinical patterns indicate that there may be several different types of diffuse large B-cell lymphomas.

Follicular Lymphoma This is the second-most frequent type of lymphoma. It is named for the microscopic pattern observed in the lymph node biopsy, which shows accumulations (follicles) of abnormal smaller B-cell-type lymphoma cells. The follicles are scattered through the lymph node(s). This is a more slowly progressive disease on average.

This type of lymphoma has a specific chromosome abnormality: a translocation between parts of chromosomes 14 and 18. This causes the overexpression of a gene, *BCL-2*, which makes the cells resistant to curative therapy. However, treatment may keep the disease in check for many years. This can be the case even when tests show that disease remains in some parts of the body.

Mucosa-Associated Lymphoid Tissue (MALT) Lymphomas These lymphomas originate in the lining of the gastrointestinal tract or closely associated lymphoid tissue. The stomach is the most frequent site, and this condition is associated with a prior infection by the bacterium that causes stomach ulcers, Helicobacter pylori. Other common sites are the lung, salivary gland and thyroid.

These lymphomas are often only slowly progressive and tend to remain localized.

Small Cell Lymphocytic Lymphoma (Chronic Lymphocytic Leukemia [CLL]) Small cell lymphocytic lymphoma is almost identical to CLL both in signs and symptoms, and the appearance of lymph nodes under the microscope. In small cell lymphocytic lymphoma, the degree of lymph node and lymphoid tissue involvement is more striking than the involvement of the marrow and blood, whereas in chronic lymphocytic leukemia the marrow and blood are strikingly affected. The disease usually affects older patients (median age 65 years) and usually manifests with widespread lymphadenopathy (enlarged lymph nodes) and slight marrow and blood involvement (stage IV lymphoma).

This lymphoma is very slowly progressive.

Mantle Cell Lymphoma In this subtype, the lymphoma cells originate from a lymphocyte in the mantle zone of a lymph node. It usually occurs in persons over 50 years of age, and is four times more frequent in men than women. The disease is usually widespread at diagnosis, involving lymph nodes, the bone marrow, and sometimes the liver, the intestines and spleen.

For more information about mantle cell lymphoma, see the Society's fact sheet.

Less Common Subtypes of B-Cell Non-Hodgkin Lymphomas

Lymphoplasmacytic Lymphoma (Waldenström Macroglobulinemia) This type of lymphoma is a slow-growing lymphoma that originates in a B-lymphocyte precursor. The final stage of lymphocyte development is the mature, immunoglobulin-producing plasma cell. B lymphocytes can become cancerous at any stage of their development. When the malignant transformation takes place at the point of development prior to the B lymphocyte becoming a mature, immunoglobulin-producing plasma cell, a resulting disease is lymphoplasmacytic lymphoma or Waldenström macroglobulinemia.

Although plasma cells represent only a minority of the tumor cells, many of the lymphocytes have an appearance that is similar to plasma cells. Waldenström macroglobulinemia is distinguished from lymphoplasmacytic lymphoma by the fact that lymph node involvement is less prominent. Both disorders show malignant lymphoplasmacytic cells in the marrow and spleen. These malignant lymphoplasmacytic cells secrete an abnormal immunoglobulin (Ig), monoclonal IgM. In the case of lymphoplasmacytic lymphoma, the diagnosis is usually made by lymph node biopsy and in Waldenström macroglobulinemia, by marrow examination. In each case, small lymphocytes, many with a staining pattern similar but not identical to plasma cells, are the predominant tumor cell type. If the monoclonal IgM is elevated sufficiently in the blood, it can lead to increased blood viscosity, inadequate blood flow, and symptoms and signs of retarded flow, (e.g., headache, visual blurring, mental confusion). This situation is referred to as the hyperviscosity syndrome. With progression, the lymphoma may involve the lung, the gastrointestinal tract and other organs.

In lymphoplasmacytic lymphoma the production of monoclonal IgM (also called immunoglobulin M) by the lymphoma cells can lead to an increase in blood viscosity and hyperviscosity syndrome. The hyperviscosity syndrome can be treated by plasmapheresis to reverse acute symptoms and signs, but long-term control requires a reduction in the mass of lymphoma cells that make the protein. Watching and waiting is one management approach, followed by multidrug chemotherapy and a monoclonal antibody. If the disease appears to be progressive, therapy may be administered at the time of diagnosis.

For more information about Waldenström macroglobulinemia, see the Society's fact sheet.

Burkitt Lymphoma A type of B-cell lymphoma first brought to wide attention in equatorial Africa by Dennis Burkitt, an Irish surgeon working in that region. In Africa, it usually appears in children as a mass in a facial bone, especially the jaw, and is associated invariably with the Epstein-Barr virus in the lymphoma cells. An abnormality of chromosome number 8 is also present. Both the chromosome abnormality and viral infection are thought to play a causal role in the onset of Burkitt lymphoma.

Outside of equatorial Africa, Burkitt lymphoma has a far lower frequency of occurrence. This disease usually appears as abdominal masses of lymphoma cells, and is not uniformly associated with Epstein-Barr virus. It may occur in older individuals, and may involve the marrow, blood, CNS and other organs.

Most Common Subtypes of T-Cell Non-Hodgkin Lymphomas

Cutaneous T-Cell Lymphoma (Mycosis Fungoides and Sézary Syndrome)

This subtype principally involves the skin and lymph nodes; in advanced disease other organs are also involved. About 3 percent of all lymphomas are of this type. The lymphoma originates in a T-cell. The disease may wax and wane 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 may 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. This disease of this description may be referred to as Sézary syndrome. 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 different forms of ray therapy directed to the skin lesions. Two types used are ultraviolet light therapy and electron beam therapy. The former 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/multidrug chemotherapy or photopheresis can be used depending on the objective of therapy and the rate of progression of the disease.

For more information about cutaneous T-cell lymphoma, see the Society's fact sheet.

Symptoms and Signs

Many patients may notice enlarged lymph nodes in the neck, armpit or groin. Less often, these swollen nodes may appear near the ears or the elbow, or in the throat near the tonsils. Occasionally, the disease may start 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 refer to that site, such as bone pain, cough, chest pain, abdominal pain, rashes or skin lumps.

Patients also may have fever, excessive sweating (especially noticeable at night), unexplained fatigue, loss of appetite or weight loss. During a medical examination, the physician may detect an enlarged spleen. In some cases, the disease may only be discovered during a routine medical examination or while the patient is under care for an unrelated condition.

