



The Lymphomas:

Hodgkin Lymphoma & Non-Hodgkin Lymphoma



**The Leukemia &
Lymphoma Society®**

Fighting Blood-Related Cancers

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*Printing of this publication is made possible by an education grant
from Genentech and IDEC Pharmaceuticals Corporation.*

Introduction

This booklet provides information about the lymphomas for patients and their families. A glossary at the end of the booklet may help the reader understand the technical terms. We hope this information is of assistance. We would welcome comments as to the clarity of the information provided or the omission of information that would have been helpful.

Lymphoma is a general term for a group of cancers that originate in the lymphatic system. The lymphomas are divided into two major categories: Hodgkin lymphoma and all other lymphomas. Hodgkin lymphoma was named for Thomas Hodgkin, an English physician who described several cases of the disease in 1832. Hodgkin lymphoma represents about 8 percent of all lymphomas.

This year (2001), nearly 64,000 persons in the United States will learn that they have lymphoma. This figure includes approximately 7,400 new cases of Hodgkin lymphoma. All of the other malignant lymphomas are referred to as non-Hodgkin lymphoma. About 56,200 new cases of non-Hodgkin lymphoma (abbreviated as NHL) will occur this year in the United States.

Lymphoma results when a lymphocyte (a type of blood cell) undergoes a malignant change and accumulates because of exaggerated multiplication and/or a failure to die, interfering with the growth of normal blood cells and creating masses of tumors in lymph nodes. Before discussing the disease further, brief descriptions of normal blood and marrow and the lymphatic system, including lymph nodes, are provided for background.

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** Words in the glossary are italicized the first time that they appear in the text.*

Bone Marrow-Blood Components

Marrow is the spongy tissue where development of all types of blood cells takes place. It occupies the central cavity of bone. All bones have active marrow at birth. 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 is actively making blood cells.

The process of blood cell formation is called *hematopoiesis*. A small group of cells in the marrow, the *stem cells*, are responsible for making all the blood cells. The stem cells eventually develop into the specific blood cells by a process of *differentiation* (see Figure 1).

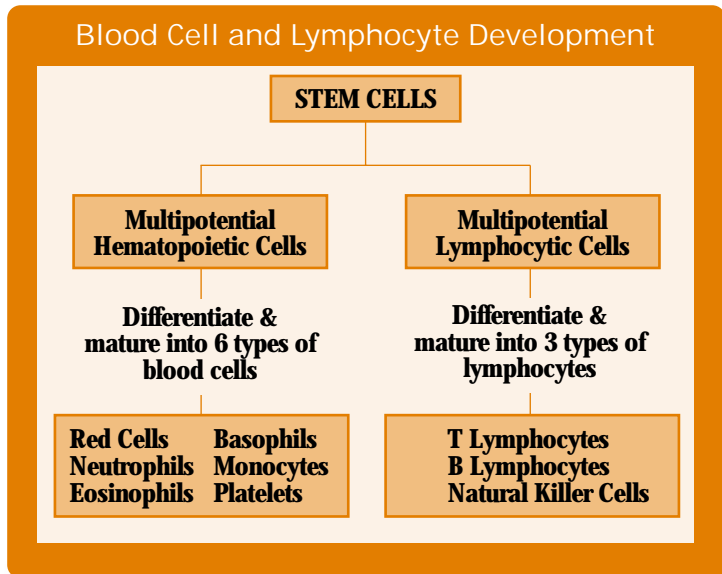


Figure 1. This figure depicts an abbreviated diagram of the process of hematopoiesis. This process involves the development of functional blood and lymphatic cells from stem cells.

Normal Blood and Marrow

Blood is composed of plasma and cells suspended in plasma. The plasma is largely 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 folic acid), and *antibodies*, including those we develop from our vaccinations (such as poliovirus antibodies). The cells include *red cells*, *platelets*, *neutrophils*, *monocytes*, *eosinophils*, *basophils*, 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 tissues. The platelets are small cells (about one-tenth the size of red cells) that help stop bleeding when injury occurs. For example, when the skin is injured, the blood vessels are torn open. Platelets stick to the torn surface of the vessel, clump together, and plug up the bleeding site. The vessel wall then heals at the site of the clot and returns to its normal state.

The neutrophils and monocytes are *white blood cells*. They are called *phagocytes* (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 move into the tissues where they can ingest invading bacteria or fungi and help prevent or cure an infection. Eosinophils and basophils are two additional types of white cells that participate in allergic responses.

Most lymphocytes, another type of white blood cell, are in the *lymph nodes*, the *spleen*, *bone marrow*, intestines, and lymphatic vessels; some enter the blood. About 20 percent of the white cells in the blood and 5 percent of cells in the marrow are lymphocytes. There are three major types of lymphocytes: *T cells*, *B cells*, and natural killer (NK) cells.

The Lymphatic System

The lymph nodes are the major components of the lymphatic system and have a special internal structure. The nodes are small, bean-sized, encapsulated collections of lymphocytes, the principal cells of the lymphatic system.

Lymph nodes are distributed throughout the body, from the head to the feet. Major lymph node clusters are present in the neck, near the collarbone, in the armpits, inside the chest, inside the abdomen, and in the groin and the pelvis. They also are found adjacent to blood vessels and organs like the lungs, liver, and kidneys. The gastrointestinal tract has special collections of lymphocytes, which appear in the tonsils and adenoids and in the lining of the stomach and intestine. The marrow and the spleen have special collections of lymphocytes within them, as well (see Figure 2).

New lymphocytes are made continuously in the nodes. They eventually develop into the three major types of lymphocytes. These lymphocytes are important cellular components of the immune system, which helps the body combat infection. B lymphocytes when stimulated by *antigens* mature into plasma cells. The latter produce antibodies to help combat infectious agents like bacteria, viruses, and fungi. T lymphocytes have several functions, including helping B cells to make antibodies and eliminating cells infected with viruses. T lymphocytes make and secrete blood chemicals, called *lymphokines*, into the tissue. These fluids play an important role in the immune response. Natural killer cells may be capable of attacking cancer cells to assist in their elimination.

