

***Blood and Marrow  
Stem Cell Transplantation:  
Leukemia, Lymphoma and Myeloma***



**The Leukemia &  
Lymphoma Society®**

*Fighting Blood-Related Cancers*

# Introduction

This booklet provides information for patients and their families about the use of blood or marrow stem cell transplantation for the treatment of leukemia, lymphoma, or myeloma. A glossary at the end of the booklet may help the reader understand the technical terms. We hope this information is of assistance. Comments as to clarity of the information provided and the omission of additional information that would have been helpful are welcome.

Between 1970—when the transplant registry began tabulating statistics—and today, the frequency of stem cell transplantation for the treatment of hematological malignancies has increased from hundreds to thousands of patients transplanted per year. Each year 9,000 persons in North America undergo stem cell transplantation for leukemia, lymphoma, or myeloma. The procedure continues to be improved in anticipation of making it available to even more patients each year. Before describing the technique and its application 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 many chemicals are dissolved. 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., polio virus antibodies). The cells include *red blood 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 (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*, *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 back bones (vertebrae), hip and shoulder bones, ribs, breast bone, 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).

In healthy individuals, there are 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 type of blood counts. Their presence in the blood

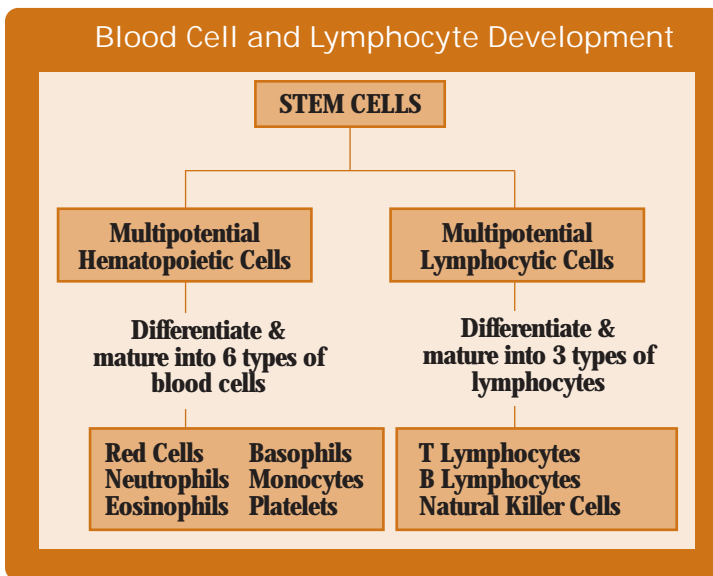


Figure 1. This figure depicts an abbreviated diagram of the process of hematopoiesis. This process involves the development of functional blood and lymphatic cells from stem cells.

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 are collectively the white blood cells, move into the tissues of the lungs, for example, and can combat infection, such as pneumonia, and perform their other functions.

## Origins of Transplantation

In the mid-19th century, Italian scientists proposed that the marrow was the source of blood cells. The idea that a factor in the blood-forming tissues from one individual might restore the injured marrow of another individual was considered a century ago. Some thought this factor was a chemical that could be transferred by eating the marrow. At the turn of the 20th century, scientists began to formulate the idea that a small number of cells in the marrow might be responsible for the development of all blood cells. They began to refer to them as “stem cells.” Attempts to use the marrow cells of a healthy individual to restore the lost marrow function of an ill patient are at least 60 years old. Early attempts at human marrow transplantation were largely unsuccessful because the scientific basis for success was not yet known.

Marrow transplantation as a form of treatment began to be explored scientifically at the end of World War II. The stem cells of marrow are very sensitive to irradiation injury. Thus, marrow injury was an important and potentially lethal side effect of exposure to the atomic bomb or to industrial accidents in the atomic weapons industry. In the late 1940s, studies of marrow transplantation as a means of treating radiation-exposed combatants or civilians was spurred by the Atomic Energy Commission's concern about the spread of nuclear technology and weapons.

The idea that medical disorders that affect blood cell or immune cell formation could be cured by marrow transplantation encouraged research by civilian scientists as well. Their research efforts led to the current success of *stem cell transplantation* as a means of medical treatment and its increased availability to patients (see Figure 2).

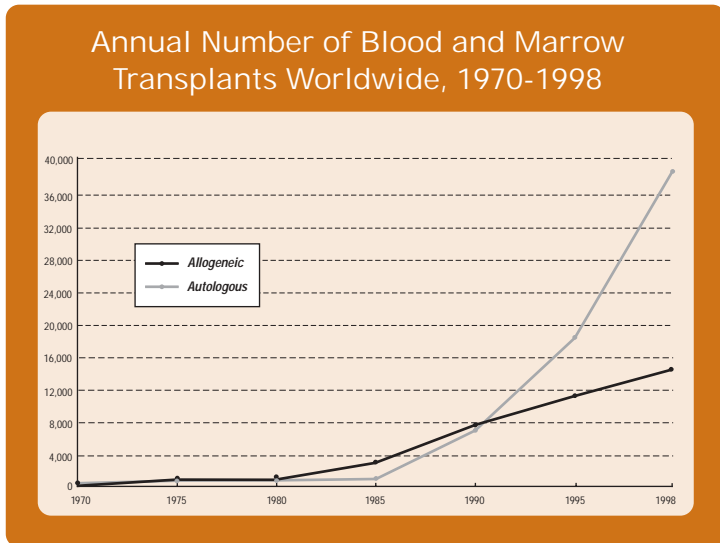


Figure 2. The number of allogeneic and autologous transplants performed each year as reported to the International Bone Marrow Transplant Registry. Improvement in techniques of transplantation in the 1980s and after have led to a marked increase in the application of this approach. Reporting is voluntary so this probably is an underestimation of the number of transplants performed world-wide. (Kindly provided by the International Bone Marrow Transplantation Registry)

## Reasons for Using Transplantation

The rationale for stem cell transplantation is based on the fact that all blood cells (e.g., red cells, phagocytes, and platelets) and immune cells (lymphocytes) arise from the stem cells, which are present in the marrow. Stem cells circulate in the blood in very small numbers. Drugs are available that increase the numbers of stem cells in the blood by drawing them out of the marrow. Sufficient quantities of these stem cells for transplantation are recovered by circulating large volumes of blood through a *hemapheresis* machine and skimming off a population of cells that contains stem cells.