Diagnosis

Enlarged lymph nodes may result from inflammation and are not necessarily a sign of cancer. However, in the absence of another explanation, such as a nearby infection, the physician may suspect lymphoma if enlarged lymph nodes are detected during a physical examination or during an imaging test (for example, a chest X-ray).

Biopsy The diagnosis can be made with certainty by a biopsy of an involved lymph node or another involved organ, such as a bone, a lung, the liver or another site. The biopsy procedure may be performed by one of two possible methods:

1. Using a special needle that passes through the skin into the tissue containing the suspicious finding or
2. By surgical removal of a lymph node or a small piece of another tissue (e.g., lung, liver) suspected of containing an abnormality.

In some cases, the diagnosis may be made by the discovery of abnormal lymphocytes (lymphoma cells) in the marrow obtained as part of the initial diagnostic evaluation.

The biopsy tissue often can be removed using a local anesthetic. Occasionally, chest or abdominal surgery may be used for diagnosis. Surgical biopsy requires general anesthesia. However, newer approaches using the laparoscope may permit biopsies within body cavities without requiring major incisions or manipulations.

When the tissue is obtained, it is prepared and then examined under the microscope by a pathologist to determine the pattern of the tissue abnormalities and types of cells involved. Sometimes, it is relatively easy for an experienced physician to determine that the abnormality is lymphoma and to determine the category or classification of the lymphoma. Occasionally, the diagnosis may be unclear and require consultation with expert hematopathologists, doctors who specialize in the diagnosis of lymphoma and other blood disorders.

Immunophenotyping In addition, cells obtained at the time of tissue biopsy can be studied by immunophenotyping to provide additional evidence that they are lymphoma cells and to determine if they are B cells, T cells or NK cells.

Cytogenetic Analysis Cells also can be studied to see if chromosomal abnormalities are present. This type of examination is referred to as a cytogenetic

analysis. Chromosome abnormalities can be important in identifying the specific type of lymphoma that is present, which may help in the choice of drugs for treatment.

Staging

"Staging" is the term used for determining the extent of the disease. This is done once the diagnosis is confirmed. Staging provides very important information to the physician who is planning treatment. Along with the specific type of lymphoma, the location of the involved lymph nodes or organs is a factor in choosing the best drugs to treat the patient and determining the appropriate duration of treatment.

Imaging Imaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT) scan are used to look for enlarged lymph nodes or organs such as the liver, spleen or kidneys. In some cases, gallium scans and positron emission tomography (PET) scans may assist the physician in identifying sites of lymphoma in the abdomen, chest or other sites.

A newer imaging procedure, FDG-positron emission tomography (FDG-PET) scanning differs from X-rays, CT, MRI and ultrasound, which only provide anatomical images; FDG-PET also measures altered tissue metabolism (activity). This functional imaging technique relies on a radioactive substance (an analogue) of glucose called FDG (2-deoxy-2[^{18}F] fluoro-D-glucose). The radiotracer is given intravenously to the patient and enters the cells. Cancer cells have a greater affinity for glucose than do normal cells. Thus, cancer cells trap more radiotracer than do nonmalignant cells, and the local tracer concentration can be measured. The FDG reveals the differences in glucose metabolism between cancer cells and normal cells. The increased FDG uptake in lymphoma cells makes FDG-PET an effective tool for detecting primary lymphoma and recurrent disease. This technique provides a very sensitive and relatively rapid assessment of a patient's response to therapy.

Blood and Marrow Tests The blood and the marrow are examined. Blood cell counts assess for anemia (low red cell levels), low white cell levels or low platelet levels, and whether lymphoma cells are present in the blood. Measurements of blood chemicals are done to evaluate organ (such as liver or kidney) involvement and determine whether immunoglobulins made by lymphocytes are deficient or abnormal.

Examination of the bone marrow may also reveal the presence of lymphoma cells.

Spinal Tap A spinal tap (lumbar puncture) and/or imaging of the brain or spinal column may be required in cases in which the type of lymphoma or the patient's symptoms suggest that the CNS might be affected.

When all of these tests are completed, the physician has information about the areas of the body that are involved.

Treatment for Non-Hodgkin Lymphomas

Factors that Influence Treatment

Six major factors are considered to determine the treatment plan. These factors are the type and grade of non-Hodgkin lymphoma, the stage of the disease, the cell type, the presence of extranodal involvement, the patient's age, and his or her symptoms. These factors are:

1. **Type and grade of non-Hodgkin lymphoma** Thirty or more subtypes of specific lymphomas or closely related lymphocytic leukemias have been categorized. Table 4 gives examples of these subtypes. To simplify this classification, many cancer specialists (oncologists) group the various subtypes according to whether, on average, the lymphoma is:
   - Growing very slowly (low grade or indolent),
   - Progressing very rapidly (high grade or aggressive), or
   - Between these two categories in rate of progression (intermediate grade).

   Classification of the specific subtypes of lymphoma requires considering the pattern of the lymph node biopsy under the microscope and whether the lymphocytes are more similar to T cells or B cells.

   Past clinical experience with the behavior of each subtype of lymphoma tells the physician, on average, whether the lymphoma will progress slowly or more rapidly.

   These categories also indicate to the physician the types of initial therapy and the intensity of treatment needed by the patient (see Table 4, page 26).

Table 4. Examples of Non-Hodgkin Lymphomas by Grade

Low-grade lymphoma of T-cell or B-cell type

Small cell lymphocytic lymphoma

Follicular lymphoma

Cutaneous T-cell lymphoma

High-grade lymphoma of B-cell or T-cell type

Large B-cell lymphoma

Mantle cell lymphoma

Burkitt lymphoma

Acute adult T-cell lymphoma

HIV/AIDS-associated lymphoma

Table 4 gives examples of subtypes based on their rate of progression. Thirty or more subtypes of specific lymphomas or closely related lymphocytic leukemias have been categorized by the World Health Organization. A listing of all the subtypes of lymphoma is shown in Table 2 (page 12).

2. **Stage of disease** The distribution of the lymphoma throughout the body may be very important in forming decisions about treatment.

   Stage I
   Lymphoma can be detected in one lymph node area or in only one organ outside of lymph nodes.

   Stage II
   Involvement of two or more lymph node regions that are near to each other, for example, all are in the neck and chest, or in the abdomen.

   Stage III
   Involvement of several lymph node regions in the neck, chest and abdomen.

   Stage IV
   Widespread involvement of lymph node areas and organs such as lungs, liver, intestines and bone.

