



Chronic Lymphocytic Leukemia



**The Leukemia &
Lymphoma Society®**

Fighting Blood-Related Cancers

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Introduction

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

Each year, about 8,100 persons in the United States learn that they have chronic lymphocytic leukemia. The disease also may be referred to as chronic lymphoid leukemia or as CLL. Before describing the disease and its management further, a brief description of normal blood and marrow is provided for background.

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

Normal Blood and Marrow

Blood is composed of plasma and cells suspended in plasma. The plasma is largely made up of water in which are dissolved many chemicals. These chemicals include proteins (e.g., albumin), hormones (e.g., thyroid hormone), minerals (e.g., iron), vitamins (e.g., folic acid), and *antibodies*, including those we develop from our immunizations (e.g., poliovirus antibodies). The cells include *red cells*, *platelets*, *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 tissues. The platelets are small cell fragments (one-tenth the size of red cells) that help stop bleeding if one is injured. For example, when one has a cut, the blood vessels that carry blood 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 *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 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*, and lymphatic channels, but some enter the blood. There are three major types of lymphocytes: T cells, B cells, and natural killer (NK) cells.

Bone marrow is the spongy tissue where blood cell development 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, the *stem cells*, are responsible for making all the blood cells in the marrow. The stem cells eventually develop into the specific blood cells by a process of *differentiation* (see Figure 1).

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

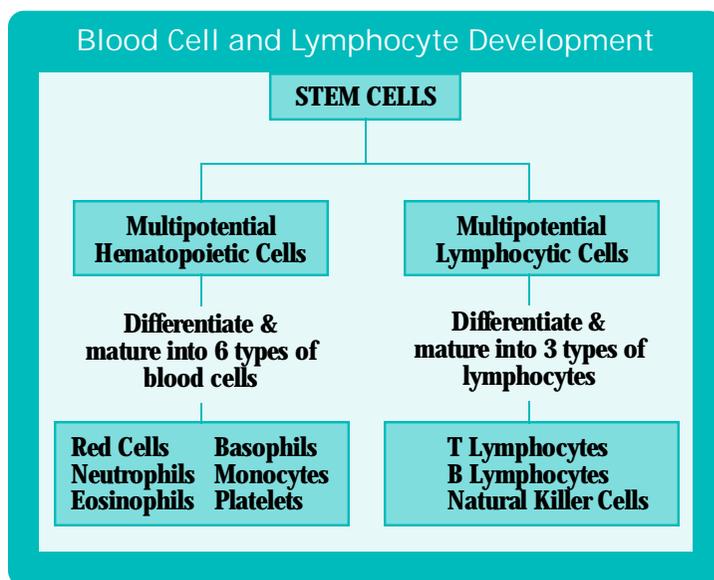


Figure 1. This figure depicts an abbreviated diagram of the process of hematopoiesis. This process involves the development of functional blood and lymphatic cells from stem cells.

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 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.

In summary, blood cells are made in the marrow, and when the cells are fully formed and able to function, they leave the marrow and enter the blood. The red cells and the platelets perform their respective functions of delivering oxygen and plugging up injured blood vessels in the circulation. The neutrophils, eosinophils, basophils, monocytes, and lymphocytes, which together make up the white blood cells, move into the tissues of the lungs, for example, and can combat infections such as pneumonia and perform their other functions.

Leukemia

Leukemia is a malignant disease (cancer) of the bone marrow and blood. The earliest observations of patients who had marked elevation of their white blood cells by European physicians in the 19th century led to their coining the term “weisses blut” or “white blood” as a designation for the disorder. Later, the term “leukemia,” which is derived from the Greek words “leukos,” meaning “white,” and “haima,” meaning “blood,” was used to indicate the disease.

The major forms of leukemia are divided into four categories. Myelogenous and lymphocytic leukemia each have an acute or chronic form. The terms myelogenous or lymphocytic denote the cell type involved.

Thus, the four major types of leukemia are acute or chronic myelogenous and acute or chronic lymphocytic leukemia.

Acute leukemia is a rapidly progressing disease that affects mostly cells that are unformed or primitive (not yet fully developed or differentiated). These immature cells cannot carry out their normal functions.

Chronic leukemia progresses slowly and permits the growth of greater numbers of more developed cells. In general, these more mature cells can carry out some of their normal functions.