Blood is an increasingly frequent source of stem cells for transplantation. Thus, bone marrow transplantation, or BMT, as a generic term for the procedure has been modified to mean blood or marrow transplantation, permitting the continued use of the familiar acronym, BMT. In many cases, the more specific term stem cell transplantation (or SCT) is now used.

## Disorders Treated with Stem Cell Transplantation

### Immune Deficiency Diseases

Children who are born with severe immune cell deficiencies are unable to make lymphocytes, the cells that help the body combat infection. In the absence of normal lymphocytes and immune function, these children may experience repeated and often life-threatening infections. Lymphocytes (descendants of the stem cells) can be restored by stem cell transplantation. Transplantation is facilitated by the recipient being deficient in immune cells. This makes it unlikely that the recipient will reject the donor stem cells. Therefore, this type of transplantation does not require intensive pretreatment (*conditioning*) of the recipient with radiation or *chemotherapy* to suppress the immune system.

## Inherited Severe Blood Cell Diseases

Marrow transplantation is now being used to treat diseases such as thalassemia or sickle cell diseases, in which a mutant gene is inherited. The mutant gene expresses itself only in the blood-forming cells. In this sense, transplantation for these patients is a form of genetic *therapy*: the genetically abnormal blood-forming stem cells are replaced with normally functioning cells. A sibling with a matching tissue type is the donor of the stem cells. The dissimilarity of certain characteristics between two siblings is an advantage in this situation. The patient may have sickle cell disease (received the mutant gene from both mother and father), and the donor may be a carrier of the gene and have sickle cell trait (received the mutant gene from mother or father, but not both), yet it is possible for stem cells from the latter to cure the former.

Major advances in the technique of stem cell transplantation were required for the procedure to be useful in these situations. These diseases, although often very serious in their manifestations, allow individuals to reach adulthood. The high risk and serious side effects of transplantation delayed its application in these settings until research advances led to acceptable results in carefully selected patients. The decision regarding who among those people with inherited blood cell disorders should take the risk of transplantation and when to undertake the procedure is still under investigation.

## Other Inherited Disorders

There is a group of inherited disorders in which there is a defect in the monocytes. Soon after birth very disabling abnormalities including blindness, mental retardation, and severe neurological dysfunction may develop in the affected infant. Like all white blood cells, monocytes are descendants of stem cells. If the defect is in the monocytes, the abnormal cells can be replaced by normal cells through the transplantation of stem cells from a healthy compatible donor.

## Marrow Failure

Stem cell transplantation has been used successfully to restore the function of marrow that has been injured. This type of marrow failure, referred to as aplastic anemia, can be drug induced, autoimmune, or, more rarely, inherited. As a result of exposure to certain drugs or to an external noxious agent, such as a chemical or unintended radiation exposure, marrow failure can occur. An autoimmune attack of the patient's lymphocytes on the blood-forming cells in the marrow can also cause failure. If the latter disease is severe, the marrow stops making blood cells. This alteration leads to the risk of serious hemorrhage from a deficiency of platelets or repeated and life-threatening infections from a deficiency of white blood cells. The marrow's blood cell manufacturing ability can be severely decreased also by the inherited disease called Fanconi aplastic anemia.

If severe, and if a compatible donor can be found, aplastic anemia can be treated by stem cell transplantation. In this situation, pretreatment of the patient with chemotherapy and/or radiation therapy is required to suppress the immune system of the patient and enhance the likelihood of success of the transplant. Chemotherapy or radiation prior to transplant decreases the risk that the recipient's immune cells will reject the transplanted stem cells. In addition, since the disease is often the result of an attack by the patient's own lymphocytes on developing blood cells (autoimmune disease), the conditioning treatment helps to rid the recipient of these disordered lymphocytes. After the transplant, the donor's lymphocytes and blood cells will replace those of the patient, thus curing the disease.

## Leukemia, Lymphoma, Myeloma

Acute leukemia, lymphoma, and myeloma have *remission* and cure rates that increase in relationship to the amount of chemotherapy given to the

patient. Large doses of chemotherapy and/or radiation are required to destroy the disease cells. These intensive therapies can destroy normal cells in the marrow as well. The capability of the marrow to make healthy blood cells is so severely impaired after very high-dose chemotherapy and radiation therapy required to treat refractory or *relapsed* disease that few patients would survive such treatment. They would succumb as a result of infections (because of the absence of white cells) or hemorrhage (because of the absence of blood platelets).

In order to administer larger doses of chemotherapy or radiation therapy, transplant physicians developed stem cell transplantation as a method to restore normal blood cell production in a timely fashion. With the infusion of sufficient stem cells from a closely matched donor, such as a sibling, marrow function and blood cell production are restored rapidly enough to allow recovery from the intensive treatment. After several decades of research, discovery, and clinical trials, *allogeneic stem cell transplantation* can be used successfully to cure patients who are at high risk of relapse, who do not respond fully to treatment, or who relapse after prior successful treatment (see Table 1). In some circumstances *autologous* stem cells (obtained from the blood and marrow of the patient) can be used.

The age, medical condition, likelihood of response of the malignancy to the conditioning regimen, and the availability of an *HLA*-matched donor are considerations in the decision to use allogeneic transplantation.