3. **Cell type** Knowing whether the lymphoma cells are most closely related to T cells, B cells or natural killer (NK) cells may give important clues to the physician as to which treatments should be used. This distinction is determined by immunophenotyping or by using molecular diagnostic techniques. These tests measure special features of the cells that distinguish them as one of these three lymphocyte types. The aggressiveness or drug responsiveness of the lymphoma can be deduced, in part, from these measurements.

4. **Extranodal involvement** If organs outside of lymph nodes are involved, the approach to therapy is often affected. If the brain, liver, or bones are involved, for example, the approach to treatment should consider these areas outside the lymph nodes.

5. **Age** Advanced age of the patient (over 60 years old) and concurrent medical conditions are also important considerations.

6. **Symptoms** The presence of a body reaction to the lymphoma also influences the approach to treatment. Factors such as fever, exaggerated sweating, and weight loss of more than 10 percent of body weight, referred to as B symptoms, are important findings. The designation A (as opposed to B) signifies the absence of these three findings.

Decision to Treat In most cases of lymphoma, treatment is begun at the time of diagnosis. However, there are some circumstances that indicate a watch and wait approach, for example with low-grade lymphomas. These are widespread at the time of diagnosis and current therapy choices are not curative. Therefore, it may be best for a patient to be followed at appropriate intervals without beginning therapy. Some patients may remain stable for years and avoid the side effects of unnecessary therapy. However, if a patient shows signs of lymphoma progression, such as new or enlarging lymph nodes, bone or other organ involvement, or a decrease in blood cell formation that causes low red cell, low white cell or low platelet counts, therapy may be started.

The goal of treatment is to destroy as many malignant cells as possible and to induce a complete remission, that is, to eliminate all evidence of disease. In some cases in which this goal is accomplished, a cure may be achieved. Treatment may also keep the lymphoma in check for many years, even though imaging or other studies may show remaining sites of disease. This situation is sometimes referred to as partial remission.

Treatment Setting Although the treatment period may be long, most of a patient's therapy can be administered in an outpatient setting. Radiation therapy, chemotherapy or immunotherapy can be administered to patients in the outpatient clinic of an oncology center. Sometimes, short periods of hospitalization are required. If therapy is particularly intensive, it may result in prolonged or severe decreases in red cell, white 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 still may be possible even in these cases. However, if fever or other signs of infection occur, hospitalization and administration of antibiotics may be necessary.

Types of Treatment

Chemotherapy and radiation therapy are the two principal forms of treatment. Radiation therapy is used less often as the sole or principal curative therapy for lymphomas. However, it is a very important ancillary form of treatment in some cases.

Chemotherapy Chemotherapy usually requires the use of combinations of several drugs to kill the malignant cells (see Table 5, page 29). Combining drugs that have different mechanisms of action helps to prevent drug resistance. Treatment with combinations of drugs is given in cycles that last for three to four weeks. Some drugs are given continuously for several days. Others are used in an interrupted fashion on only a few days during the cycle. These choices are based on the duration of the drug's effect, the patient's tolerance of the drug, and the maintenance of adequate levels of the drug in blood or tissues. The treatment may consist of six or more cycles, lasting from 4 to 12 months. Drugs are dissolved in fluids and given to the patient via an indwelling catheter. The catheter is sometimes called a central line, a port or a Port-a-cath®.

Sometimes, two different combinations of drugs are administered in alternate cycles. Examples of combinations of drugs used in lymphoma treatment are shown in Table 6 (page 30).

Table 5. Some Drugs Used in the Treatment of Hodgkin and Non-Hodgkin Lymphomas

DNA-Damaging Drugs
These drugs react with DNA to alter it chemically and keep it from permitting cell growth.

- carboplatin (Paraplatin®)
- carmustine (BCNU, BiCNU®, Ciliadel)
- chlorambucil (Leukeran®)
- cisplatin (Platinol®)
- cyclophosphamide (Cytoxan®, Neosar®)
- dacarbazine (DTIC, DTIC-Dome®)
- ifosfamide (Ifex®)
- lomustine (CCNU, CeeNu®)
- mechlorethamine (nitrogen mustard, Mustargen®)
- melphalan (Alkeran®)
- procarbazine (Matulane®)

Antitumor Antibiotics
These drugs interact directly with DNA in the nucleus of cells, interfering with cell survival.

- bleomycin (Blenoxane®)
- doxorubicin (Adriamycin®, Rubex®)
- idarubicin (Idamycin®)
- mitoxantrone (Novantrone®)

Antimetabolites
These are chemicals that are very similar to the building blocks of DNA or RNA. They are changed from the natural chemical sufficiently so that when they substitute for it, they block the cells' ability to form RNA or DNA, preventing cell growth.

- cladribine (Leustatin®)
- cytarabine (cytosine arabinoside, Ara-C, Cytosar-U®)
- fludarabine (Fludara®)
- gemcitabine (Gemzar®)
- 6-mercaptopurine (6-MP, Purinethol®)
- methotrexate (Rheumatrex®, Trexall®)
- 6-thioguanine (Thioguanine Tabloid®)

DNA Repair Enzyme Inhibitors
These drugs act on certain proteins (enzymes) in the cell nucleus that normally repair injury to DNA. These drugs prevent the enzymes from working and make the DNA more susceptible to injury.

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

Drugs That Prevent Cells from Dividing by Blocking Mitosis
These drugs impair structures in the cell that are required for a cell to divide into two daughter cells.

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

Hormones that can Kill Lymphocytes
In high dosages these synthetic hormones, relatives of the natural hormone cortisol, can kill malignant lymphocytes.

- dexamethasone (Decadron®, Dexone®, Dexpak®)
- methylprednisolone (Medrol®)
- prednisone (Deltasone®, Meticorten®, Pred-Pak®, Sterapred®)

Immunotherapy
A new class of agents for treatment of lymphomas, called monoclonal antibodies, targets and destroys cancer cells with fewer side effects than conventional chemotherapy.

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

Unknown Mechanisms

- bexarotene (Targretin®)

Table 6. Some Examples of Drug Combinations Used to Treat Lymphomas

ABVD: Adriamycin® (doxorubicin), bleomycin, vinblastine, dacarbazine.

R-CHOP: Rituximab, cyclophosphamide, hydroxydaunomycin, Oncovin® (vincristine), prednisone.

R-FCM: Rituximab, fludarabine, cyclophosphamide, mitoxantrone.

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

R-HCVAD: Rituximab, cyclophosphamide, vincristine, Adriamycin® (doxorubicin), dexamethasone.