The ability to measure additional specific features of cells has led to further subclassification of the major categories of leukemia. The categories and subsets allow the physician to decide what treatment works best for the cell type and how quickly the disease may develop.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia results from an acquired (not inherited) injury to the DNA of a single cell, a lymphocyte, in the bone marrow. This injury is not present at birth. Scientists do not yet understand what produces this change in the DNA of CLL patients.

This change in the cell's DNA confers a growth and survival advantage on the cell, which becomes abnormal and malignant (leukemic). The result of this injury is the uncontrolled growth of lymphocytic cells in the marrow leading invariably to an increase in the number of lymphocytes in the blood. The leukemic cells that accumulate in the marrow in chronic lymphocytic leukemia do not impede normal blood cell production as profoundly as in the case of acute lymphocytic leukemia. This important distinction from acute leukemia accounts for the less severe early course of the disease.

Causes and Risk Factors

Unlike the other three major types of leukemia, chronic lymphocytic leukemia is not associated with high-dose radiation or benzene exposure. First-degree relatives of patients with the disease have about a threefold greater likelihood of getting the disease than other people. This should be put into perspective, however. For example, the 60-year-old sibling or offspring of a patient with chronic lymphocytic leukemia would have three chances in ten thousand of developing the disease compared with the one chance in ten thousand for a 60-year-old person without a family history of the disease. The disease is very uncommon in individuals under 45 years of age. At the time of diagnosis, 95 percent of patients are over age 50, and the incidence of the disease increases dramatically thereafter (see Figure 2).

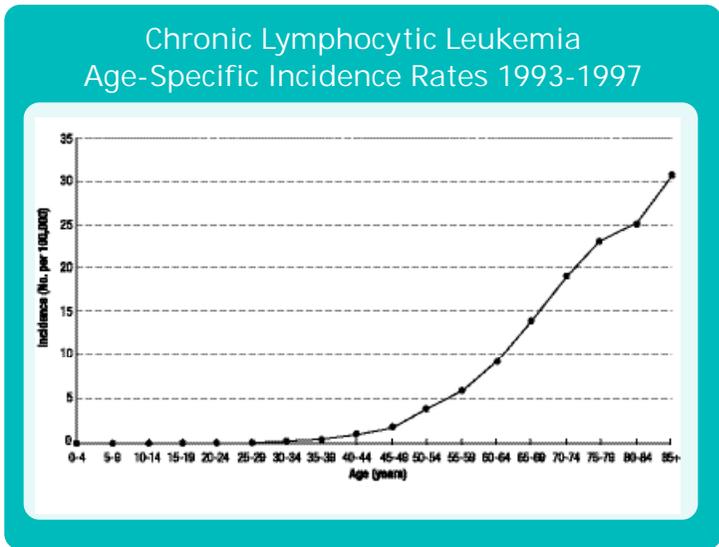


Figure 2: The horizontal axis shows the age at diagnosis of Americans who develop chronic lymphocytic leukemia. Age is grouped into 5-year periods. The vertical axis represents the number of new cases of chronic lymphocytic leukemia per 100,000 people in a particular 5-year age grouping. The risk of chronic lymphocytic leukemia becomes measurable after age 40 and increases dramatically over succeeding decades. (The data are from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program.)

Symptoms and Signs

The symptoms of chronic lymphocytic leukemia usually develop gradually. Patients tire more easily and may feel short of breath when physically active. They may lose weight. They may experience infections, sometimes recurrent, of the skin, lungs, kidneys, or other sites.

Early in the disease, chronic lymphocytic leukemia may have little effect on a person's well being. The disease may be discovered after finding an abnormal blood count during the course of a periodic medical examination or while the patient is under care for an unrelated condition. The report of an elevated white blood cell count is the most common clue that leads a physician to consider the diagnosis of chronic lymphocytic leukemia. These large numbers of leukemic lymphocytes (white cells) can collect in the lymphatic system and the lymph nodes may become enlarged.

Diagnosis

To diagnose the disease the blood and, in most cases, the marrow cells are examined. The white cell count invariably increases in the blood. The increase is the result of an increase in blood lymphocytes. A bone marrow examination also will show a marked increase in the proportion of lymphocytes in the marrow, often accompanied by some decrease in the normal marrow cells.

Low platelet counts and low red cell counts (*anemia*) may be present but are usually only slightly decreased in the early stage of the illness.