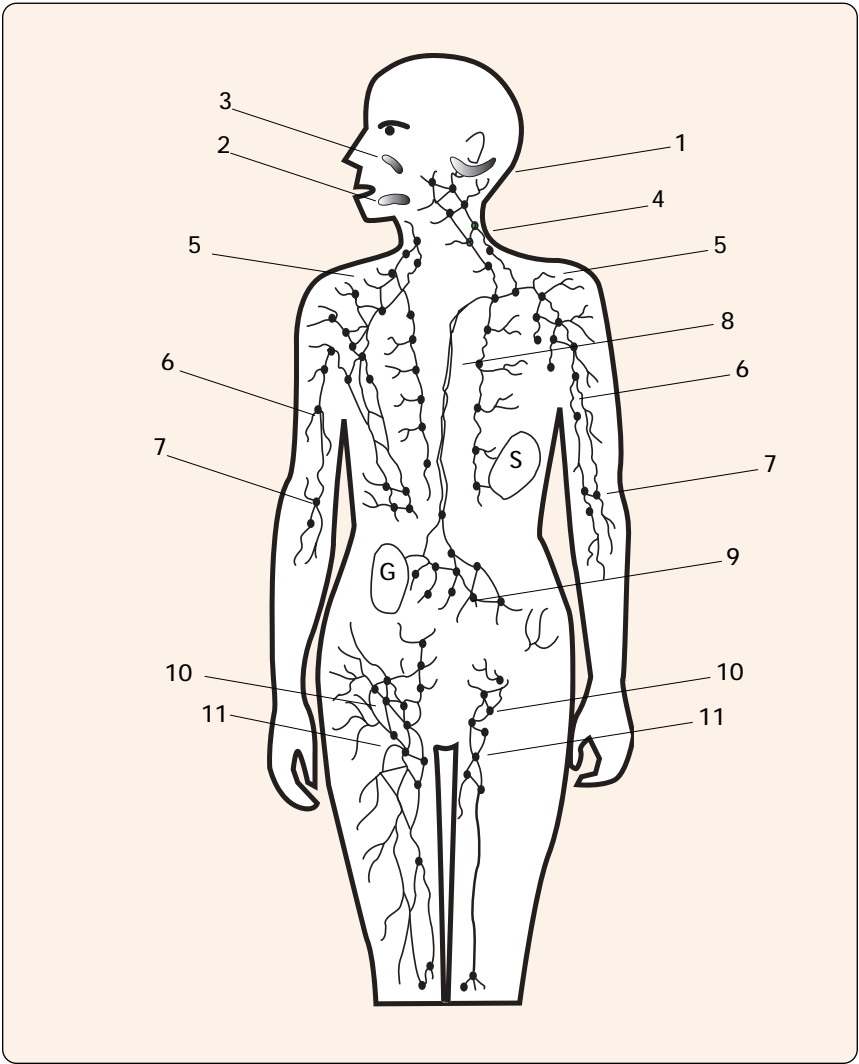


Figure 2. A Silhouette of the Human Body. It has been estimated that there are about 600 lymph nodes in the human body. The numbers denote areas of lymph nodes that frequently are involved in Hodgkin and other lymphomas. Lymph nodes: 1) around the ears, 2) around the jaw, 3) comprising the tonsils and adenoids, 4) in the front and back of the neck, 5) above and below the collar bone, 6) in the armpit, 7) near the elbow, 8) in the chest, 9) in the abdomen, 10) in the pelvis, and 11) in the groin. "S" shows the location of the spleen, which contains many clusters of lymphocytes. These clusters may be involved in the malignant process, grow, and lead to involvement and enlargement of the spleen. "G" indicates the gut-associated (intestinal) lymph tissue that may be the site of lymphoma development.

The lymph nodes are connected by an elaborate system of tiny channels, called lymphatic vessels. Lymphatic vessels contain lymph, a fluid that has a milky appearance. Lymphocytes are suspended in the lymph and circulate through the lymph nodes via these vessels. The lymphatic vessels drain into a few very large lymphatic vessels that empty into a blood vessel, thus permitting lymphocytes to enter the blood. Lymphocytes circulate freely through the lymphatic system and blood to all parts of the body (see Table 1).

Table 1. Some Elements of the Lymphatic System

lymph nodes	intestinal lymph areas	plasma cells
tonsils and adenoids	lymphatic vessels	natural killer (NK) cells
spleen	T lymphocytes	lymphokines
marrow	B lymphocytes	

The Lymphomas

Lymphomas are cancers that begin by the malignant transformation of a lymphocyte in the lymphatic system. The prefix “lymph-” indicates their origination in the malignant change of a lymphocyte and the suffix “-oma” is derived from the Greek word meaning “tumor.”

Lymphomas, including Hodgkin lymphoma, result from an acquired injury to the DNA of a lymphocyte. Scientists know that the damage to the DNA occurs after birth and, therefore, is acquired rather than inherited. The change or *mutation* of DNA in one lymphocyte produces a malignant transformation. This mutation results in the uncontrolled and excessive growth of the lymphocyte, and confers a survival advantage

on the malignant lymphocyte and the cells that are formed from its multiplication. The accumulation of these dividing cells results in the tumor masses in lymph nodes and other sites.

Lymphomas generally start in lymph nodes or collections of lymphatic tissue in organs like the stomach or intestines. Lymphomas may involve the marrow and the blood in some cases. Spread from a lymphoma site is not unexpected. Lymphocytic leukemias originate and are most prominent in the marrow and spill over into the blood. They may spread to and involve the lymph nodes.

Causes and Risk Factors

The annual incidence of lymphoma has nearly doubled over the last 35 years. The reasons for this increase are not certain and are probably multiple. This increase was prior to the entry and spread of the immunodeficiency virus in the human population. Since the mid 1980s, the incidence of lymphoma in individuals infected with the *human immunodeficiency virus (HIV)*, which is between 50 and 100 times the incidence rate expected in uninfected individuals, has contributed modestly to the increase in lymphoma incidence. The principal cause of the increase in lymphoma is unknown. There is an apparent increase in lymphoma incidence in communities where farming is prevalent. Studies point to specific ingredients in herbicides and pesticides as being associated with lymphoma occurrence but the quantitative contribution of such exposures to the frequency of lymphoma has not been defined.

Exposure to infectious agents, both viruses and bacteria, is implicated in lymphoma. In certain geographical regions, infection with Epstein-Barr virus may foster some subtypes of lymphoma, such as African *Burkitt's*

Non-Hodgkin Lymphoma Age-Specific Incidence Rates 1993-1997

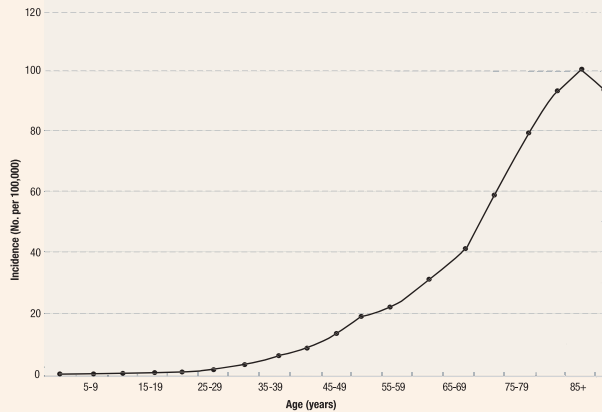


Figure 3: The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of non-Hodgkin lymphoma each year per 100,000 people in the relevant age group. (Data: National Cancer Institute SEER Program.) Although lymphoma occurs at virtually all ages, it is very uncommon under age 10 and increases significantly with age. Whereas 10 cases per 100,000 occur in people in their late 30s, the incidence increases progressively to 90 cases per 100,000 in 80-year-olds.

lymphoma. Even in these lymphoma cases, an alteration in DNA results in the malignant transformation to cancer. The high frequency of the viral infection may be a contributing factor. Human T cell lymphocytotropic virus (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 lymphoma in the stomach wall.

The cause of Hodgkin lymphoma also is uncertain. Many studies of environmental, especially occupational, linkages have been conducted with ambiguous results. The Epstein-Barr virus has been associated with about one-third of cases of the disease. It has not been established

conclusively as a cause of Hodgkin lymphoma, however. Persons infected with HTLV and HIV also have an increased probability of developing Hodgkin lymphoma. As with many cancers, there are occasional cases of familial clustering. There is an increase in incidence of Hodgkin lymphoma in siblings of patients with the disease. Most cases of the disease occur in persons without identifiable risk factors and most persons with presumptive risk factors do not get the disease.