ProMace-Cytabom: Prednisone, methotrexate, Adriamycin® (doxorubicin), cyclophosphamide, etoposide, cytarabine, bleomycin, Oncovin® (vincristine), methotrexate.

Patients with slow-growing, indolent lymphomas often are treated with one to five drugs, depending on the disease rate of growth and other factors. Slow-growing lymphomas often come 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 faster-growing, aggressive lymphomas are frequently treated with chemotherapy that consists of four or more drugs. Intensive, multidrug chemotherapy can be very effective for the aggressive lymphomas, and cures can be achieved. Monoclonal antibody treatment has been an important addition to traditional drug therapy programs.

Clinical investigators use acronyms to communicate among themselves about specific drug combinations. The acronyms are composed of the first initials of the drugs to be used in a particular treatment regimen. Many other combinations have been developed, as clinical investigators try to determine the best grouping of drugs for a given circumstance. These circumstances include treatment of 1) a newly diagnosed lymphoma, 2) lymphoma that is not fully responsive to the initial treatment, and 3) lymphoma that returns after apparently successful initial therapy.

Radiation Therapy Few cases of lymphoma are treated solely with radiation therapy because of the likelihood that lymphoma cells are present in widespread areas. 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.

Immunotherapy There are several approaches being used to harness immune mechanisms to treat lymphoma. Examples of these therapies include monoclonal antibodies and vaccine therapy. Monoclonal antibodies target features on the surface of lymphoma cells. Antibodies are proteins that can be made in the laboratory and react with or attach to antigens on the cell of interest. These antibodies can be used in therapy in three ways: as "naked" antibodies (monoclonal antibodies), as antibodies to which radioactive isotopes are attached (radioimmunotherapies), and as antibodies to which toxins are attached (immunotoxins). The antibodies can be injected into patients in an attempt to destroy the malignant cells that carry the complementary antigen.

Antibody therapy has been an important addition to treatment programs for lymphoma. Rituximab has been used alone and is now frequently added to chemotherapy programs. It may serve to increase the frequency, quality, and duration of remissions in several types of lymphomas. Rituximab is a naked antibody that targets the antigen CD20 on the surface of B lymphocytes, the cells most frequently involved in lymphoma. It is thought that when the monoclonal antibody attaches to the B lymphocyte, either the immune system responds by destroying the cancer cell or the cell undergoes internal injury that leads to its destruction. A very important aspect of this therapy is that it does not result in some of the toxic side effects of chemotherapeutic agents, making it possible to add rituximab to chemotherapy programs.

Rituximab is an approved treatment for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma and for the first-line treatment of diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or other anthracycline-based chemotherapy regimens. Rituximab is being studied for first-line treatment of low-grade or follicular CD20-positive B-cell non-Hodgkin lymphoma.

There are two additional antibodies that are useful in therapy: iodine-131-bearing tositumomab (Bexxar®) and yttrium-90-bearing ibritumomab tiuxetan (Zevalin®).

Their use is referred to as radioimmunotherapy in that a principal effect is to carry a radioactive substance to the lymphoma cells. This approach, in effect, radiates lymphoma cells locally and selectively, minimizing the radiation effect on normal tissues. Radioimmunotherapy is currently approved for relapsed or refractory CD20-positive, low-grade, follicular or transformed B-cell lymphomas and is being studied as a possible front-line therapy.

In both naked monoclonal antibody and radioimmunotherapy treatments, normal lymphocytes are also affected but the treatment is more selective than standard chemotherapy or radiation therapy. These agents have been added to the arsenal that can be used for the treatment of lymphoma.

Finally, there are vaccine therapies that are designed to attack lymphoma cells, although they remain experimental at this time. For more information on this topic, see the Society's free publication, *Vaccine Therapy*.

Allogeneic Stem Cell Transplantation Healthy individuals have sufficient stem cells in their marrow to keep producing new blood cells continuously. Allogeneic stem cell transplantation is a technique that can restore the marrow function of patients who have had severe injury to that site. It is used for some non-Hodgkin lymphoma patients with disease that is resistant to chemotherapy. This approach is usually reserved for patients with high-grade (aggressive) non-Hodgkin lymphoma. The purpose is to be able to use very potent chemotherapy regimens, which damage the marrow severely. Without transplant, the patient would be unable to make new blood cells for a long period following treatment. Replacement of the patient's stem cells via stem cell transplantation from a compatible donor allows the use of such intensive chemotherapy.

The transplant is achieved by infusing a very small fraction of the marrow cells called stem cells. Stem cells not only reside in the marrow but a small number also circulate in the blood. They can be harvested from the blood by treating the donor with agents that cause a release of larger numbers of stem cells into the blood. They can then be collected by a process known as hemapheresis. Stem cells also circulate in large numbers in fetal blood and can be recovered from placental and umbilical cord blood after childbirth. The harvesting, freezing, and storing of cord blood provide another source of stem cells for transplantation. Since blood and marrow are both good sources of stem cells for transplantation, the term "stem cell transplantation" has replaced "bone marrow transplantation" as the general term for this procedure.

If the donor and recipient are identical twins, the transplant is called syngeneic, the medical term for "genetically identical." With a syngeneic transplant there is no immune difference and no likelihood of a host versus graft or a graft versus host reaction. If the donor and recipient are not identical twins, the transplant is called "allogeneic." An allogeneic transplant means the donor is the same species and, in practice, nearly always a match in tissue type to the recipient. The term "matched unrelated" is applied to the donor who is not a family member, but has been recruited from a large pool of potential donors by searching for the rare individual who is identical or very similar in human leukocyte antigen (HLA antigen) type to the recipient. Only a small proportion of patients will have a genetically similar sibling (brother or sister) who can be a donor. A patient's age and coexisting medical conditions are considered in deciding whether a transplant should be performed.

Nonmyeloablative Allogeneic Stem Cell Transplantation Studies of nonmyeloablative allogeneic stem cell transplantation are under way to determine the usefulness of this approach in older patients. Patients being conditioned for a nonmyeloablative transplant receive lower dosages of chemotherapy drugs and/or radiation in preparation for the transplant. Immunosuppressive drugs are used to prevent rejection of the graft and the engraftment of donor immune cells may allow these cells to attack the disease (graft versus cancer effect).

Autologous Stem Cell Infusion The important technique of harvesting patients' stem cells in marrow or blood, freezing the collection and then returning it to patients after they have received intensive chemotherapy and/or radiation therapy for their underlying disease is known as autologous transplantation. This term is misleading since transplantation implies transferring tissue from one individual to another. This technique would better be referred to as "autologous stem cell infusion."