The pattern of the lymphocytes in the biopsy of the marrow can be one useful factor in determining the probable rate of progression of the disease. In addition, a sample of marrow cells is examined to determine if there is an abnormality of *chromosomes*. The examination of cells to determine if an abnormality of chromosomes is present is referred to as a *cytogenetics* analysis.

Determining the *immunophenotype* of the lymphocytes in the blood or marrow is important. This distinguishes whether the lymphocytes that accumulate are derived from a malignant transformation of a lymphocyte in the B cell developmental pathway or the T cell developmental pathway (see Figure 3). Although the T cell type of disease, called T cell chronic lymphocytic leukemia, is very infrequent, it affects the skin, nervous system, and lymph nodes more often and may be more rapidly progressive than is the B cell type. Immunophenotyping also permits assessment of whether the lymphocytes in the blood are derived from a single malignant cell (in other words, whether or not they are *monoclonal*). The test for monoclon-

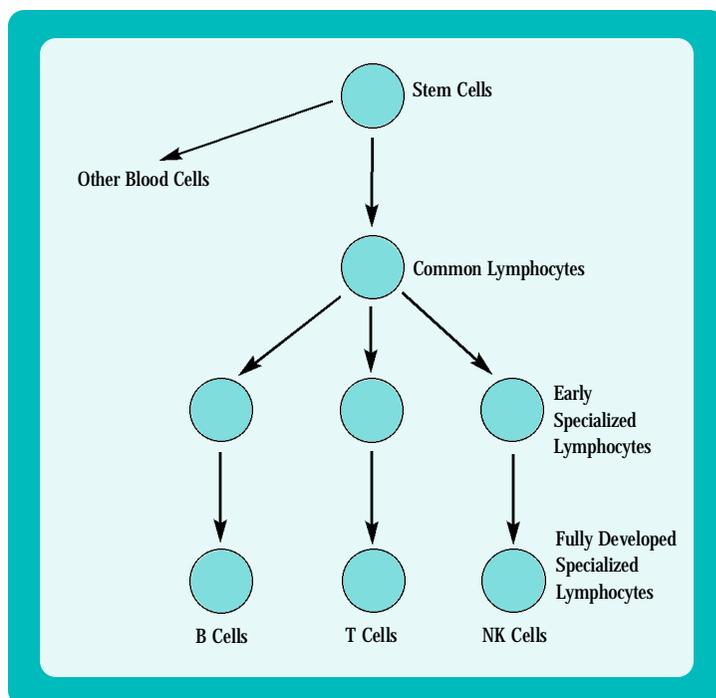


Figure 3: Depending on the place in lymphocytic cell development in which the malignant transformation occurs, the leukemic cells may be principally B cells, T cells, or NK cells. Most patients have a B cell type of leukemia. A minority have T or NK cell types. These distinctions may be accounted for by the malignant transformation occurring after the common lymphocyte has differentiated into one of the three types of lymphocytes. The malignant event (mutation of DNA) would therefore occur at the point, or after, the early specialized lymphocytes were formed.

ality is important because it distinguishes leukemia from the very infrequent increase in the blood lymphocytes in adults that is not the result of a malignant transformation characteristic of cancer. This test is especially important if the lymphocytes in the blood are just slightly elevated.

Another very important test that is performed is the measurement of the concentration of gamma globulins (immunoglobulins) in the blood. Immunoglobulins are proteins called antibodies that the B cells of healthy individuals make to protect themselves from infection. They are often deficient in persons with chronic lymphocytic leukemia. The leukemic B lymphocytes do not make protective antibodies effectively. At the same time, the leukemia acts to prevent residual normal lymphocytes from doing so. This inability to make antibodies efficiently causes CLL patients to be susceptible to infections.

Disease Course and Treatment

Some patients with chronic lymphocytic leukemia have minimal changes in their blood cell counts: a slight increase in blood lymphocytes and little or no decrease in red cells, normal white cells, and platelets. These patients may remain stable for relatively long periods (years). Patients with minimal changes in their blood may have few related problems, such as infections. These patients usually are not treated.

When patients learn that they have leukemia but will not receive treatment, they may become concerned. A decision to delay treatment should not produce concern. Chronic lymphocytic leukemia (and its closely related variants) is the a major type of leukemia that can be stable and not disturb the patient's well being for prolonged periods without treatment. Untreated patients are followed periodically to be sure progression is not occurring. They also are advised to seek medical assistance if they develop a fever or other signs of infection or illness.