Thus, leukemia, lymphoma, or myeloma, if poorly responsive to standard therapy, or if biological features are present that are known to predict for a poor response to chemotherapy, may be treated with very intensive chemotherapy and/or radiotherapy, which requires complementary stem cell transplantation.

**Table 1. Malignant Hematologic Diseases in Which Allogeneic Stem Cell Transplantation Has Been Used**

<b>Acute myelogenous leukemia (all subtypes)</b>	<b>Hodgkin lymphoma (if refractory to treatment or recurrent)</b>
<b>Adult acute lymphocytic leukemia</b>	<b>Idiopathic myelofibrosis (Agnogenic myeloid metaplasia)</b>
<b>Childhood acute lymphocytic leukemia (if very high risk type or does not enter remission or relapses)</b>	<b>Lymphoma (all subtypes, if refractory to treatment or recurrent)</b>
<b>Chronic lymphocytic leukemia (all subtypes)</b>	<b>Myeloma</b>
<b>Chronic myelogenous leukemia</b>	<b>Oligoblastic myelogenous leukemia (myelodysplasia)</b>

### Deciding to Use Stem Cell Transplantation for Leukemia, Lymphoma, or Myeloma

Two central questions should be answered when considering a transplant for a patient in remission: Does the current evidence indicate that stem cell transplantation will be more likely to cure the disease than other forms of therapy? Is there a compatible donor available as a source of stem cells? Other important factors that influence the decision include the patient's age, the specific disease being treated, biologic features at the time of diagnosis that indicate a poor prognosis, and the presence of complicating medical conditions (see Figure 3).

The age of the patient is a compelling factor in the decision to do a transplant. About three-quarters of individuals who develop leukemia, lymphoma, or myeloma are over 50 years of age. Patients over that age are less likely to have a favorable outcome after transplantation.

Indeed, the results of transplantation are best in children and become less favorable with each advancing decade. Older individuals are: 1) more

susceptible to *graft versus host disease*; 2) more likely to have complicating medical problems; and 3) more likely to have a decreased *tolerance* for the accumulated effects of the prior intensive chemotherapy and the conditioning treatments required for transplantation. These are generalizations and allogeneic transplantation can be used in older individuals when judgment favors that decision. Moreover, new techniques that require less harsh conditioning therapy are being explored for certain types of leukemia and lymphoma.

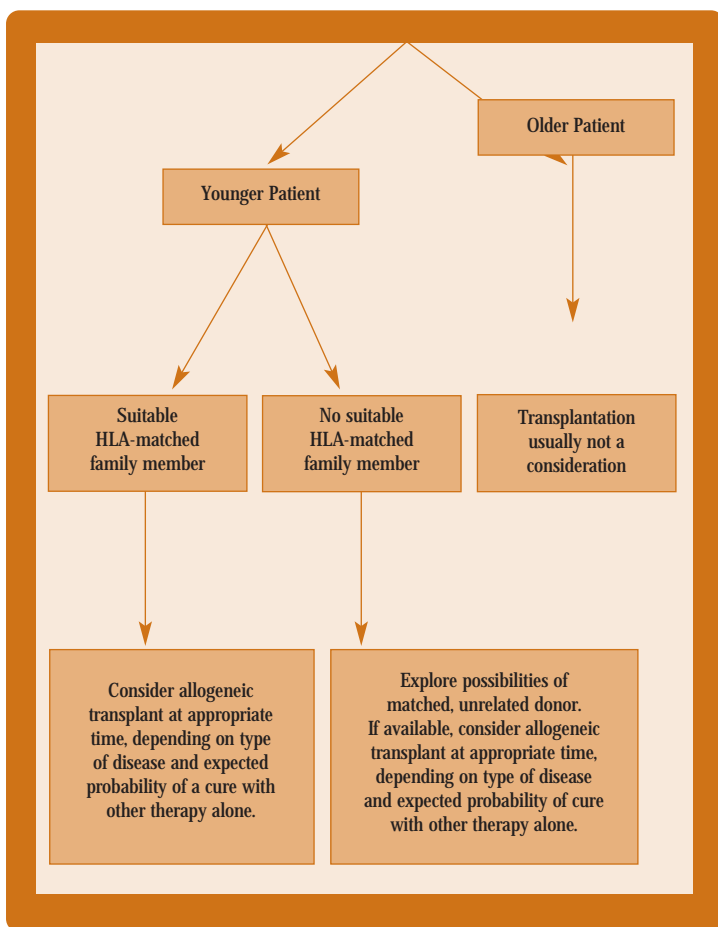


Figure 3. Allogeneic Stem Cell Transplantation Decision Tree

Although the risks of allogeneic transplantation have decreased with each succeeding decade of experience, the procedure requires careful analysis of the circumstances and in-depth and thoughtful discussions with the patient. Continued research may further change the risk-to-benefit equation in favor of transplantation. Alternatively, new drugs and new modalities may do the reverse.

## Testing Donor Compatibility

When a transplant is under consideration, the patient and his or her siblings will be tested to determine their tissue type or human leukocyte *antigen* (HLA) type.

The tissue type of an individual is determined by proteins on the surface of cells. Like other tissue cells, the *leukocytes* contain these surface proteins. By testing the leukocytes obtained from a blood sample, transplant physicians can determine the HLA type of the patient and potential donors. The immune reactions that occur when nonidentical individuals receive a transplant are governed largely by these cell surface proteins. The lymphocytes of the recipient can sense the foreignness of the donor's cells and attempt to kill (reject) them. The donor's immune cells can sense the foreignness of the patient's cells and attack them.