Autologous stem cell infusion permits more patients and older patients with a relapse of their disease to receive intensive chemotherapy and rescue of their marrow function by infusing stem cells but it may not be as effective as allogeneic transplantation. Some patients with aggressive lymphomas may benefit from this treatment. In addition, patients with low-grade lymphomas, including refractory or relapsed Hodgkin lymphoma (uncommonly), whose disease continues to progress after receiving other forms of treatment, may benefit from this approach.

See the Society's free publication, *Blood and Marrow Stem Cell Transplantation* for more information.

Relapse Recurrence (relapse) of lymphoma months or years after treatment occurs in many patients. In such cases additional treatment is often successful at restoring a remission. There are so many drugs and approaches to lymphoma treatment that a physician has many choices from which to select additional therapy. If relapse occurs long after treatment, sometimes the same or similar agents may be effective. In other cases, new approaches may be used.

Side Effects of Treatment of Hodgkin and Non-Hodgkin Lymphomas

When side effects do occur, most are short-lived and disappear when therapy is completed. In recent years, new drugs have increased physicians' ability to control other side effects, such as nausea and vomiting, which used to be very troubling for many patients. The benefit of treatment, with its goal of remission and, in some cases, cure, outweighs the risks, discomfort, and unpleasantness in most cases. (See The Leukemia & Lymphoma Society's free publication, *Understanding Drug Therapy and Managing Side Effects.*)

Early Effects of Treatment 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, chronic renal disease, and others). In addition, certain drugs have a specific tendency to affect certain tissues. Two examples are the tendencies for vincristine to affect nervous tissue and bleomycin to affect the lungs.

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 cell counts are severe and continue for extended periods of time, infection may develop and require antibiotic treatment. Sometimes, doses of chemotherapy or the time between chemotherapy cycles must be altered to allow the patient's blood counts to recover from the effects of treatment.

Oral and Gastrointestinal Effects Treatment for the lymphomas may cause mouth sores, nausea, vomiting, diarrhea, constipation, bladder irritation and blood in the urine.

Other Effects Therapy can induce extreme fatigue, fever, cough, lung function impairment, and cardiac function impairment. Patients also may 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 the individual patient's susceptibility.

Effects on Fertility Patients may have a decrease in fertility after treatment. The risk of infertility varies according to the nature of the treatment, depending on the type and amount of chemotherapy, the location of radiation therapy, and the patient's age. Men who are at risk of infertility can consider sperm banking. Women who have ovarian failure after treatment will have premature menopause and require hormone replacement therapy. When childbearing is possible, whether the male or the female partner has received treatment, the incidence of fetal loss and the health of the newborn are very similar to those of healthy couples.

Late Effects of Treatment There is an increased risk of secondary cancers in patients treated for Hodgkin lymphoma and non-Hodgkin lymphomas. Radiation therapy has been associated with cancers of the breast, lung, stomach, bone and soft tissues. Often, they occur many years after treatment. Radiation therapy to the chest has been associated with various types of heart disease, including inflammation of the surrounding sac (pericardium) or myocardial infarction (classic heart attack). Injury to the thyroid gland may cause decreased thyroid gland function (hypothyroidism) and injury to the lung may also follow radiation therapy. Advances in radiotherapy have decreased the frequency of side effects but these may still occur in patients who have been treated in past decades. Exposure to chemotherapy has been associated with an increased incidence of myelogenous leukemia.

Clinical Trials

New approaches to therapy are under study in clinical trials that permit physicians to determine the beneficial effects of new treatments and what side effects they have. New drugs, new types of immunotherapy, and new approaches to stem cell transplantation are continually being explored to bring new and better treatments to the patient. Clinical trials are examining improvement in therapy for each type of lymphoma, for example, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, cutaneous T-cell lymphoma and other subtypes. New agents including the proteasome inhibitor, bortezomib (Velcade®), are being examined for the treatment of mantle cell lymphoma. A new chemotherapy agent bendamustine (Treanda™) is being tested in relapsed follicular lymphoma patients and, in combination with rituximab, for various types of lymphoma that have not responded to previous chemotherapy. Several clinical trials are studying the potential benefits of rituximab as maintenance treatment as compared to re-treatment with rituximab at the time of disease progression.

The Society's Information Resource Center, (800) 955-4572, offers guidance on how patients can work with their physicians 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 the Society's Web site at www.LLS.org.

Gene Expression Profiling It is possible to determine the expression of thousands of genes in lymphoma cells. By analyzing the pattern of expression of these genes within diagnostic categories, such as large B-cell lymphoma, two subgroups have been identified. One such category responds much better to therapy than another, indicating that lymphomas that appear to be the same according to their microscopic appearance may actually be made up of distinct groups genetically and biologically. These gene expression profiling methods will be used increasingly in the future to tease apart subgroups of lymphomas so as to design more specific, hence more effective, treatment. These complicated methods will require special automation to make them easy to apply to all patients.

Cytokines Cytokines are natural products made by certain cells. They can be mass produced using biotechnical methods. Several cytokines have been shown to enhance the immune system and may become useful to facilitate immune attack on leukemia or lymphoma cells.

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 keep them from causing a relapse. Vaccines have been used most extensively in trials studying follicular lymphoma, but all B-cell lymphomas present tumor antigens that might allow for the possibility of a potentially useful vaccine to work against them.

Social and Emotional Aspects

Living with a serious disease is a challenge. Patients may need to make lifestyle changes, which can be distressing. Lymphoma also places a strain on family members and friends. Talking to the physicians, nurses and social workers on your healthcare team may help ease concerns about the disease and the future. The professional staff is also prepared to offer referrals to other resources. Many patients feel emotional relief once they can reestablish a sense of control in their lives. The following information may assist in the management of common health problems for patients with the disease.

The diagnosis of a lymphoma may provoke a profound emotional response in patients, family members and friends. Denial, depression, a feeling of hopelessness, and fear are normal and usual reactions. No one response is either expected or unexpected.

"Why me?" is a common question patients ask. It is a normal reaction to a diagnosis of cancer and the need for treatment. Many emotions surface at the time of diagnosis and during treatment. The need for drug and other therapies, and the realization that illness and treatment will cause some changes in one's life, can prompt a range of feelings.

People newly diagnosed with cancer face uncertainty about what comes next. Together, you and your family, and your healthcare providers, can address your concerns in a clear and straightforward manner. For many people, the beginning of treatment and chance for remission bring emotional relief as the focus shifts to the treatment process ahead and the prospect of recovery.