A classification used in treating CLL patients is called the staging system. Patients are assigned a specific stage of disease to judge disease progression and the need for treatment. Several staging classifications have been proposed. The Rai or Binet staging systems are commonly used. These systems consider the elevation of blood and marrow lymphocyte counts, the size and distribution of lymph nodes, the spleen size, the degree of anemia, and the extent of the decrease of the blood platelet count. Those patients who have more progressive disease (higher numbers in the staging system) are usually treated with *chemotherapy*. Some signs of progressive disease are shown in Table 1.

Chemotherapy

The drugs most commonly used to treat progressive chronic lymphocytic leukemia are shown in Table 2. Drug combinations are sometimes used, depending on the patient's health status, age, and the apparent rapidity of disease progression.

Table 1. Some Signs that Influence the Decision to Treat Patients with CLL*

Relatively rapid increase of blood lymphocyte counts
Enlarging lymph nodes
Enlarging spleen
Worsening anemia
Falling platelet count
Other signs or symptoms resulting from progressing leukemia

*Often several occur concurrently.

Monoclonal Antibody Therapy

Several monoclonal antibodies that were introduced as treatments for lymphoma may be useful in the treatment of CLL (Table 2). These antibodies are made by biotechnology methods and target the leukemic lymphocytes causing them to die after attachment. The antibodies may affect related normal lymphocytes but spare most other tissues, limiting their undesirable effects.

Stem Cell Transplantation

This is a treatment option for carefully selected younger patients with a marrow donor. A special form of *stem cell transplantation* that uses very low doses of pretreatment radiation and/or chemotherapy to prepare the patient to receive the donor marrow is being studied. This treatment is referred to as “nonablative” or “mini” transplantation because it does not lead to severe decreases in blood cell counts and can be used in older persons. It does not “ablate” or knock out the marrow

Table 2. Some Drugs and Monoclonal Antibodies Used in the Treatment of Chronic Lymphocytic Leukemia

alemtuzumab (Campath-1H)
chlorambucil (Leukeran)
cladribine (Leustatin)
cyclophosphamide (Cytoxan, Neosar)
doxorubicin (Adriamycin, Rubex)
fludarabine (Fludara)
prednisone (Deltasone)
vincristine (Oncovin, Vincasar)

blood forming function. The beneficial effects develop gradually over months and are thought to result from an immune attack by the donor's lymphocytes against the chronic leukemia cells. Eventually the donor marrow and immune cells become dominant. This approach is experimental.

Other Ancillary Treatments

Radiation treatments may be used occasionally to shrink large lymph node masses or lymph node masses in locations that interfere with the function of a neighboring structure (like the excretory duct of the kidney [ureter] or the intestine).

In selected CLL patients, surgical removal of a very enlarged spleen (**splenectomy**) may improve their blood cell counts. Leukemic lymphocytes can accumulate in the spleen, become troublesome to patients, and need to be removed by splenectomy.

Ancillary treatments include blood cell growth factors (*cytokines*), which may help to improve low blood cell counts. The use of such agents may also permit larger amounts of chemotherapy to be administered.

Complications and Their Treatment

Recurrent infections are a very frequent complication for patients with chronic lymphocytic leukemia. A higher risk of infections results when chemotherapy depresses certain infection-fighting white cells in the blood, specifically the phagocytes (microbe-eating) white cells. The deficiency of phagocytes permits bacteria and fungi to establish infections. Antibiotic therapy is usually required to treat bacterial or fungal infections during the course of the disease. Very low neutrophil and monocyte (phagocyte) counts, along with the inability of the patient's