The incidence of non-Hodgkin's lymphoma increases with age, as depicted in Figure 3. About 4 cases per 100,000 persons occur in 20-year-old individuals. The rate increases tenfold to 40 cases per 100,000 by age 60 and over twenty-fold to 80 cases per 100,000 persons after age 75.

Hodgkin lymphoma has a different risk pattern (see Figure 4). The disease increases to a peak incidence of 5 to 6 cases per 100,000 persons in their mid-20s. It falls to less than half that rate in middle age and increases in frequency in older individuals. This pattern differs among ethnic groups. For example, the disease occurs more frequently in younger individuals (ages 10-40) of European descent than those of African, Asian, or Hispanic descent.

Hodgkin Lymphoma

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

The terms used to describe the diseases have a historical context. Hodgkin lymphoma was so named because Thomas Hodgkin described several such cases in 1832 that were accepted as a new malignant condition involving lymph nodes. It was about 40 years later that the

concept of lymphomas (originally called lymphosarcoma), as 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, which influences disease classification throughout the world. The disease was called Hodgkin's disease for about 170 years and was officially changed to Hodgkin lymphoma when sufficient evidence accrued that the cancer originated in a lymphocyte. Even though the disease was principally manifest in lymph nodes and lymphatic tissues, it was not certain what the cell of origin was until the late 20th century.

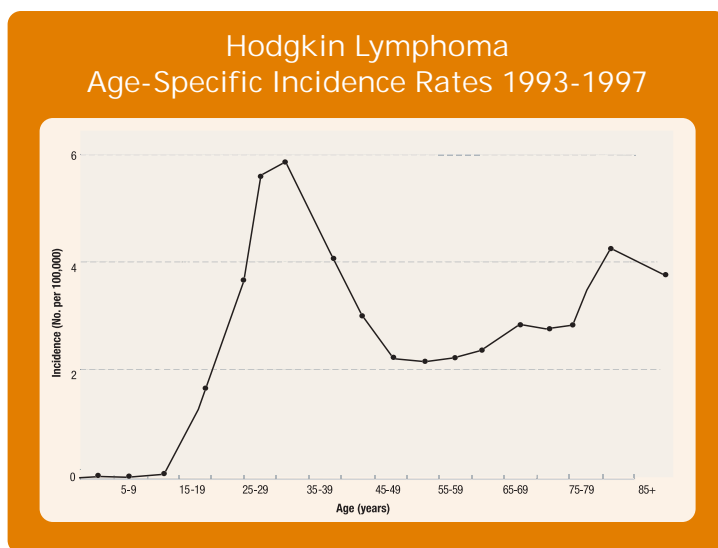


Figure 4: The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of Hodgkin lymphoma each year per 100,000 people in the relevant age group. (Data: National Cancer Institute SEER Program.)

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 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 distinctive finding in Hodgkin lymphoma. The spleen may be enlarged.

The physician may order an imaging test if the patient's medical history and physical exam lead to suspicion of Hodgkin lymphoma (see below). These tests may reveal enlarged nodes in either the chest or abdomen, or both. Tumor masses can occur outside the lymph nodes in the lung, bones, or other tissues, as well.

Diagnosis

The steps taken in determining the presence of Hodgkin lymphoma and its extent are important for diagnosis and for assessing the approach to treatment. 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. Several patterns of lymph node changes are characteristic and diagnostic of Hodgkin lymphoma. The changes can be categorized into four patterns: lymphocyte predominance, nodular sclerosis, mixed cellularity, or lymphocyte depletion types of Hodgkin lymphoma.

In some cases, the use of *immunophenotyping* can help distinguish Hodgkin lymphoma from other types of lymphomas or other lymph node reactions that are not cancerous. The pathologist also uses the

presence of special cells to confirm the diagnosis. These cells are called Reed-Sternberg cells in recognition of the pathologists who first described them. Other related cells are referred to as Hodgkin's cells.

The pathological diagnosis of Hodgkin lymphoma can be difficult. Diagnosis often requires an experienced pathologists to analyze the biopsy slides.

Staging (Determining the Extent of Disease)

In addition to physical examination, the physician can use imaging procedures 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 tumor in one site or another. In most cases, these procedures will include *computed tomography (CT)* or *magnetic resonance (MR) imaging* of the abdomen.

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 these studies permits the patient to be assigned to a "stage" of disease.

- **Stage I** represents apparent involvement of a single lymph node region or a single organ, such as bone.
- **Stage II** indicates the 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** represents the involvement of several lymph node regions in the neck and chest and abdomen.

• **Stage IV** means there is widespread involvement of lymph nodes and other organs, such as lungs, liver and bone.

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 these symptoms belong to the “B” category. For example, Stage IIB indicates that the patient has two nearby lymph node sites involved by the disease and has fever, exaggerated sweating, or weight loss. Examples of two nearby sites include enlarged lymph nodes in the neck and near the collarbone or in the neck and the armpit.

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

Patients with B symptoms often require a more aggressive treatment approach. The extent of disease and the presence of B symptoms determine whether radiation *therapy*, *chemotherapy*, or both are recommended for treatment (see Table 2).

Table 2. Special Considerations in the Treatment of Hodgkin Lymphoma

Large chest lymph nodes	Organs (e.g., lungs, liver, bone) involved
Large spleen	Severe anemia
Large number of lymph node groups affected	Advanced age

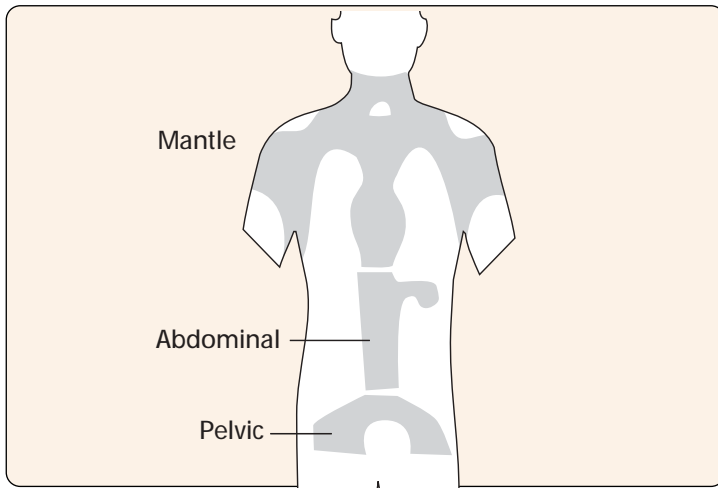


Figure 5. Three Principal Radiation Fields Used in the Treatment of Hodgkin lymphoma. The principle of treatment is to cover neighboring lymph nodes into which small clumps of malignant cells have migrated through connecting lymphatic vessels. These lymph nodes may not have enlarged sufficiently to be detected. Early studies of patients who had recurrences at the margins of smaller x-ray fields led to the policy of using larger fields to prevent recurrence and increase the cure rate.

Treatment

The goal of treatment is to cure the patient. Either radiation therapy or chemotherapy can result in cures. If the disease is localized, radiation therapy is often used alone. Radiation therapy is usually given in large blocks, or fields, so that the cancerous lymph nodes as well as the neighboring lymph nodes are treated (see Figure 5). These fields are referred to as “mantle,” referring to the neck and chest; “abdominal,” referring to the lower chest and upper abdomen; and “pelvic,” referring to the lower abdomen and groin.