Treatment Choices The process of making choices about chemotherapy and other treatment options can cause a great deal of anxiety. Often, if people with blood cancers talk to their healthcare providers about the medical questions they have, they feel some sense of relief in making treatment choices. In addition, the patient's physicians, nurses, social workers, and other health professionals understand the complexity of emotions and special needs of those undergoing chemotherapy. They are available to spend time with the patient, answer questions, lend emotional support, and provide referrals to other useful resources.

Family and Friends The support of family and friends can contribute to a patient's ability to cope with what lies ahead. Many healthcare providers recommend that a friend or family member accompany a patient to treatments, especially for the first several times. The presence of a friend or family member may help ease anxiety. In addition, this person can act as an advocate, asking questions for the patient and listening to and retaining treatment information. Often, patients with cancer become acquainted with one another, and these friendships, too, can provide a support system.

Lifestyle Changes A change in lifestyle will occur for a patient with cancer and his or her family. Daily routines may have to be adjusted to accommodate treatment schedules. However, many individuals are able to carry out their day-to-day routines with few or no changes.

Stress and side effects associated with the diagnosis of cancer and its treatment often will cause a person to question his or her self-worth, identity and appearance. These feelings are common and may affect one's relationships, including sexual relationships. Sexual desire may decrease for a period of time, then return. Recognition that these feelings are normal, and that many side effects are temporary, may be reassuring. Open, honest communications regarding fears and concerns can be very helpful. Your healthcare team will work toward minimizing any discomforts of treatment. Ask any questions and raise any concerns related to emotional or social issues, so that your physician, nurses, and social workers can help provide the answers and make referrals to available support groups, counseling services, or community programs. For more information, see the Society's free booklet, *Coping: Support for People Living with Leukemia, Lymphoma or Myeloma*.

The Leukemia & Lymphoma Society offers programs through its local chapters to help ease the emotional and economic stress that come with a blood cancer diagnosis. Visit the Society's Web site at www.LLS.org or contact the Society's Information Resource Center at (800) 955-4572 to locate a chapter in your area, order free publications, or speak directly to an Information Specialist.

Glossary

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

Antibodies
Proteins that are made by B lymphocytes (especially their derivatives, plasma cells) in response to foreign substances called antigens. For example, infectious agents like viruses or bacteria cause lymphocytes to make antibodies against them. In some cases (for example, the measles virus) the antibodies are protective and prevent a second infection. These antibodies can be used to identify specific cells and improve the classification of lymphoma (see Immune Globulins, Gamma Globulins).

Antigens
Any part of a molecule capable of being recognized by the immune system. The immune system responds by producing antibodies that bind to the antigen.

Antiglobulin Test
This laboratory procedure can identify antibodies on the surface of red cells or platelets. Patients with lymphoma may make antibodies to their own red cells or platelets (auto or self-directed antibodies). These autoantibodies may lead to anemia or a low platelet count in patients. The antiglobulin test can be used to identify the presence of autoantibodies on blood cells.

Apheresis
The process of removing components of a donor's blood and returning the unneeded parts. The process uses continuous circulation of blood from a donor, through an apparatus, and back to the donor. Apheresis makes it possible to remove desired elements from large volumes of blood. Platelets, red cells, white cells, or plasma can be removed separately. For example, this technique permits the harvest of enough platelets for transfusion from one donor (rather than six to eight separate donors). In so doing, the recipient of the platelets is exposed to fewer donors or can be given human leukocyte antigen (HLA antigen) matched platelets from a single related donor. This technique is also used to remove circulating blood stem cells that can be frozen, stored, and later used instead of marrow stem cells for transplantation.

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 is necessary (lymph node biopsy). The tissue is placed in preservative, stained with dyes, and examined under a microscope by a pathologist.

Bone Marrow

The bones are hollow and their central cavity is occupied by marrow, a spongy tissue that plays the major role in the development of blood cells. After puberty, marrow in the backbones, ribs, breastbone, pelvis, shoulders and skull is most active in blood cell formation.

Chromosomes

All normal human cells with a nucleus contain 46 structures called chromosomes. The genes, specific stretches of DNA, are the principal structures that make up the chromosomes. An average-sized chromosome contains enough DNA to account for about 2,000 genes. The X and Y chromosomes are the determinants of our gender and are referred to as the sex chromosomes: two X chromosomes in females and an X and Y chromosome in males. The number or shape of chromosomes may be altered in lymphoma cells.

Colony-Stimulating Factor (see Cytokines)

Computed Tomography (CT) Scan

This is 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 or abdomen 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.

Cytogenetics

The process of analyzing the number and shape of the chromosomes of cells. The individual who prepares, examines, and interprets the number and shape of chromosomes in cells is called a cytogeneticist.

Cytokines

These are cell (cyto)-derived chemicals that are secreted by various types of cells and act on other cells to stimulate or inhibit their function. Chemicals derived from lymphocytes are called lymphokines, and chemicals derived from lymphocytes that act on other white blood cells are called interleukins, because they interact between two types of leukocytes. Some cytokines can now be made commercially and used in treatment. Granulocyte colony-stimulating factor (G-CSF) is one such cytokine. It stimulates the production of neutrophils and shortens the period of low neutrophil counts in the blood after chemotherapy. Cytokines that stimulate cell growth are sometimes referred to as growth factors.

Gallium Scintography (Scan) Gallium-67

A radioactive isotope that is used to image lymph nodes and lymphoma masses in persons with lymphoma. Gallium behaves like iron and thus it combines with an iron-binding protein in lymphoma cells. The radioactivity given off can be measured and related to areas in the body that contain lymph node masses of lymphoma cells. The location, for example abdomen or chest, and an estimate of size of the enlarged lymph nodes or masses can be determined from the scans. Usually, the gallium scan is combined with other imaging approaches such as computed tomography (CT) or magnetic resonance imaging (MRI) in an effort to locate all areas of lymphoma involvement.

Gamma Globulins

A portion or fraction of the proteins that are in the plasma. When plasma proteins were separated by chemical methods, they were given the designation of albumin or globulin. The latter were separated into three major groups, called alpha, beta, or gamma globulins. The gamma globulins contained the antibodies in the plasma. These antibodies, or gamma globulins, are now sometimes referred to as immune globulins or immunoglobulins because immune cells, specifically B lymphocytes and their derivatives, plasma cells, make them. Gamma globulins, or immunoglobulins, are key elements of the immune system because they contain the antibodies that protect us from infection. Patients with immune deficiencies, such as those with chronic lymphocytic leukemia and some patients with lymphoma, whose B lymphocytes cannot make gamma globulin, may be given injections of gamma globulin periodically in an effort to decrease the risk of infection.