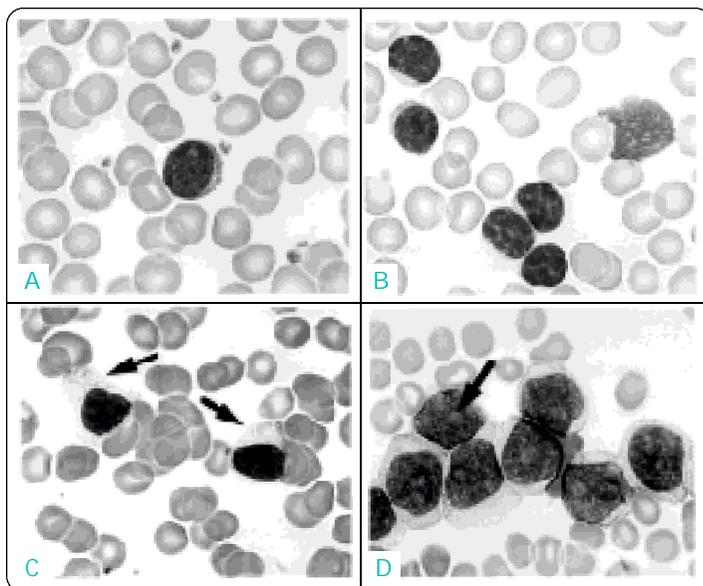


Figure 4: Panel A shows a normal lymphocyte in the blood film of a healthy person. Panel B shows the increased frequency of lymphocytes in the blood film of a patient with chronic lymphocytic leukemia. Panel C shows the appearance of large granular lymphocytes in a patient with this type of chronic lymphocytic leukemia (the arrows point to the cluster of granules in the cells), and Panel D shows the cells of prolymphocytic leukemia, which are larger than those in panel A or B and have a light area in their nuclei, called a nucleolus (see arrow). This structure in the nucleus is a sign of a more immature, or primitive, cell.

leukemic lymphocytes to make antibodies (immunoglobulins), combine to greatly heighten the risk of infections. Patients with recurrent infections may also receive injections of gamma globulin on a regular basis in order to correct the patient's immune deficiency (see top of page 9).

Some CLL patients produce a very restricted type of antibody against their own cells. These "autoantibodies" are usually directed against the patient's own red cells or, less often, platelets and cause the cells to be removed from the blood rapidly. This effect can worsen the anemia or markedly decrease the platelets. A test called the antiglobulin, or *Coombs' test*, is used to identify the autoantibodies. Treatment with

prednisone is sometimes needed to improve this type of anemia, which may be referred to as “autoimmune hemolytic anemia” or the low platelet count, which may be referred to as “immune thrombocytopenia.”

A small proportion of CLL patients has a change in their disease that causes it to behave like a more rapidly progressive lymphoma. This pattern has been referred to as a “Richter transformation,” after the physician who first called it to medical attention. Lymph node enlargement may be more apparent, fever and weight loss more prominent, and tumors of lymphocytes may develop in sites other than lymph nodes.

In other patients the change in their disease may more closely resemble prolymphocytic leukemia. The cells in the blood may change to be composed predominantly of another type of white blood cell, called prolymphocytes (see Figure 4, Panel D). The spleen may enlarge further and the response to treatment may be diminished. Prolymphocytic leukemia is more rapidly progressive than chronic lymphocytic leukemia but less progressive than acute lymphocytic leukemia. Very rarely, the pattern of disease may mimic that of acute lymphocytic leukemia. In the aggregate, these changes to a more aggressive pattern affect only a small proportion of CLL patients.

Other Related Lymphocytic Leukemias

Several diseases mimic chronic lymphocytic leukemia (see Table 3). In 95 percent of cases, the cell type that represents the malignant cell in chronic lymphocytic leukemia is a B lymphocyte. In the remainder, the cell that transforms from normal to leukemic has the features of a T lymphocyte or a natural killer (NK) cell. Thus, the three major types of lymphocytes (T cells, B cells, or NK cells) can undergo a malignant transformation that causes diseases similar to chronic lymphocytic leukemia (see Figure 3).

Large granular lymphocytic (LGL) leukemia is another type of chronic leukemia. It is characterized by larger lymphocytes containing conspicuous granules, which appear when examined under a microscope (see Figure 4, Panel C). These are not features of cells in other types of chronic lymphocytic leukemia. The immunophenotype of cells in large granular lymphocytic leukemia is either a T cell or an NK cell type, but not a B cell type, as in most CLL patients.

Certain types of **lymphoma cell leukemia** may mimic chronic lymphocytic leukemia, but distinctions are apparent between the two diseases. Chronic lymphocytic leukemia starts in the marrow and involves principally the marrow and blood. Lymph nodes are not prominently involved. Lymphomatous leukemia (leukemia with prominent lymph

Table 3. Types of Lymphocytic Leukemia

Less rapidly progressive:
chronic lymphocytic leukemia
hairy cell leukemia
large granular lymphocytic leukemia
macroglobulinemia

More rapidly progressive:
prolymphocytic leukemia
lymphoma cell leukemia

Most rapidly progressive:
acute lymphocytic leukemia

In most cases, the leukemia is composed of B lymphocytes, less often of T lymphocytes, or uncommonly of NK lymphocytes.

node enlargement caused by the invasion of leukemia cells) can develop in some patients. Lymphoma cell leukemia is a lymphoma with prominent marrow and blood lymphoma cells. In the latter case, the lymph nodes are principally involved but the blood and marrow are affected as well.