Radiation involves the use of special machines that produce high energy rays that are capable of killing the lymphoma cells. Shielding of 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 of severity, such as fever or weight loss, chemotherapy is often used alone. In a circumstance intermediate to these extremes, individualized decisions regarding the use of either radiation therapy or chemotherapy, or both, are made. In some cases of Hodgkin lymphoma, it may be advisable to combine chemotherapy with radiation therapy for improved survival.

Course and Outcome

The effectiveness of therapy depends upon the age of the patient and the extent (stage) of the disease. A large proportion of patients is cured after initial treatment. For the smaller proportion that may have a *recurrence* of disease, or a *relapse*, re-treatment with radiation therapy or chemotherapy is often successful. These patients may be cured or have very prolonged disease-free periods after their second treatment. In occasional patients with evidence of progressive disease, use of *autologous* blood or marrow stem cell infusion permits intensive chemotherapy that can induce *remission* and a long-term, disease-free interval. Over 75 percent of patients diagnosed with Hodgkin lymphoma can be cured by current treatment approaches.

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. The effects of chemotherapy and radiation therapy can enhance susceptibility 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.

The improvement in the treatment of Hodgkin lymphoma, the 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. When patients are cured, their immune function may improve. The risk of severe or unusual infectious disease complications may then decrease during the post-treatment period. Herpes zoster (“shingles”) is an example of a viral disease that occurs with increased frequency in patients with Hodgkin lymphoma.

Non-Hodgkin Lymphoma

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, like a bone, a lung, or the skin. In these circumstances, patients may experience symptoms that refer to that site, such as bone pain, cough, chest pain, rashes, or skin lumps. Patients also may have fever, exaggerated sweating (often most noticeable at night), unexplained fatigue, loss of appetite, or weight loss. During a medical examination, their physician may find 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

Most enlarged lymph nodes are usually a reaction to infection and are not cancer. The physician may suspect lymphoma by finding enlarged lymph nodes during a physical examination or in an imaging test (for

example, a chest X-ray) in the absence of another explanation, such as a nearby infection. 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 other sites. 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 major incisions or manipulations being required.

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 decide that the abnormality is lymphoma and what the category or classification of the lymphoma is. Occasionally, the diagnosis may be unclear and require consultation with expert hematopathologists, doctors who specialize in lymphoma diagnosis.

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, T, or NK lymphocyte types.

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 (Determining the Extent of Disease)

The diagnosis based on biopsy specimens and determining the extent of the disease provides very important information to the physician planning treatment. The specific type of lymphoma, whether it is a B or T cell type, and the location of the involved nodes or organs will be a factor in the drugs selected and the duration of treatment.

After the diagnosis is confirmed, the extent of the disease is determined. This is called “staging.” Imaging techniques such as MRI or CT are used to look for enlarged lymph nodes or organs like the liver, spleen or kidneys. The blood and the marrow are examined. Blood cell counts assess if *anemia* or low white cells or platelets are present or if lymphoma cells are in the blood. Examination of the bone marrow can detect the presence of lymphoma cells, as well. Measurements of blood chemicals and other constituents look for chemical evidence of other organ involvement, such as liver or kidney dysfunction, and indicate whether *immune globulins* made by lymphocytes are deficient or abnormal.

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 the central nervous system (brain or spinal cord) might be affected. When all of the tests are completed, the physician determines the areas involved using the evidence at hand.

Factors That Influence Treatment

Six major factors are used to determine what type of treatment should be used.

1) Type of lymphoma. Thirty or more subtypes of specific lymphomas or closely related lymphocytic leukemias have been categorized. Table 3 gives examples of these subtypes. To simplify this classification, many

oncologists group the various subtypes into whether, on average, the lymphoma is growing very slowly (*low-grade*) or progressing very rapidly (*aggressive*). Because of experience with the way specific types of lymphoma progress, one can determine the likelihood of slow or rapid progression and the types of therapy needed initially. Classification of the specific subtypes of lymphoma consider the pattern of the lymph node biopsy under the microscope and whether the lymphocytes are more like T cells or B cells. The past clinical experience with the behavior of each subtype of lymphoma tells the physician, on average, whether the lymphoma will progress slowly (*low-grade*) or more rapidly (*high-grade*). These categories also indicate to the physician whether less or more intensive treatment is likely to be needed initially.

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

- **Stage I** signifies the lymphoma can be detected in one lymph node area or in only one organ outside of lymph nodes.

Table 3. Types of Lymphoma

Low-grade lymphoma of T cell or B cell type (e.g, follicular, cutaneous T cell)	Intermediate-grade lymphoma of B cell or T cell type (e.g, large B cell lymphoma, intestinal T cell lymphoma)
Intermediate-grade lymphoma of B cell or T cell type (e.g, mantle B cell, angiocentric T cell)	High-grade lymphoma of B or T cell type (e.g, Burkitt's B cell, acute adult T cell)

Thirty or more subtypes of specific lymphomas or closely related lymphocytic leukemias have been categorized. The Table gives examples of these subtypes.

- **Stage II** indicates the involvement of two or more lymph node regions, which are near to each other, for example all are in the neck and chest, or in the abdomen.

- **Stage III** represents the involvement of several lymph node regions in the neck and chest and abdomen.

- **Stage IV** is used if there is widespread involvement of lymph node areas and organs such as lungs, liver, intestines and bone.

3) *Cell type.* Knowing if the lymphoma cells are most closely related to T cells, B cells, or NK cells may give important clues to the physician as to the treatments to be used. This distinction is determined by the use of immunophenotyping or by molecular diagnostic techniques. These tests measure special features of the cells that distinguish them as one or another 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) and concurrent medical conditions are also important considerations.

6) The presence of a body reaction to the lymphoma also influences the approach to treatment. Factors such as fever, exaggerated sweating, and weight loss over 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.

Treatment

The goal of treatment is to eliminate as many malignant cells as possible and to induce a complete remission, that is, the disappearance of all evidence of disease. In some cases in which this goal is accomplished, a cure may be achieved. Treatment may also maintain 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.

Locale of Treatment

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 the red cell, white cell and/or platelet count. Transfusion of appropriate blood products and administration of *cytokines* (hormones that enhance marrow blood cell production) may be required. Even in such cases, outpatient treatment still may be possible.

Thus, although the treatment period may be long, most of the therapy can be administered to patients who are not hospitalized. If fever or other signs of infection occur, however, hospitalization and administration of antibiotics may be necessary. If this is anticipated, and treatment intervention is early, patients may return home after a short period of hospitalization, depending on the particular circumstances.

Chemotherapy and radiation therapy are the two principal forms of treatment. Unlike Hodgkin lymphoma, radiation therapy is used less often as the sole or principal curative therapy for non-Hodgkin lymphomas. It is, however, a very important ancillary form of treatment in some cases.