Growth Factors (see Cytokines)

HLA Antigen

The abbreviated term for human leukocyte antigens. These proteins are on the surface of most tissue cells and give each individual his or her unique tissue type. Hence, the reason that the testing for HLA antigens is referred to as tissue typing. There are four major groups of HLA antigens: A, B, C and D. These proteins act as antigens when donated (transplanted) to another recipient/candidate, e.g., a bone marrow or stem cell recipient. If the antigens on the donor cells are identical (e.g., in identical twins) or very similar (e.g., in HLA antigen matched sibling), the transplantation (donated marrow or cells) is more likely to survive in the recipient (engraft). In addition, the recipient's body cells are less likely to be attacked by the donated cells (graft versus host disease).

Hematologist

A physician who specializes in the treatment of blood cell diseases. This person is either an internist who treats adults, or a pediatrician who treats children. Hematopathologists are pathologists who specialize in the diagnosis of blood cell diseases and who perform the specialized laboratory tests often required to make a conclusive diagnosis.

Hematopoiesis

The process of blood cell development in the marrow. The most primitive cells in the marrow are stem cells. They start the process of blood cell development. The stem cells turn into young or immature blood cells, such as red cells or white cells, of various types. This process is called differentiation. The young blood cells then further develop into fully functional blood cells in a process known as maturation. The cells then leave the marrow, enter the blood and circulate throughout the body. Hematopoiesis is a continuous process that is active normally throughout life. The reason for this activity is that most blood cells live for short periods and must be continuously replaced. About five hundred billion blood cells are made each day. Red cells live about four months, platelets about 10 days and most neutrophils for two or three days. This requirement for very rapid replacement explains the severe deficiency in blood cell counts when the marrow is injured by replacement with leukemia, lymphoma, or myeloma cells or by intensive cytotoxic treatment.

Human Immunodeficiency Virus (HIV)

The agent that leads to the development of the acquired immunodeficiency syndrome (AIDS). Individuals with HIV infection have an increased risk of developing lymphoma. The lymphomas are of the B-cell type and may involve the brain or be very widespread at the time of occurrence.

Immune Globulins or Immunoglobulins (see Gamma Globulins)

Immunophenotyping

A method that uses the reaction of antibodies with antigens to determine the specific types of cells in a sample of blood cells, marrow cells, or lymph node cells. A tag is attached to antibodies that react with specific antigens in the cell. The tag can be identified by the laboratory equipment used for the test. This method helps to subclassify cell types that may, in turn, help the physician to decide on the best treatment for that type of lymphoma.

Indwelling Catheter

Several types of catheters (e.g., Hickman®, Broviac® and others) are used in patients receiving intensive chemotherapy and/or nutritional support. An indwelling catheter is a special sort of tubing that is inserted into a large vein in the upper chest. The catheter is tunneled under the skin of the chest to keep it firmly in place. The exposed end of the catheter can be used to inject medications, fluids, or blood products or to withdraw blood samples. With meticulous care, catheters can remain in place for very long periods of time (many months), if necessary.

Lactic 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 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 aggressive lymphomas are often associated with marked elevations in serum LDH.

Leukocytes

A synonym for white cells (see White Cells).

Leukopenia

Below normal counts in the number of blood leukocytes (white cells).

Lymph Nodes

Small structures the size of beans that contain large numbers of lymphocytes and are connected to each other by small channels called lymphatics. These nodes are distributed throughout the body. In patients with lymphoma, Hodgkin lymphoma, and some types of lymphocytic leukemia, the malignant lymphocytes grow and expand the lymph nodes so that they may be enlarged in size. 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 location.

Lymphadenopathy

Enlargement of lymph nodes.

Lymphocytes

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

Magnetic Resonance Imaging (MRI)

This technique provides detailed images of body structures. It differs from a CT scan in that the patient is not exposed to X-rays. Computer images of body structures convert the signals generated in the tissues in response to a magnetic field produced by the instrument. Thus, the size (or change in size) of organs such as the lymph nodes, liver and spleen, or tumor masses can be measured.

Minimal Residual Disease (MRD)

After treatment blood and marrow may appear normal. Minimal residual disease (MRD) is the term used to describe the small amounts of lymphoma cells that may remain after treatment, which are identified only by sensitive molecular techniques.

Multidrug Resistance (MDR)

A characteristic of cells that makes them resistant simultaneously to the effects of several different classes of drugs. There are several forms of MDR. Genes that govern how the cell will respond to the chemical agents determine each form of MDR. The first identified mechanism of MDR involves the cell's ability to pump several drugs out of its interior. A pump in the cell membrane rapidly ejects drugs out of the cell,

preventing them from reaching a toxic concentration. A second mechanism of the resistance to drugs can be traced to the expression of genes that direct the formation of high amounts of the protein that prevent the drugs from having their effects on the malignant cells.

Mutation

An alteration in a gene that results from a change (injury) to the DNA in a cell. A germ cell mutation is present in the egg or the sperm and is transmitted from parent(s) to offspring. A somatic cell mutation occurs in a specific tissue and can result in the growth of that tissue cell into a tumor. In leukemia, lymphoma, or myeloma, a primitive marrow or lymph node cell undergoes a mutation(s), which leads to the formation of a tumor. In these cases, the tumors usually are widely distributed when detected; they typically involve the marrow or lymph nodes in many sites.

Neutropenia

A lower than normal number of blood neutrophils, a type of white cell.

Neutrophils

The principal phagocyte (microbe-eating) cell in the blood. This blood cell is the main cell that combats infections. Often, it is not present in sufficient quantities in patients after chemotherapy, which increases their susceptibility to infection. A neutrophil may be called a "poly" or "seg."

Oncologist

A physician who diagnoses and treats patients with cancer. Oncologists are usually internists who treat adults, 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 treat cancer. These physicians cooperate and collaborate to provide the best treatment plan (surgery, radiation therapy or chemotherapy) for patients.

Oncogene

A mutated gene that is the cause of a cancer. Several subtypes of acute myelogenous leukemias, acute lymphocytic leukemia, lymphomas, and nearly all cases of chronic myelogenous leukemia have a consistent mutated gene (oncogene).