Hairy cell leukemia is another type of chronic leukemia of lymphocytes. It is discussed in The Leukemia & Lymphoma Society patient education booklet entitled *Hairy Cell Leukemia*.

Macroglobulinemia is a disease that also has several features in common with chronic lymphocytic leukemia. It is always a tumor of B cells that occurs in older individuals and principally involves the marrow. As in chronic lymphocytic leukemia, the marrow's ability to make normal cells is impaired and anemia is a common complication. Unlike chronic lymphocytic leukemia, the leukemic lymphocytes do not usually enter the blood in large numbers. Macroglobulinemia is also related to myeloma because, in both diseases, the malignant cells produce proteins called monoclonal immunoglobulins in an abnormal manner (see The Leukemia & Lymphoma Society's patient education booklet *Myeloma* for further information on macroglobulinemia). The disease is sometimes called Waldenström's macroglobulinemia after the Swedish physician who described the first recognized cases.

Prolymphocytic leukemia is a disease that features large numbers of lymphocytes in the blood but they are a mixture of small lymphocytes akin to chronic lymphocytic leukemia and large, more immature appearing lymphocytes akin to acute lymphocytic leukemia. The disease progresses more rapidly than the chronic form but more slowly than the acute form and is sometimes referred to as subacute lymphocytic leukemia. It is treated with the same drugs used for other lymphocytic leukemias.

In each of the diseases mentioned above, there are distinguishing characteristics that permit the *hematologist* or *oncologist* to label them. They all result from the malignant transformation of a type of lymphocyte and the accumulation of these cells occurs principally in the marrow, blood, and the spleen. Lymph node enlargement may also occur.

There are special distinguishing features (appearance and immunophenotype) of the malignant cells as well, such as their varying effects on normal marrow and blood cell development and their varying effects on other organs (e.g., kidney, bowel, nervous system). Also, most of them have a broad range of clinical severity. At one extreme, the disease may be stable, not advance in severity, and be of little consequence for months or years, occasionally indefinitely. At the other extreme, associated difficulties may be present at diagnosis and may progress in one form or another, requiring immediate treatment, frequent observation, and a readiness to deal with new and unexpected problems.

Lymphoma versus Lymphocytic Leukemia

The lymphomas and the lymphocytic leukemias are each the result of a malignant transformation of a cell that was destined to be a lymphocyte. The distinction in name is made based on whether the disease started in a lymphocyte in a lymph node or other lymphatic tissue such as skin, bowel, or other organ in which case the disease is designated “lymphoma” or whether the disease originated in a lymphocyte in the lymphatic tissue present in marrow in which case the disease is designated “leukemia.” In some cases of lymphocytic leukemia, lymph nodes may be prominently involved as well, and in some cases of lymphoma, marrow and blood contain the abnormal lymphocytes.

Social and Emotional Aspects

The diagnosis of chronic lymphocytic leukemia may provide 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 leukemia. 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 following Society publication: *Coping With Survival*, a booklet dealing with the psychosocial aspects of the disease for leukemia patients.

There are programs to help ease the emotional and economic strain created by leukemia. The Leukemia & Lymphoma 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 public information resource line at (800) 955-4572.

You may also want to 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.

The Future

New Drug Treatments

New drugs and new combinations of drugs are being tested to contribute to more effective treatments for CLL patients. This is an ongoing process as pharmaceutical companies cooperating with academic health centers introduce new drugs into clinical trials. In some cases existing drugs used in different doses and schedules may be found to be useful. Since chronic lymphocytic leukemia is thought to result in part from a change in the cell that prevents its natural death, the cells accumulate in large numbers. Drugs are being developed that encourage the leukemic cells to die. *Apoptosis* is the term that refers to the normal process of cell death. Genes in the cell nucleus normally govern this process. If these genes or the products they encode go awry cell death may not occur or be unduly delayed. Drugs that enhance cell death are under study to see if they may be of benefit in patients with CLL.