Table 4. 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)
- chlorambucil (Leukeran)
- cisplatin (Platinol)
- cyclophosphamide (Cytoxin, Neosar)
- dacarbazine (DTIC-Dome)
- ifosfamide (Ifex)
- lomustine (CCNU)
- mechlorethamine (nitrogen mustard, Mustargen)
- melphalan (Alkeran)
- procarbazine (Matulane, Natulane)

Antitumor Antibiotics

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

- bleomycin (Blenoxane)
- doxorubicin (Adriamycin, Rubrex)
- 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)
- fludarabine (Fludara)
- 6-mercaptopurine (Purinethol)
- methotrexate (Folex, Mexate)
- 6-thioguanine (Thioguanine)

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 (VP-16, VePesid)

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, Velsar)
- vincristine (Oncovin)
- paclitaxel (Taxol)

Hormones That Can Kill Lymphocytes

In high doses these synthetic hormones, relatives of the natural hormone cortisol, can kill malignant lymphocytes.

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

Immunotherapy

A new class of agents for treatment of lymphomas, 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)

*Not yet approved by FDA

Table 5. Some Examples of Drug Combinations Used to Treat Lymphomas

CP: <i>Chlorambucil, Prednisone</i>	ProMace-CytaBom: <i>Prednisone, Methotrexate, Adriamycin (doxorubicin), Cyclophosphamide, Etoposide, Cytarabine, Bleomycin, Oncovin (vincristine), Methotrexate</i>
CVP: <i>Cyclophosphamide, Vincristine, Prednisone</i>	ABVD: <i>Adriamycin (doxorubicin), Bleomycin, Vinblastine, Dacarbazine</i>
CHOP: <i>Cyclophosphamide, Hydroxydaunomycin, Oncovin (vincristine), Prednisone</i>	ICE: <i>Ifosfamide, Carboplatin, Etoposide</i>
m-BACOD: <i>Methotrexate, Bleomycin, Adriamycin (doxorubicin), Cyclophosphamide, Oncovin (vincristine), Dexamethasone</i>	

Chemotherapy

Chemotherapy usually requires the use of combinations of several drugs (see Table 4) to kill the malignant cells. Combining drugs with 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 reflect the duration of the drug’s effect, the patient’s tolerance of the drug, and the duration of adequate levels of the drug in question in blood or tissues. The treatment may consist of from six to 12 cycles, lasting, therefore, from about six to 12 months.

Sometimes, two different combinations of drugs are administered in alternate cycles. Examples of combinations of drugs used in lymphoma treatment are shown in Table 5.

Patients with slow growing, indolent lymphomas often are treated with one, two, or three drugs depending on the disease rate of growth and

other factors. These drugs usually can be given orally and cause limited side effects. 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. *Monoclonal* antibody treatment has been an important addition to traditional drug therapy.

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.

Clinical investigators use acronyms composed of the first initials of the drugs to be used in a particular treatment regimen to communicate among themselves about specific drug combinations. Many other combinations have been developed, as clinical investigators try to determine the best grouping of drugs for a given circumstance. These circumstances include 1) treatment of a newly diagnosed lymphoma, 2) lymphoma that is not fully responsive to the initial treatment, and 3) treatment of 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, radioimmunotherapies, immunotoxins, and vaccine therapies. One approach is to use antibodies to 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 so-called “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.

There is currently one antibody that is FDA approved, rituximab. This antibody is naked, and targets B lymphocytes, the cells most frequently involved in lymphoma. It is thought that when the monoclonal antibody attaches to the B lymphocyte, the immune system will respond and destroy the cancer cell. 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 these to chemotherapy programs.

There are two additional antibodies, tositumomab and yttrium-90 ibritumomab tiuxetan, that have a radioactive substance attached to them. This approach, currently in phase 3 clinical trials, in effect radiates lymphoma cells selectively, minimizing the radiation effect on normal tissues.

In both monoclonal antibody and radioimmunotherapy treatment, normal lymphocytes are also affected but the treatment is more selective

than standard chemotherapy or radiation therapy. These agents have and will be added to the arsenal that can be used for the treatment of lymphoma patients.

Finally, there are vaccine therapies, prepared to attack lymphoma cells that are also being studied and remain experimental at this time (see The Future.)

Stem Cell Transplantation

Allogeneic *stem cell transplantation* is used in some patients who have lymphoma that is resistant to prior chemotherapy. The objective is to be able to use more potent chemotherapy regimens. These chemotherapy regimens damage the patient's marrow severely. For long periods, the patient is unable to make blood cells. Replacement of the marrow by a stem cell transplantation from a compatible donor is mandatory to permit such intensive treatment.

Healthy individuals have sufficient 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 types of blood counts. Their presence in the blood is important because they can be collected by special techniques and transplanted into a recipient if enough stem cells are harvested from a compatible donor. This stem cell circulation from marrow to blood and back occurs in the fetus as well. That is why, after birth, the placental and umbilical cord blood can be used as a source of stem cells for transplantation.

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

co-existing medical conditions are considered in deciding whether a transplant should be performed.

Autologous (self) stem cell infusion is a method that uses the patient's own stem cells to restore blood and immune cell function after intensive therapy with radiation and/or high-dose chemotherapy. This approach 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 may not be as effective as allogeneic transplantation.

In the past, stem cells were obtained from the patient's marrow. But many patients have inadequate stem cell numbers in their marrow or have many lymphoma cells in their marrow. Stem cells can be induced to enter the blood after the administration of cytokines, which increases production of the blood cells. Next, stem cells in the blood are harvested by *apheresis* to obtain a sufficient quantity for successful transplantation. Blood stem cells, sometimes cleansed (purged) of contaminating lymphoma cells, can be frozen, stored, and then thawed and later returned to the patient after intensive chemotherapy. The stem cells are suspended in a fluid and infused through a vein. They return to the marrow, lodge there, and begin to make blood cells. (See The Leukemia & Lymphoma Society publication *Blood and Marrow Stem Cell Transplantation*.)

The use of stem cell transplantation is infrequent in Hodgkin lymphoma because the vast majority of patients can be treated successfully with radiation therapy or chemotherapy. In the small proportion of patients with Hodgkin lymphoma who have a return of disease after treatment, transplantation can be considered.

Side Effects of Treatment of Hodgkin and Non-Hodgkin Lymphomas

Early Effects of Treatment

The side effects of treatment depend on the intensity and type of treatment, 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.

Suppression of Blood 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 protracted, 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 skin 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 dose used and the individual patient's susceptibility.

(See The Leukemia & Lymphoma Society publication *Understanding Chemotherapy*.)

Loss of Fertility. Patients may have a decrease in fertility after treatment. The risk of infertility varies by the nature of the treatment depending on the type and amount of chemotherapy, the location of radiation therapy, and their 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 that of healthy couples.

Although this is a daunting list, most patients do not get serious side effects. 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 that 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.

Late Effects of Treatment

There is an increased risk of secondary cancers in patients treated for Hodgkin lymphoma and non-Hodgkin's 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 with 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 treated in past decades. Exposure to chemotherapy has been associated with an increased incidence of myelogenous leukemia.

Social and Emotional Aspects

The diagnosis of 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.

A lack of understanding of what's in store, the unknown, and what's next should be met by thoughtful, straightforward, and frequent discussions between physician, nurse, patient, and family. An inability to work, tend to business affairs, or interact with family and friends in the usual manner may contribute to emotional distress. Thorough explanations, including the prospects for remission and the plans for treatment, may bring emotional relief as the patient focuses on the treatment ahead and the prospect of recovery.