The degree of disparity between donor and recipient is the major determinant of the intensity of host versus graft or graft versus host disease. These reactions do not happen if the recipient and donor are identical twins but do happen in nonidentical siblings, even if they are matched by tissue typing. The latter observation indicates that HLA testing does not examine all relevant tissue type factors. This expectation requires that two methods be used to permit a successful transplant: suppression of the immune system of the recipient before transplant and suppression of the donor's immune cells in the recipient after transplant.

A person's HLA type is governed by genes that reside on chromosome number 6 in tissue cells. Every human nucleated cell has 46 *chromosomes*: a pair of each chromosome numbered from 1 to 22 plus the two sex chromosomes (either XX in a female or XY in a male). The genes that determine tissue or HLA type are transmitted to a child in a manner shown in Figure 4. One of each pair is inherited from one's mother and the other of the pair from one's father. The genes on one chromosome 6, of the pair AB from mother and on one chromosome 6 of the pair CD from father, determine the HLA type. Each parent's contribution is referred to as a *haplotype*. Thus, the term haploidentical indicates that the person being typed shares half the tissue type of the potential recipient. In the example shown in Figure 4, siblings AC and AD are haploidentical, sharing their mother's chromosome A but receiving different chromosomes from their father.

This pattern of inheritance explains why parents usually are not sufficiently tissue-type compatible to be donors.

On average, a person has one chance in four of having the same HLA antigens as his or her sibling. Since the average family in the United States has about two children, many patients will not have a sibling of the same tissue type.

The HLA system is broken down into two groups of cell surface antigens: Class I and Class II. Class I antigens are determined by genes referred to as A, B, and C. Class II antigens are determined by genes referred to as D. In populations, these genetic loci A through D have many variations called alleles which give each individual uniqueness. For example, one person may have A1, another A2, and another A3, and so on. In families, these variations are minimized and provide the opportunity to find a sibling that is matched, making transplantation possible, if immune system suppression is also used.

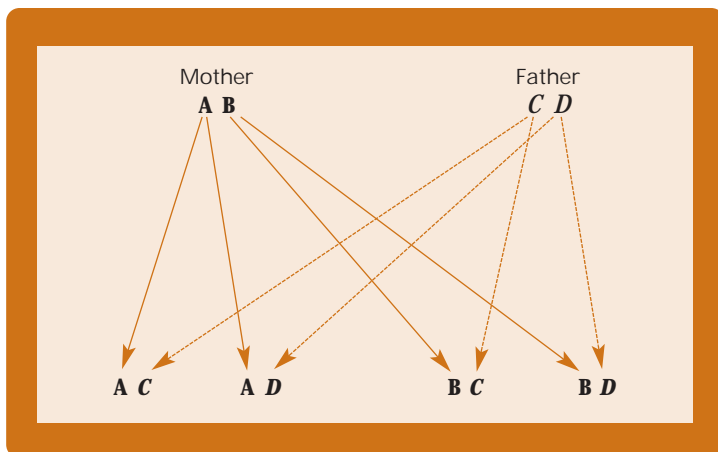


Figure 4. **Inheritance Pattern of HLA Characteristics.** A and B depict the two chromosomes number 6 of mother and C and D the two chromosomes number 6 of father. The term haplotype indicates the specific HLA characteristics determined by the genes on one of the chromosome 6 pair received by the child. The probability is that among four children, each will inherit the chromosome pairs shown, either A or B from mother and either C or D from father. The estimate that a match will occur on average one in four times is based on these outcomes. Thus, if child AC requires a match, that combination should occur in one of four siblings on average. Of course, this expectation holds true in large sample sizes; in an individual family, deviations in a favorable or unfavorable direction would occur often.

Until recently, HLA typing had been done by a procedure called serological typing. In this procedure, the white blood cells of the recipient and prospective donor are tested to see if their tissue types are identical. This procedure was very useful but less refined than the new method of molecular typing. In the latter technique, the DNA of the recipient and prospective donor are characterized to identify specific genes that direct the formation of the HLA antigens on the surface of cells. Defining the genotype of the individual gives more specific results than serological testing. This requirement is particularly important when searching for a match among unrelated donors.

Since the probability of finding a match among siblings is only one in four, efforts are being made to develop methods to permit transplantation

between individuals who are only partially matched. For example, the ability to transplant from parent to child would make the availability of transplantation nearly universal for childhood disorders. Such experiments are being conducted. Children are more tolerant of such deviations from ideal matching, and hope exists that with better control of the immune reactions involved, moderately mismatched transplants may be feasible.

## Sources of Stem Cells

### Marrow

Obtaining marrow stem cells for transplantation requires that a compatible donor receives a thorough health examination, which includes an electrocardiogram, chest X-ray, blood chemistry evaluation, and confirmation that blood cell counts are normal. The donor is tested to insure that the hepatitis virus and *human immunodeficiency virus (HIV)* are not present in the blood. The presence of a positive test for cytomegalovirus (CMV) does not necessarily preclude one from being a donor. If all is in order, the donor is given anesthesia in an operating room suite. The transplant physicians use a special wide bore needle attached to a large syringe to suck out samples of marrow from the top edge of the pelvic bones. This area can be easily felt under the skin of the sides and back just below the waist. The insertion of the needle through the skin and into the rim of the pelvic bone is repeated until several pints of marrow is removed. The entire process takes place under sterile conditions.

The amount of marrow removed is related to the size of the recipient. For the transplanted stem cells to engraft, a large adult requires more marrow cells than does a small child. The marrow is filtered to remove fragments of bone or tissue, passed through a screen to break up cell aggregates, and placed in a plastic bag from which it can be infused into the recipient's

vein. The infusion of a suspension of cells containing the stem cells into the recipient's vein is similar to a blood transfusion. This type of administration is used whether the source of stem cells is marrow or blood.