Improvements in Stem Cell transplantation

New procedures for allogeneic stem cell transplantation are being studied. Research teams are now trying novel ways to reduce the toxicity of transplantation and make it a possible therapy for more CLL patients. One approach may permit less toxic drug therapy prior to transplant, making this procedure available to older patients.

Immunotherapy

Research is being conducted on several approaches that may permit the use of immune cells or their products to fight the disease. One approach is to use an antibody that targets the leukemic lymphocytes and which may block a critical function of the cell causing it to die. Sometimes antibodies may have a cell toxin, a drug, or a radioactive molecule attached which causes the death of the leukemic cells and limits the effects on other tissues. These approaches have been introduced to treat lymphoma and may be useful in some cases of lymphocytic leukemia. Stem cell transplantation can be a form of immunotherapy in which donor lymphocytes attack and kill the lymphocytes of the patient.

Cytokines

These naturally occurring growth hormones can be made commercially using the techniques of biotechnology. These growth hormones can be used to help restore normal blood cells during treatment or enhance the immune system to attack the leukemia cells.

These and other new approaches, many of which are being supported by the research programs of The Leukemia & Lymphoma Society, hold the promise of increasing the rate of remission and finding the cure for chronic lymphocytic leukemia.

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. Severe anemia can cause a pale complexion, weakness, fatigue, and shortness of breath on exertion.

Antibodies

Proteins that are made by B lymphocytes 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 Immunophenotyping).

Antiglobulin Test

This laboratory procedure can identify antibodies on the surface of red cells or platelets. Patients with chronic lymphocytic leukemia and other lymphocytic malignancies may make antibodies to their own red cells or platelets (auto or self-directed antibodies). These autoantibodies may lead to anemia or low platelet counts. 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 to the donor. 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.

Apoptosis

The process of programmed cell death of a cell. Normally genes in the cell nucleus govern the life span of a cell. These genes encode proteins that determine this process. In some blood cell cancers too rapid cell death may prevent normal cell development or too slow cell death may lead to the accumulation of an abnormal number of cells. The term apoptosis is derived from the Greek terms for falling leaves, drawing an analogy to the death of the leaves on deciduous trees to be replaced later by new leaves as dead cells are replaced by new cells in normal processes. This process is carefully controlled to keep just the right number of cells in each tissue in a healthy person.

Autologous Marrow (Stem Cell) Infusion

This technique, often referred to as transplantation, involves the harvesting of a patient's marrow or blood. The stem cells are usually frozen for later use. The patient is then given intensive therapy, and the stem cells are reinfused via an indwelling catheter. The blood or marrow may be obtained from a patient with a disease of the marrow (for example, acute myelogenous leukemia) when in remission or when the marrow is not overtly abnormal (for example, lymphoma requiring intensive therapy). Technically, this procedure, which formerly used marrow stem cells, 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 may be supplanted by

autologous blood stem cell infusion since marrow stem cells circulate in the blood and can be recovered there by apheresis (see *Apheresis*).

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 technique 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.

Blast Cells

This term 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 up to 80 percent of all marrow cells. In acute myelogenous leukemia, myeloblasts accumulate; in acute lymphocytic leukemia, lymphocytes accumulate. The distinction 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 a 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)

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 sex 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 myeloma, lymphoma, or leukemia cells.

Clonal (Monoclonal)

A population of cells derived from a single primitive cell. Virtually all neoplasms (cancers), benign and malignant, 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* and 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 clonal cancers, that is, derived from a single abnormal cell.

Colony Stimulating Factor

(see Cytokines)

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 for 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 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.

Cycle of Treatment

The term designates an intensive, clustered period of chemotherapy (and/or radiotherapy). A treatment may be given for several days or weeks and represents one cycle. The treatment plan may call for two, three, or more cycles.

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 substances that are secreted by various types of cells and act on other cells to stimulate or inhibit their function. Substances derived from lymphocytes are called “lymphokines,” and those 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 specific characteristics into cells of a single blood cell line. The red cells, platelets, neutrophils, monocytes, eosinophils, basophils, or lymphocytes are formed by this process.

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).

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, and D. These proteins act as antigens when donated (transplanted) to another individual, the 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 transplant (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

This term describes 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, 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 abnormalities in blood cell counts when the marrow is injured by replacement with leukemia, lymphoma, or myeloma.

Hepatomegaly

The term used to indicate enlargement of the liver.