Family members or loved ones may have questions about chemotherapy and alternative methods of treatment. It is best to speak directly with physicians regarding specific medical questions. Family members or loved ones should discuss any problems or reactions they may have with their healthcare professionals, who understand the complexity of emotions and the special ongoing needs of those living with lymphoma. Nurses and other healthcare professionals will spend much time with patients, becoming their confidants, and can be very helpful in their emotional support. For more information about the social and

emotional aspects of the disease, you may request a copy of the Society publication *Coping With Survival*, a booklet dealing with the psychosocial aspects of the disease.

There are programs to help ease the emotional and economic strains created by a diagnosis of lymphoma. The Society offers patients financial assistance and also provides the opportunity to join a support group or talk with a successfully treated patient with the same diagnosis.

To order publications or obtain information, call your local Society chapter or call the Society's Information Resource Center at (800) 955-4572. You may also visit our Web site at www.leukemia-lymphoma.org to view publications and obtain more information about the Society's programs and services for patients.

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.

The Future

Clinical Trials

New approaches to therapy are under study in clinical trials, which permit physicians to determine the beneficial effects of new treatments and what if any adverse 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.

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 responds much better to therapy than another, indicating that lymphomas that appear the same using the microscopic appearance to classify them may be made up of distinct groups genetically and biologically. These methods will be used increasingly in the future to tease apart subgroups of lymphoma so as to design more specific 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 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.

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 leukemia or lymphoma (see Immune Globulins, Gamma Globulins).

Antigen

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 recognize 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. This process 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 HLA-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.

Autologous Blood or Marrow Stem Cell Infusion

This technique, often referred to as transplantation, involves the harvesting of a patient's blood or marrow stem cells, which are often frozen for later use. The patient is then given intensive therapy, and the stem cells reinfused via an indwelling catheter. The blood or marrow stem cells may be obtained from a patient with a disease of the marrow when in remission (for example, acute myelogenous leukemia), or when the marrow is not overtly abnormal (for example, lymphoma requiring intensive therapy). Technically, this procedure is not transplantation, which implies taking tissue from one individual (donor) and giving it to another (recipient). The purpose of the procedure is to restore blood cell production from the preserved and reinfused stem cells after intensive therapy has severely damaged the patient's remaining marrow. This procedure often uses autologous blood stem cells since marrow stem cells circulate in the blood and can be recovered there by apheresis (see Apheresis).

B Cell Lymphomas

A lymphoma subtype that is composed of malignant lymphocytes with features of B cells. B cells received their name from the “B” in bursa, a structure 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.

Banding of Chromosomes

The staining of chromosomes with dyes that bring out or highlight bands or regions on the chromosome. The bands give the chromosomes more specific features, allowing individual distinctions to be made among them. This permits more precise identification of each of the 23 pairs of chromosomes.

Basophils

A type of white blood cell that participates in certain allergic reactions.

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.

Blast Cells

This term, when applied to normal marrow, refers to the earliest marrow cells identified by the light microscope. Blasts represent about 1 percent of normally developing marrow cells. They are largely myeloblasts, which are cells that will develop into neutrophils. In

normal lymph nodes, blasts are usually lymphoblasts, that is, cells that are part of lymphocyte development. In the acute leukemias, blast cells, similar in appearance to normal blast cells, accumulate in large numbers, perhaps in up to 80 percent of all marrow cells. In acute myelogenous leukemia, myeloblasts accumulate and in acute lymphocytic leukemia or some lymphomas, lymphoblasts accumulate. The distinction between leukemia myeloblasts and lymphoblasts sometimes can be made by examination of stained marrow cells through the microscope. Often, immunophenotyping or use of special staining of marrow cells is required to be sure of the difference.

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.

Bone Marrow Transplantation (see Stem Cell Transplantation)

Burkitt's 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 with a facial mass around the jaw, frequently in children. It invariably is associated 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 its onset. In North America, Burkitt's lymphoma is far less frequent. This disease usually appears with abdominal masses of lymphoma cells, is not uniformly associated with Epstein-Barr virus, may occur in older individuals, and may involve the marrow and blood.

Chemotherapy

The use of chemicals (drugs or medications) to kill malignant cells. Numerous drugs have been developed for this purpose. Most act to injure the DNA of cells. When the DNA is injured, the cells cannot grow or survive. Successful chemotherapy depends on the malignant cells being at least somewhat more sensitive to the drugs than normal cells. Because the cells of the marrow, the intestinal tract, the skin, and hair follicles are most sensitive to these drugs, effects on these organs are common side effects of chemotherapy, i.e., mouth sores, diarrhea, rashes, and hair loss.

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 an Y chromosome in males. The number or shape of chromosomes may be altered in lymphoma or leukemia cells.

Clonal (Monoclonal)

A population of cells derived from a single primitive cell. Virtually all neoplasms, benign and malignant (cancers), are derived from a single cell with an injury to DNA (mutated) and, thus, are clonal. The mutated cell has an alteration in its DNA that forms an oncogene. This leads to its transformation into a cancer-causing cell. The cancer is the total accumulation of cells that grow from the single mutated cell. Leukemia, lymphoma, and myeloma are examples of cancers that are clonal, that is, derived from a single abnormal cell.

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.

Coombs Test (see Antiglobulin Test)

Cultures

If an infection is suspected, it is helpful to know the principal site involved and the type of bacterium, fungus, or other microorganism involved so that the most specific antibiotics can be selected as treatment. To determine the site and organism, samples of body fluids such as sputum, blood, urine, and swabs of the inside of the nose and throat, as well as the rectum, are placed on culture medium in special sterile containers and incubated at body temperature (37° C, 98.6° F) for one to several days. These cultures are examined to see if bacteria, fungi, or sometimes other organisms are present in significant numbers. If they are present, the organisms can be tested with several antibiotics to learn which antibiotic kills the organism. This is called determining the “antibiotic sensitivity” of the organism.

Cutaneous T Cell Lymphomas

This subtype of lymphoma principally involves the skin and lymph nodes, or, later, other organs. About 3 percent of all lymphomas are of

this type. The lymphoma cells have features of T lymphocytes. The disease may wax and wane for many years and may be difficult to diagnose with certainty in its early phases even with biopsy of the skin. It can be referred to as *mycosis fungoides* when there is prominent skin involvement. The malignant lymphocytes may enter the blood and, if sufficiently prominent, 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 phase of the disease has been referred to as *Sézary syndrome* after the French physician who in 1938 highlighted the unusual and distinctive type of lymphoma cell that entered the blood. Mycosis fungoides and Sézary syndrome are now usually referred to as cutaneous T cell lymphoma.

Cycle of Treatment

The term designates an intensive, clustered period of chemotherapy (and/or radiation therapy). This treatment, given for several days or weeks, represents one cycle of treatment. The treatment plan may call for two, three, or more cycles of the same or a slightly modified treatment. Cycles of treatment are the usual approach to the use of chemotherapy in the treatment of Hodgkin lymphoma or other lymphomas.

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.

Differentiation

The process by which stem cells transform from cells without a specific direction into functional cells of a single blood cell line. The red cells, platelets, neutrophils, monocytes, eosinophils, basophils, or lymphocytes are formed from a stem cell by this process.

Diffuse Lymphomas

This term is used to include the subtypes of lymphoma that have a uniformly disrupted pattern in the lymph node biopsy. When the biopsy is examined under the microscope, the lymphoma cells are spread diffusely throughout the lymph node, in contrast to follicular lymphoma in which there are clusters or follicles of lymphoma cells.