The harvested marrow is administered to the recipient usually within a few hours (in most cases, less than 24 hours). The donor usually remains in the hospital for about 12 hours before going home. During this time, the donor recovers from anesthesia and the pain at the needle insertion sites. If necessary, the harvested marrow cells can be frozen and stored for later use. The marrow can be frozen for years and remain suitable for stem cell transplantation. For example, freezing is commonplace in anticipation of autologous marrow infusion. In this circumstance, the patient is the source of the marrow during a period of disease remission following treatment and may be the recipient if a relapse occurs later and very intensive treatment is required.

## Blood

The technique of human transplantation began with the supposition that the principal source of blood cell-forming stem cells is the marrow since this is the sole location for blood cell production after birth. It had been known that the stem cells leave the marrow, circulate in the blood, and re-enter the marrow. The rarity of these cells in the blood, however, made it seem an improbable source for transplantation.

Methods were developed to move stem cells from the marrow into the blood in sufficient numbers to be harvested and used for transplantation. This procedure requires that a donor be treated with a drug that mobilizes stem cells into the blood. In some cases of autologous transplantation, stem cells can be mobilized by a combination of chemotherapy used to treat the underlying disease and stem cell-releasing *cytokines*. Then the cells are removed from the donor by a process called hemapheresis. In this process, the donor is linked to a special type of refrigerated centrifuge.

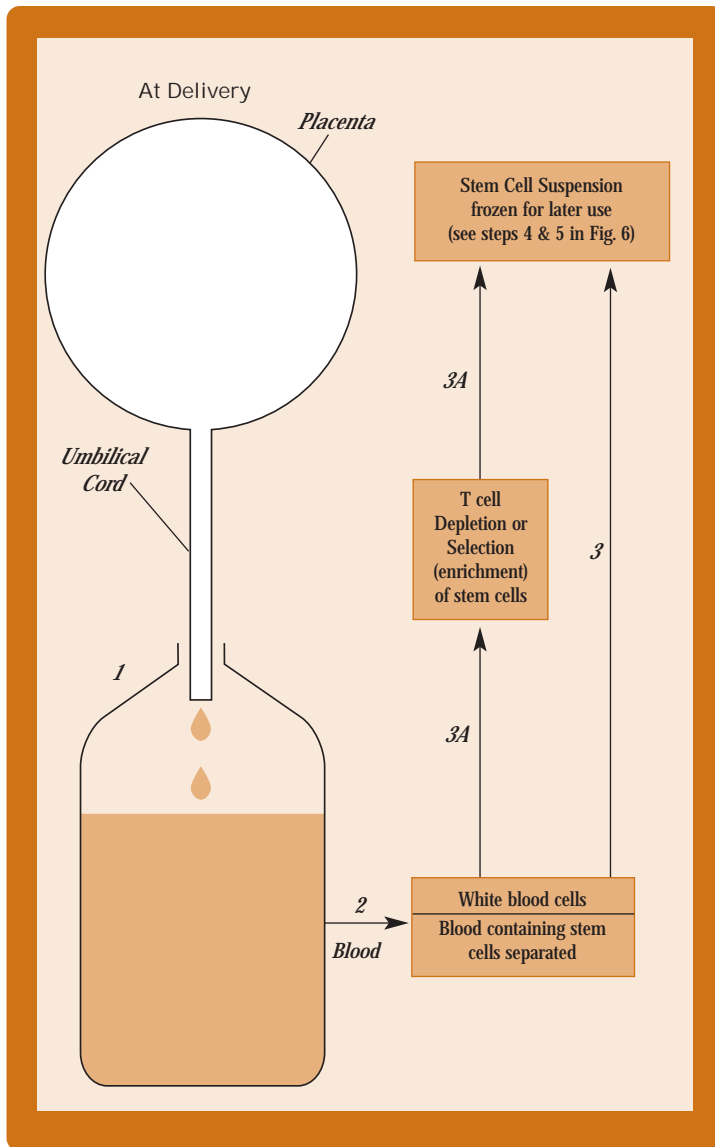
The blood of the donor is pumped through the instrument which separates the blood into four components: red cells, plasma, white cells, and platelets. The latter two fractions are harvested because they contain the stem cells. The red cells and plasma are returned to the donor. Hemapheresis permits blood to be recirculated through the machine for several hours. The procedure may be repeated at a later time, after which the collections are pooled. It generally takes two or more sessions to collect an adequate amount of stem cells from the bloodstream.

In this way, ample stem cells may be recovered to insure a successful transplant. The procedure avoids the general or spinal anesthesia required to harvest marrow stem cells from the donor and the day or two of discomfort from the pelvic bone needle insertions required to recover marrow stem cells.

### Umbilical Cord and Placental Blood

Stem cells circulate in the blood of the fetus as well as in children and adults. In the fetal circulation, the concentration and growth potential of blood cell-forming stem cells is even greater than in the blood of adults. At the time of delivery, the umbilical cord is severed and discarded as the “afterbirth” along with the attached placenta. Instead of being discarded, the blood can be carefully drained into a sterile plastic container. The suspension of cells containing stem cells can then be frozen and used for transplantation at a later date (see Figure 5). When used as a transplant product, it is referred to as “cord blood cells.”

Banks are being developed that contain the frozen donated samples from placental and cord blood. Since there are millions of healthy births each year, even a small proportion of these afterbirth specimens can provide a potential source of stem cells for recipients who do not have a sibling with a similar tissue type. The number of stem cells from the cord and placenta may be insufficient to transplant large recipients successfully.



**Figure 5. Placental and Cord Blood Stem Cell Recovery.** To collect cord blood stem cells, the placenta and attached umbilical cord are drained and the blood collected under sterile conditions (Step 1). The white blood cells are separated from the red blood cells (Step 2). After adding an agent that protects frozen cells from damage (*cryoprotective* agent), the suspension of cells, which includes stem cells, is frozen for later use (Step 3). Alternatively, the T lymphocytes present in the blood can be depleted or the stem cells enriched before freezing (step 3A). (see T Lymphocyte Depletion and Stem Cell Selection Procedure on page 19)

Children and small- and medium-sized adults usually can be treated from this source of stem cells.