Opportunistic Infections

The lymphomas may be complicated by unusual infections because of the susceptibility of intensively treated patients and other factors that might suppress the immune system. "Opportunistic" is the term used to describe infections with bacteria, viruses, fungi, or protozoa to which individuals with a normal immune system are not susceptible. These organisms take advantage of the opportunity provided by immunodeficiency, especially when coupled with very low white cell counts resulting from therapy or the disease.

Phagocytes

Cells that readily eat (ingest) microorganisms like bacteria or fungi and can kill them as a means of protecting the body against infection. The two principal phagocytes in the blood are neutrophils and monocytes. A decrease in the number of these blood cells is the principal cause of susceptibility to infection in patients treated with intensive radiation therapy and/or chemotherapy, which suppress blood cell production in the bone marrow.

Platelets

Small cells (about one-tenth the volume of red cells) that stick to the site of blood vessel injury, aggregate with each other, and seal off the injured blood vessel to stop bleeding.

Platelet Transfusion

The transfusion of donor platelets is frequently needed to support patients treated for lymphoma. The platelets can be pooled from several unrelated donors and given as "pooled random-donor platelets." It takes an amount of platelets from about six one-unit blood donors to significantly raise the platelet count in a recipient. Sufficient platelets can be given by one donor if his or her platelets are obtained by apheresis. The apheresis machine skims the blood passing through it of large volumes of platelets. The red cells and plasma are returned to the donor. The advantage of single-donor platelets is that the patient is not exposed to the different antigens on platelets from many different people and is less likely to develop antibodies against donor platelets. HLA antigen-matched platelet transfusion can be given from a related donor with an identical or very similar HLA antigen tissue type.

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 using a microscope. The technique can detect the presence of one leukemia cell among 500,000 to one million nonleukemia cells. PCR requires a specific DNA abnormality or marker, such as an oncogene, in the leukemia or lymphoma cells for its use.

Positron Emission Tomography Scan (PET)

This procedure is another means to image lymphoma masses. In this technique, a type of sugar called glucose, 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 is concentrated in areas of lymphoma. As a result, the lymphoma sites can be localized to areas of the body by scanning areas of intense positron particle emission. PET is combined with CT to establish precise localization of lymphoma masses, and PET can detect very small lymphoma masses compared to other imaging procedures. In some cases, successfully treated lymphomas may convert to fibrous tissue that may look like a mass in imaging studies, perhaps making the physician 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 follow-up after treatment.

Radioactive Isotope

A form of a molecule that emits radiation. Certain types of radiation can damage cancer cells. Physicians use radioactive isotopes to treat cancer in several ways, including attaching the isotope to antibodies. The antibodies can attach to the cancer cell and the radiation can destroy it.

Radiotherapy

The use of X-rays and other forms of radiation in treatment. Radiotherapy is useful in the treatment of localized lymphomas, especially Hodgkin lymphoma, central nervous system lymphoblastic leukemia, and localized myeloma.

Red Cells

Blood cells that carry hemoglobin, which binds oxygen and carries it to the tissues of the body. Also known as erythrocytes, the red cells make up about 45 percent of the volume of the blood in healthy individuals.

Relapse or Recurrence
A return of the disease after it has been in remission following treatment.

Remission
A complete disappearance of a disease, usually as a result of treatment. The terms "complete" or "partial" are used to modify the term "remission." Complete remission means all evidence of the disease is gone. Partial remission means the disease is markedly improved by treatment, but residual evidence of the disease is present.

Resistance to Treatment
The ability of cells to live and divide despite their exposure to a drug that ordinarily kills cells or inhibits their growth. This is the cause of refractory malignant disease, whereby a proportion of malignant cells resists the damaging effects of a drug or drugs. Cells have several ways to develop drug resistance (see Multidrug Resistance [MDR]).

Somatic Mutation
The alteration of a gene in the cells of a specific tissue causes the gene to become a cancer-causing gene (oncogene). It is called somatic to distinguish it from a germ cell mutation, which can be passed from parent to offspring. Most cases of cancer are caused by a somatic mutation in a primitive marrow (blood-forming) cell. If the mutation results from a major abnormality of chromosomes such as a translocation, it can be detected by cytogenetic examination. Often the alteration in the gene is more subtle and requires more sensitive tests to identify the oncogene.

Spleen
An organ of the body that is in the left upper portion of the abdomen just under the left side of the diaphragm. Just like lymph nodes, the spleen contains clusters of lymphocytes and it also filters out old or worn-out blood cells. It is often affected in leukemia, especially the lymphocytic leukemias, lymphomas, and Hodgkin lymphoma. Enlargement of the spleen is referred to as splenomegaly. Removal of the spleen by surgery is called splenectomy. Removal of the spleen can be done without any ill effect since other organs such as the lymph nodes and liver can perform most of its functions.

Stem Cells
Primitive cells in marrow that are important in making red blood cells, white cells, and platelets (see Hematopoiesis). Generally, the 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 therapy.

Thrombocytopenia
A lower than normal number of blood platelets.

Toxin
A naturally derived substance that is a poison for cells. A toxin can be attached to antibodies, which attach to cancer cells. The toxin may kill the cancer cells.

Translocation
An abnormality of chromosomes in marrow or lymph node cells, which occurs when a piece of one chromosome breaks off and sticks to the end of another chromosome. In a balanced translocation, each of two chromosomes breaks off and the lost piece sticks to the broken end of the other chromosome. The gene at which the break occurs is altered. This is one form of a somatic mutation, which may transform the gene into an oncogene, or cancer-causing gene.

Tumor Suppressor Gene (Anti-oncogene)
A gene that acts to prevent cell growth. If a mutation occurs in this gene, it may make the individual more susceptible to the development of cancer in the tissue in which the mutation occurs.

White Cells
A synonym for leukocytes. There are five major types of white cells: neutrophils, eosinophils, basophils, monocytes, and lymphocytes.

The Leukemia & Lymphoma Society would like to acknowledge Marshall A. Lichtman, M.D., Executive Vice President, Research and Medical Programs, who contributed the material presented in this booklet.

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Call Our Information Resource Center
The Society's Information Resource Center (IRC) provides patients, families and healthcare professionals with the latest information on leukemia, lymphoma and myeloma. Our information specialists – master's level oncology professionals – are available by phone (800.955.4572) Monday through Friday, 9 am to 6 pm (ET); via email (infocenter@LLS.org); or chat online at www.LLS.org (click on "Live Help").
Call 800.955.4572 for a complete directory of our patient services programs.
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