Diffuse Large Cell Lymphoma (see High-Grade Lymphoma)

Eosinophils

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

Erythrocytes A synonym for red cells (see Red Cells).

Extranodal Lymphoma

A lymphoma that appears to originate in an organ other than a lymph node. Virtually every organ has been recorded as the origin of lymphoma. The stomach and intestines, brain, thyroid gland, testis, urinary tract, skin, bone, lung, and others may be the first site at which malignant lymphocytes accumulate and form a tumor. Primary extranodal origin of the disease is much less frequent as a manifestation of Hodgkin lymphoma than of other lymphomas.

Follicular Lymphoma

This term is used to describe the subtype of lymphoma in which the lymphoma cells are grouped in clusters or follicles (see Low-Grade Lymphoma). This pattern is distinct from diffuse lymphomas.

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.

Granulocytes

A type of white blood cell that has a large number of prominent granules in the cell body. Other blood cells have fewer granules (e.g., lymphocytes). Neutrophils, eosinophils, and basophils are types of granulocytes.

Growth Factors (see Cytokines)

HLA

The acronym 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 testing for HLA antigens is referred to as “tissue typing.” There are four major groups of HLA antigens: A, B, C, D. These proteins act as antigens when donated (transplanted) to another individual, e.g., a bone marrow, or stem cell recipient. If the antigens on the donor cells are identical (e.g., identical twins) or very similar (e.g., HLA-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, like 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. This process is called “maturation.” The cells then leave the marrow and 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.

Hepatomegaly

Enlargement of the liver.

High-Grade Lymphoma

The term for several subtypes of lymphoma that progress relatively rapidly if untreated. These subtypes include AIDS-associated lymphoma, anaplastic large cell lymphoma, Burkitt’s lymphoma, *diffuse* large cell lymphoma, and lymphoblastic lymphoma. Although these represent more rapidly progressive lymphomas, some are also among those that respond very well to combinations of drugs used in treatment protocols.

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.

Iliac Crest

The edge of the hipbone from which marrow is usually sampled for diagnosis of blood cell diseases.

Immune Globulins or Immunoglobulins (see Gamma Globulins)

Immunophenotyping

A method that uses the reaction of antibodies with antigens to determine the specific types of cell 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. As cells carrying their array of antigens are tagged with specific antibodies they can be identified; for example, myelogenous leukemia cells can be distinguished from lymphocytic leukemia cells. This method helps to subclassify cell types that may, in turn, help to decide on the best treatment to apply in that type of leukemia or 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 tubing 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.

Interleukin (see Cytokine)

Karyotype

The systematic arrangement, using photographs, of the 46 human chromosomes of a cell in 23 matched pairs (maternal and paternal member of each pair) by length from longest to shortest and other features. The sex chromosomes are shown as a separate pair (either XX or XY).

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 the serum 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 it may reflect the extent of the tumor and the rapidity of tumor growth. It is used in some cases along with other measures to plan the intensity of therapy for lymphoma. Burkitt lymphoma and other aggressive lymphoma often have marked elevation in serum LDH.

Leukocytes

A synonym for white blood cells (see White Blood Cells).

Leukopenia

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

Low-Grade Lymphoma

This term encompasses several subtypes of lymphoma that have a rate of progression that is, on average, relatively slow. Usually, the lymphoma cells have features of B lymphocytes. Several subtypes included in this designation are small lymphocyte lymphoma, follicular lymphoma, mantle cell lymphoma, and marginal zone lymphoma. The disease names, given to these subtypes by pathologists, relate the lymphomas to cells in a normal lymph node area. The follicle, mantle zone, and marginal zone are parts of the organization of normal nodes.

Lymph Nodes

Small structures, the size of beans that contain large numbers of lymphocytes and are connected with each other by small channels called lymphatics. These nodes are distributed throughout the body. In patients with lymphoma, 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 (MR) imaging, depending on the degree of enlargement and location.

Lymphadenopathy

Enlargement of lymph nodes.

Lymphoblastic Lymphoma (see T cell lymphoma)

Lymphocytes

A type of white blood cell that participates in the body's immune system. There are three major types of lymphocytes: B lymphocytes that produce antibodies to help combat infectious agents like bacteria, viruses and fungi; T lymphocytes that have several functions including

assisting B lymphocytes to make antibodies and attack virus-infected cells, and natural killer (NK) cells that can attack tumor cells.

Lymphokine (see Cytokines)

Magnetic Resonance (MR) Imaging

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 structure converts the signals generated in the tissues in response to a magnetic field produced by the instrument. Thus, the size and a change in size of organs or tumor masses, such as the lymph nodes, liver and spleen can be measured.

MALT Lymphomas (see Mucosa-Associated Lymphoid Tissue Lymphomas)

Mantle Cell Lymphoma (see Low-Grade Lymphoma)

Marginal Zone Lymphoma (see Low-Grade Lymphoma)

Mitosis

The process by which a single cell divides into two cells. This process is also referred to as cell division, cell replication, or cell growth.

Monoclonal (see Clonal)

Monocytes (Macrophages)

A type of white blood cell that assists in fighting infection. The monocyte, along with the neutrophil, is the two major microbe-eating and killing cells in the blood. When monocytes leave the blood and enter the tissue they are converted to macrophages. The macrophage is the

monocyte in action and can combat infection in the tissues or can serve other functions such as ingesting dead cells (scavenger).

Mucosa-Associated Lymphoid Tissue (MALT) Lymphomas

Lymphomas that originate in the lining of the intestinal tract or closely associated glandular tissue. The stomach is the most frequent site and is associated with infection by the bacterium that causes stomach ulcers, *Helicobacter pylori*. These lymphomas are often only slowly progressive and tend to remain localized.

Multidrug Resistance

A characteristic of cells that makes them resistant simultaneously to the effects of several different classes of drugs. There are several forms of multidrug resistance. Genes that govern how the cell will respond to the chemical agents determine them each. The first identified mechanism of multidrug resistance (or MDR) involves the cell's ability to pump several drugs out of cells. A pump in the cell wall rapidly ejects drugs out of the cell preventing them from reaching a toxic concentration. In cells, 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 the specific 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 dis-

tributed when detected; they involve the marrow or lymph nodes, usually, in many sites.

Mycosis Fungoides (see Cutaneous T Cell Lymphoma)

Neutropenia

A decrease below normal in the number of blood neutrophils, a type of white blood cells.

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 with acute leukemia or 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 leukemia, acute lymphocytic leukemia, lymphoma, 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 applied to 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.

Pancytopenia

A decrease below normal in the concentration of the three major blood cell types: red cells, white cells, and platelets.

Peripheral T Cell Lymphoma (see T Cell lymphoma)

Performance Status

The performance status semi-quantifies the ability of a patient to perform daily activities. This semi-quantification is very helpful in clinical trials in assessing the state of health of patients under treatment. If one group has a significant difference in their performance status, the interpretation of treatment results will be influenced. The performance status also plays a role in determining whether a patient can tolerate intensive therapy. The following short version of the definition of activities level describes the performance status in terms of a scale decreasing from normal activities and capabilities. Other versions use percent of normal as an indicator.

Status	Definition
0	Normal Activity
1	Symptoms but ambulatory
2	In bed < 50 percent of time
3	In bed greater than >50 percent of time
4	100 percent bedridden

Petechiae

Pinhead-sized sites of bleeding in the skin. This type of bleeding results from a low platelet count. The small punctate hemorrhages are frequently seen on the legs, feet, trunk, and arms. They disappear gradually when the platelet count increases.