There are several important considerations in using cord stem cells. The possibility that the newborn's blood carries an infectious agent or that the newborn carries gene *mutations* that will lead to a serious inherited blood cell disease are examples of issues that are particular to cord blood stem cells. These and other considerations are being studied as this source of stem cells becomes more prevalent.

## T Lymphocyte Depletion

T lymphocytes in a donor's marrow or blood cause graft versus host disease. In order to minimize this harmful reaction, the marrow or blood cell collection to be used for transplant can be treated with agents that can decrease the number of T lymphocytes infused with the stem cells. This technique reduces the incidence and severity of graft versus host disease. The procedure is known as *T lymphocyte depletion*.

The T lymphocytes are beneficial as well. They help the donated stem cells take hold and grow in the recipient's marrow. In some cases, T lymphocytes attack the leukemia cells, enhancing the suppressing effects of treatment. Known as "*graft versus leukemia*," this effect can be seen mostly in myelogenous leukemia. The attack on the residual tumor cells makes it less likely that the malignancy will return after transplant. Thus, transplant physicians must be careful about how many T cells are removed during this procedure.

## Stem Cell Selection Procedure

When an allogeneic donor's marrow or blood is collected, the stem cells are mixed with many other cells that are present in those sites. Lympho-

cytes are among the other cell types present. There are specific features on the outer coat of stem cells that permit them to be removed selectively from a mixture of cells and then recovered. When this selection procedure is done, it results in a cell population that is enriched in stem cells and has many fewer other cells, including lymphocytes. By reducing the number of T lymphocytes, the frequency or severity of the graft versus host immune reaction can be decreased.

## Types of Stem Cell Transplantation

### Syngeneic Transplantation

Syngeneic transplantation is the term for a transplant in which the donor and recipient are identical twins and have an identical tissue type since their genetic make-up is the same. In such a transplant the donor cells would not be rejected and the recipient's tissues would not be attacked by the donor's immune cells (lymphocytes).

### Allogeneic Transplantation

Allogeneic transplantation is the technical term for a transplant between two individuals of the same species. In practice, the term also implies that the donor was chosen because his or her tissue type very closely matched the recipient's. The donor who matches the prospective recipient most closely is the sibling of the patient since both received their genetic composition from the same parents. This fact does not insure compatibility but greatly increases its probability.

Transplant physicians can test to determine the degree of compatibility before a decision is made to use the donor. Compatibility is assessed by laboratory tests that identify the tissue type of donor and recipient. There are two types of allogeneic donors: related, usually sibling donors and unrelated, usually found from very large pools of volunteers and matched

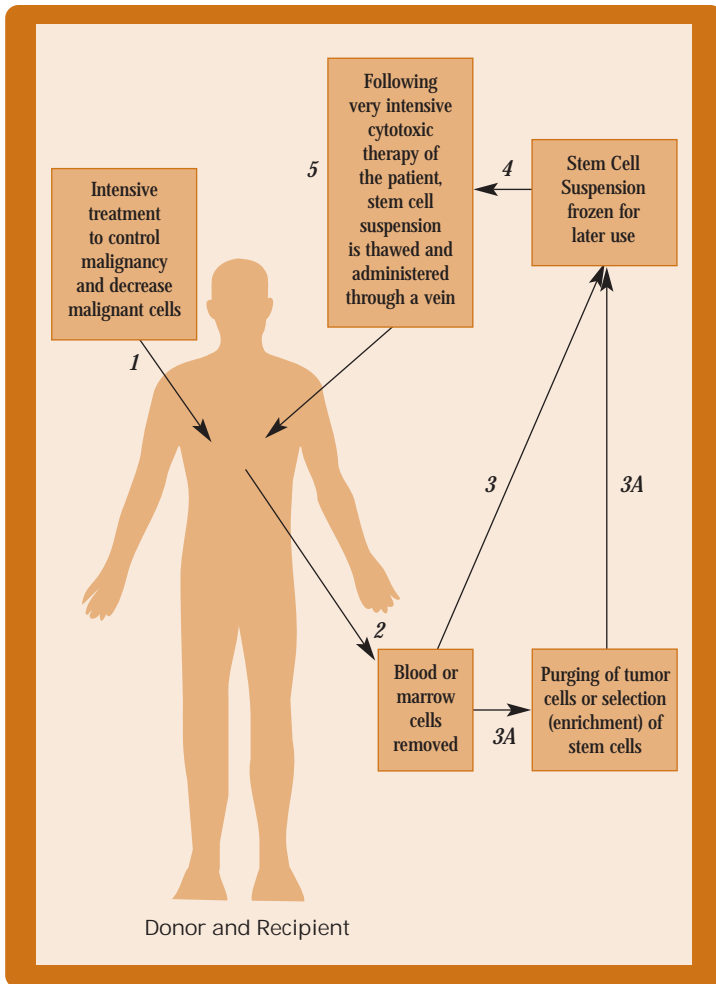
to a tissue type that is the same as the patient's. Transplantation from matched unrelated donors is sometimes referred to by the acronym "MUD."

Allogeneic transplantation, whether from a related or unrelated donor, differs from either syngeneic or autologous transplantation in that the potential exists for immune rejection of the donated stem cells by the recipient (host versus graft effect) and the immune reaction by the donor's cells against the tissues of the recipient (graft versus host disease). The immune rejection is usually prevented by intensive treatment of the recipient before the transplant (conditioning) to suppress the immune system. The immune reaction is combatted by giving drugs to the recipient after the transplant to reduce the ability of the donated immune cells to attack and injure the patient's tissues (see Graft Versus Host Disease on page 29).