Iliac Crest

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

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 laboratory equipment used for the test can identify the tag. 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 available for patients receiving intensive chemotherapy and/or nutritional support. An indwelling catheter is a special tube 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 external end of the catheter can be used to administer medications, fluids, or blood products or to withdraw blood samples. With meticulous care, catheters can remain in place for 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).

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).

Lymph nodes

Small structures, the size of beans, that contain large numbers of lymphocytes; they are connected with each other by small channels called lymphatics. These nodes are distributed throughout the body. In patients with lymphoma, Hodgkin's disease, 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

The term used to indicate enlargement of lymph nodes.

Lymphocytes

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

Lymphokine

(see Cytokines)

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).

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.

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 mutation occurs in a cell 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 are usually widely distributed when detected; they involve the marrow or lymph nodes, usually in many sites.

Neutropenia

A decrease below normal in the number of blood neutrophils, a type of white blood 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 with acute leukemia or after chemotherapy, which increases their susceptibility to infection. A neutrophil may be called a "poly" or "seg."

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).

Oncologist

A physician who diagnoses and treats patients with cancer. They 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.

Pancytopenia

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

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

Platelets

Small cell 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 acute leukemia. The platelets can be pooled from several unrelated donors and given as “pooled random-donor platelets.” It requires 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 by apheresis. The latter technique skims the platelets of large volumes of blood passing through the apheresis machine. 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 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 nonleukemic cells. PCR requires a specific DNA (or RNA) abnormality or marker, like an oncogene, in the myeloma, leukemia, or lymphoma cells for its use.

Red Cells

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

Relapse

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*).

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 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 the blood of old or worn out blood cells. It is often affected in leukemia, especially the lymphocytic leukemias,

lymphoma, and Hodgkin's disease. 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 its function.

Stem Cells

These are primitive cells in marrow that are important in making red blood cells, white blood cells, and platelets (see Hematopoiesis). Generally, the stem cells are found largely 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

This is 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 exposures. As first designed, 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.

The transplant product is, specifically, 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 also circulate in large numbers in fetal blood 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, the term “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 radiotherapy for their underlying disease has been referred to as autologous (self) or auto-transplantation. This term is an 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*).

Therapy

The curative treatment of leukemia, lymphoma, or myeloma is thought of in different phases. 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 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 in consolidation therapy. In addition to chemotherapy, therapy of leukemia or lymphoma also refers to radiation therapy and ancillary therapy such as use of antibiotics, blood products, and cytokines.

Thrombocytopenia

A decrease below normal in the number of the blood platelets.

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 (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.

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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.

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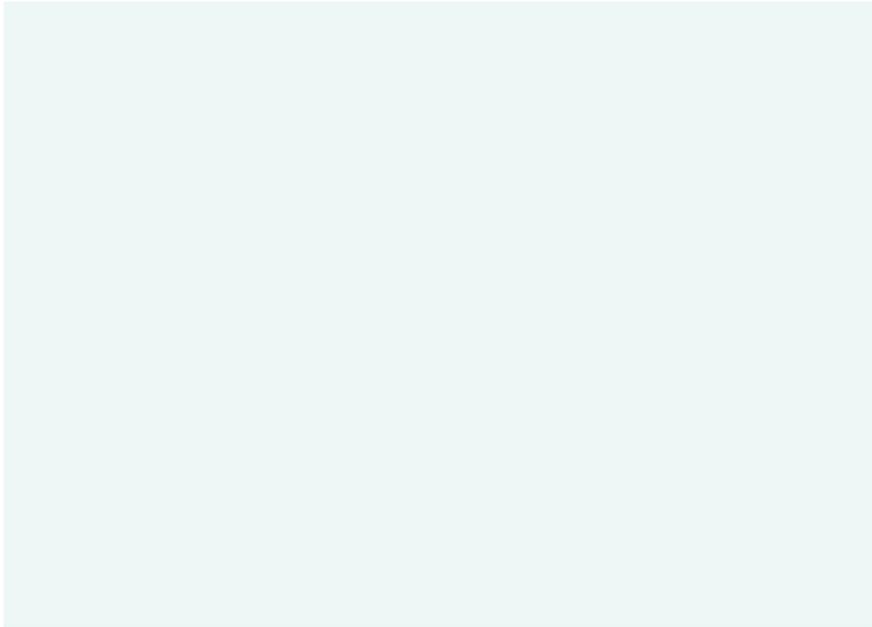
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Free Literature: (800) 955-4572
www.leukemia-lymphoma.org

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



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