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 these blood cells is the principal cause of susceptibility to infection in patients with leukemia or those treated with intensive radiation therapy and/or chemotherapy, which suppress blood cell production in the bone marrow.

Platelets

Small blood fragments (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 leukemia or lymphoma. The platelets can be pooled from several unrelated donors and given as “pooled random-donor platelets.” It takes the platelets from about six one-unit blood donors to

significantly raise the platelet count in a recipient. Sufficient platelets can be obtained from one donor if his or her platelets are obtained by apheresis. The latter technique skims the blood passing through the apheresis machine 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-matched platelet transfusion can be given from a related donor with an identical or very similar HLA tissue type. The platelets are collected by apheresis.

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 technique has become useful in detecting a very low concentration of residual leukemia or lymphoma cells, too few to be seen using a microscope. The technique can detect the presence of one leukemia cell among five hundred thousand to one million non-leukemia cells. PCR requires a specific DNA abnormality or marker, like an oncogene, in the leukemia or lymphoma cells for its use.

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).

Sézary Syndrome (see Cutaneous T Cell Lymphoma)

Somatic Mutation

The alteration of a gene in the cells of a specific tissue causes the gene to become a cancer-causing gene or oncogene. It is called “somatic” to

distinguish it from a germ cell mutation, which can be passed from parent to offspring. Most cases of leukemia 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 subtler 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. It contains clusters of lymphocytes like lymph nodes do and also filters out old or worn-out blood cells. It is often affected in leukemia, especially the lymphocytic leukemias, lymphoma, and Hodgkin lymphoma. Enlargement of the spleen is referred to as “splenomegaly.” Removal of the spleen by surgery is referred to as “splenectomy.” Removal of the spleen can be done without 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 blood 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.

Stem Cell Transplantation

A technique that was developed to restore the marrow of patients who had lethal injury to that site. Such injury can occur because of primary

marrow failure, destruction of marrow by disease, or intensive chemical or radiation exposure. When first used, the source of the transplant was the marrow of a healthy donor who had the same tissue type (*HLA* type) as the patient. Usually, the source was a brother or sister. Donor programs have been established to identify unrelated donors who have a matching tissue type. This approach requires screening tens of thousands of unrelated individuals of similar ethnicity.

Specifically, the transplant product is a very small fraction of the marrow cells called “stem cells.” These stem cells not only reside in the marrow but also circulate in the blood. They can be harvested from the blood of a donor by treating the donor with an agent or agents that cause a release of larger numbers of stem cells into the blood and collecting them by apheresis. The stem cells circulate in large numbers in fetal blood also and can be recovered from the placental and umbilical cord blood after childbirth. The harvesting, freezing, and storing of “cord blood” have provided another source of stem cells for transplantation. Since blood as well as marrow is a very good source of cells for transplantation, “stem cell transplantation” has replaced “bone marrow transplantation” as the general term for these procedures.

If the donor is an identical twin, the transplant is called “syngeneic,” the medical term for genetically identical. If the donor is not an identical twin, the transplant is called “allogeneic,” indicating it is from the same species and in practice nearly always matching in tissue type. The term “matched unrelated” is applied to the donor recruited from large volume screening programs searching for the rare individual who is very similar in tissue type to the patient.

Unfortunately, the important technique of harvesting patients’ marrow, freezing it, and returning it to them after they have received intensive

chemotherapy and/or radiation therapy for their underlying disease has been referred to as autologous (self) or auto-transplantation. This term is a well-entrenched misnomer since transplantation implies transferring tissue from one individual to another. This technique would better be referred to as autologous marrow infusion. (See Autologous Stem cell Infusion)

T Cell Lymphomas

The term peripheral T cell lymphomas is applied to those lymphomas in which the malignant cells have the features of T lymphocytes by immunophenotyping or special molecular diagnostic studies. The four major types of T cell lymphoma 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, a gland in the chest that shrinks and disappears as people grow into adulthood but is the source of T lymphocytes early in life.

Therapy

The curative treatment of leukemia, lymphoma, or myeloma is thought of in different segments. Induction therapy refers to the methods used to destroy visible leukemia cells in blood and marrow so as to favor a remission, which results in return of normal blood cells. Consolidation therapy refers to the additional treatment given after remission is induced. Often, high doses of drugs are used in several short periods of treatment. The goal is to further decrease the concentration of residual leukemia cells. The greater the reduction in leukemia cells, the higher the probability that natural defenses will suppress the disease and result in a very long-term remission. Maintenance or continuation therapy refers to the administration of drugs periodically for a long period of time (months

or years), usually in lower doses than consolidation therapy.

Thrombocytopenia

A decrease below normal in the number of the 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 (antioncogene)

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 Blood Cells

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

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

Further Readings

Society Patient Booklets

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* Medical Textbook

Chapters and Free Information

Information about leukemia, lymphoma and myeloma is available from The Leukemia & Lymphoma Society's offices located in the states and cities listed below. Please refer to your telephone directory for local address and telephone number, or call 800-955-4572.

Alabama Birmingham	Georgia Atlanta	Mississippi Ridgeland	Pennsylvania Harrisburg Philadelphia Pittsburgh
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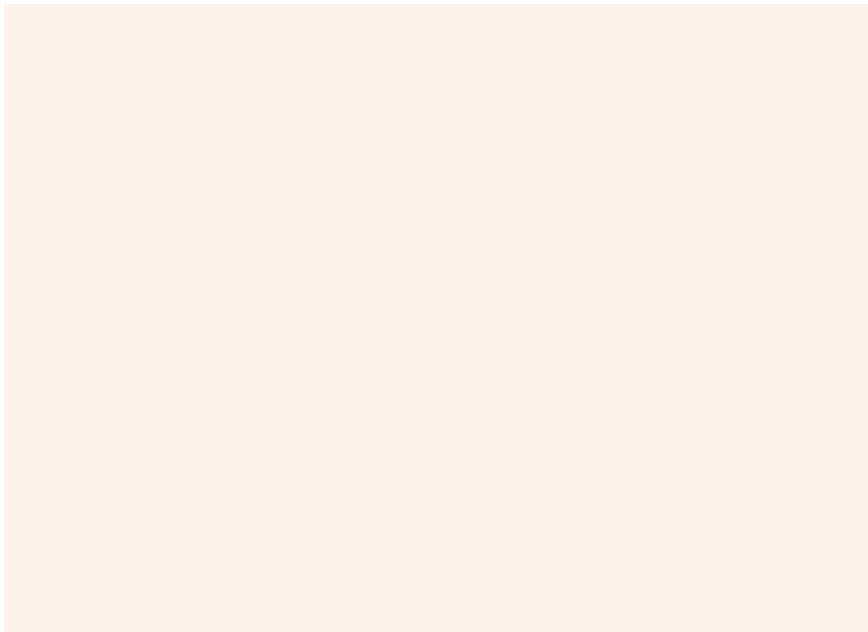
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Mission

The mission of The Leukemia & Lymphoma Society is to cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families.

Contact for more information:



or the Home Office numbers listed above



The Society acknowledges the generosity of Genentech and IDEC. Printing of this publication was made possible by education grants from the companies.

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Hodgkin's Disease and Myeloma***

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