### Autologous Transplantation

Autologous stem cell transplantation is an important therapy. But, strictly speaking, it is not transplantation; rather it is a technique of obtaining stem cells from blood or marrow and returning them to the same individual. Therefore, immunologic transplantation barriers do not exist. Nonetheless, the procedure is usually conducted in a transplant facility, is supervised by transplant specialists, and is usually referred to as autologous blood or marrow stem cell transplantation. To be feasible, the procedure requires that an individual has sufficient numbers of healthy stem cells in marrow or blood despite the disease for which he or she is being treated. For example, in patients with acute leukemia, remission is usually achieved before the patient's marrow or blood is harvested and frozen for later use (see Figure 6).

The patient's marrow may contain small but significant numbers of residual malignant cells that are not apparent when a marrow sample is microscopically examined. "*Purging*" may selectively rid the marrow of



**Figure 6. Autologous Transplantation for a Hematologic Malignancy.** For autologous transplantation, stem cells are obtained from the patient with leukemia, lymphoma, or myeloma. The patient is intensively treated (Step 1) to control the malignancy and to markedly decrease the malignant cells in marrow and blood. If the marrow is the source of stem cells, the patient is taken to the operating room, anesthetized, and the marrow is removed under sterile conditions. If blood is used as the source of stem cells, the patient is treated with *granulocyte-colony stimulating factor* (G-CSF, Filgrastim, Neupogen) alone or after chemotherapy, which draws stem cells out of the marrow and into the blood (see Sources of Stem Cells on page 15) (Step 2). The cells are treated with a cryoprotective agent so that they can be frozen and later thawed without injury (Step 3). In some cases, the marrow may be purged of tumor cells or, alternatively, stem cell selection employed, which also serves to deplete contaminating tumor cells (Step 3A). At a later time, when the patient is treated intensively again, the frozen stem cell suspension is thawed (Step 4) and infused into the patient so that blood cell production can be restored (Step 5).

these unwanted cells. Autologous blood or marrow transplantation does not carry the risk of either graft rejection or graft versus host disease and thus does not require conditioning treatment or immunosuppressive treatment. However, the patient does receive very intensive cytotoxic therapy to kill residual leukemia, lymphoma, or myeloma cells. The autologous stem cells are used to restore blood cell production, thereby making the treatment tolerable.

The principal concerns in autologous transplantation are: 1) that the amount of stem cells harvested is adequate to engraft when returned to the patient and 2) that tumor cells in the cell suspension used for transplant are removed or made incapable of re-establishing the tumor. The use of autologous stem cells to restore blood cell production after intensive radiation and/or chemotherapy has been expanded to the treatment of pediatric and adult patients with a variety of cancers other than leukemia, lymphoma, or myeloma.

## Purging Autologous Marrow

When autologous marrow or blood stem cells are the source of the transplant, the possibility that the patient's tumor cells (e.g., leukemia, lymphoma or myeloma cells) are reintroduced after intensive therapy is a concern. For example, if a patient with acute myelogenous leukemia in remission is to be heavily treated and transplanted with stem cells harvested from his or her own marrow (during that remission), the risk exists of reintroducing residual, inapparent leukemia cells. To avoid this, the marrow may be treated after it is harvested to rid it of tumor cells before it is frozen. Several techniques are being studied to determine the best method for purging tumor cells, including using antibodies specifically targeted to the malignant cells but not injurious to the stem cells. The effect of purging in the long-term success of autologous transplantation is still unresolved, however.

# The Transplant Procedure

## Conditioning

Patients with a hematologic malignancy receiving an allogeneic transplant are treated initially with a conditioning regimen. This treatment has two functions: 1) to inactivate the patient's immune system and minimize the chance that the stem cell graft will be rejected and 2) to intensively treat the residual malignant cells so as to make a recurrence of the malignancy less likely.

Conditioning regimens are modified depending on the disease being treated. Although programs vary at different transplant centers, generally two regimens are used for treatment. Either several drugs are given together, such as cyclophosphamide (Cytosan), busulfan (Myleran), cytarabine (Cytosar), melphalan (Alkeran), or etoposide (VePesid, VP-16), or chemotherapy is given along with total body irradiation. Radiation is administered in several smaller daily doses. This technique is referred to as *fractionation of the dose*. Fractionation minimizes side effects such as lung injury, nausea, and vomiting (see Table 2).

The drugs and radiation are given during the week before transplant. The precise duration and sequence of administration depends on the specific conditioning regimen. The days prior to the transplant are labeled minus 6, minus 5, etc., with the transplant (stem cell infusion) on day zero. The period after the transplant starts with day 1, day 2, and so forth, thereafter.

## Nonmyeloablative Transplantation

This procedure is a technique that uses low rather than very high doses of either radiation or chemotherapy to condition the recipient of an allogeneic stem cell transplant. It may be advantageous for older patients, those with slowly progressive diseases, and those with non-malignant inherited

Table 2. Side Effects of Conditioning Treatment

<b>Nausea and vomiting</b>	<b>Occlusions of veins in liver</b>
<b>Diarrhea</b>	<b>Congestive heart failure</b>
<b>Ulcers in mouth</b>	<b>Premature menopause*</b>
<b>Bleeding into urine from bladder</b>	<b>Sterility*</b>
<b>Hair loss</b>	<b>Growth retardation*</b>
<b>Loss of blood cell formation</b>	<b>Cataracts*</b>
<b>Pneumonitis (pneumonia)</b>	

*\* These effects are more likely to occur if total body irradiation is required for conditioning*

(e.g., sickle cell disease) or acquired diseases (severe immune diseases). Potent immune therapy can suppress the recipient's T lymphocytes so as to avoid rejection of the donor stem cells in order to insure that over time the latter will take up residence and dominate in the recipient's marrow. The immune cells made from the donor's stem cells attack and suppress the residual leukemia or lymphoma cells in the recipient. Thus, this technique relies on an immune suppression of the patient's hematopoietic malignancy over a more protracted period of time for success.

### Infusion of Stem Cells

The cell suspension, derived from marrow or blood and containing the stem cells of the donor, is collected in a plastic blood transfusion bag. Similar to a blood transfusion, the cell suspension is infused through the patient's vein. Special filters are used to remove bone fragments, fatty particles, and large clusters of cells from the cell suspension before it enters the bloodstream if marrow is infused. Infusion of the cell suspension usually requires several hours; patients are checked frequently for signs of fever, chills, hives, a fall in blood pressure, or shortness of breath. Patients often

experience no side effects from the infusion. Occasionally side effects occur, but these can be treated and the infusion completed (see Figure 7). In patients receiving frozen-thawed stem cell suspensions, reactions may occur from the cryopreservative.

### The Immediate Post-Transplant Period

By the second or third day after the transplant, the effects of the intensive conditioning regimen and the decrease in marrow function begin to have their effects. The patient is kept in a protected environment to minimize contact with infectious agents (see Infections, page 28).

Two to five weeks after the transplant, the *engraftment* of donated cells becomes apparent by the appearance of normal white cells in the blood of the patient. Red cells and platelets are transfused periodically until marrow function is restored by the transplanted stem cells. The patient is monitored carefully by physical examinations, blood chemistries, imaging studies, and other tests to be sure major organs such as the heart, lung, kidneys, and liver are functioning normally. Periods of intravenous feeding, called hyperalimentation, may be needed in some patients to insure adequate nutritional intake in spite of poor appetite and diarrhea.

### Special Problems

Most patients undergoing allogeneic transplantation for leukemia, lymphoma, or myeloma require blood cell replacement, nutritional support, and special drugs to treat graft versus host disease. The drug dosages are carefully adjusted, depending on the severity of the graft versus host reaction and whether the donor is related or unrelated. The conditioning treatment prior to transplant can impair any system that is dependent on replacement by stem cells. In particular, the gastrointestinal tract, the skin, and hair follicles are very sensitive to cytotoxic drugs and radiation therapy. Ulcers and dysfunction of the gastrointestinal tract are frequent. Mouth

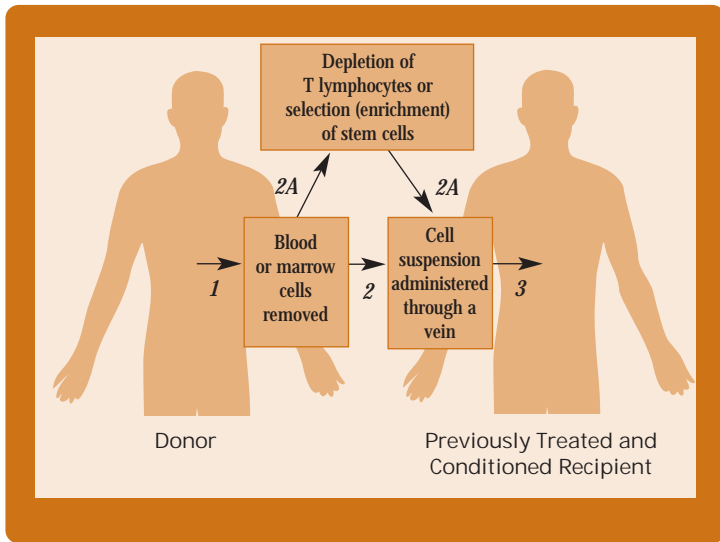


Figure 7. **Allogeneic Transplantation for Leukemia, Lymphoma, Myeloma.** A histocompatible donor is identified, usually among the patient's siblings (see Testing Donor Compatibility on page 12). Marrow stem cells are harvested in an operating room after the donor has received anesthesia. If blood is used as the source of stem cells, the donor is treated with granulocyte-colony stimulating factor (G-CSF, Filgrastim, Neupogen), which draws stem cells out of the marrow and into the blood. The stem cells are recovered by hemapheresis (see Sources of Stem Cells: Blood on page 15) (Step 1). The marrow cell suspension is filtered and placed in a plastic bag (Step 2). The cell suspension is administered through a vein to the recipient, who has been intensively treated with total body irradiation and/or intensive chemotherapy (Step 3). In some cases, the stem cell suspension may be depleted of most T lymphocytes. Alternatively, stem cell selection may be employed, which also results in a marked decrease in T lymphocytes (Step 2A). Thereafter, the marrow is administered to the recipient.

sores, nausea, diarrhea, intestinal cramps, and rectal or anal ulceration may be troublesome. Rashes may develop. Hair loss is inevitable.

The lungs are particularly sensitive to the conditioning regimen, especially total body irradiation superimposed on prior chemotherapy. A reaction called *interstitial pneumonitis* (pneumonia) can occur. This lung change is caused by a tissue reaction and does not mean that an infection is present. However, it can be very severe and prevent the efficient exchange of oxygen in the lungs.

Leaky blood vessels can result from the accumulated injury of chemotherapy and radiotherapy. Chemicals released from the immune reactions that occur after transplant also contribute to this effect by damaging vessel walls. Fluid escapes from the circulation and causes edema or waterlogging of tissues. In the lung, fluid accumulation can cause congestion and poor exchange of oxygen and shortness of breath.

The blood vessels that lead into and pass through the liver are prone to blockage after transplantation. This serious side effect is called veno-occlusive disease (or VOD) because the veins are plugged. This effect results from toxic changes in the liver from chemotherapy and radiotherapy. The changes cause injury to the liver, which is reflected in jaundice (yellowing of the skin and eyes), and accumulation of fluid in the abdomen and elsewhere. Sometimes toxins normally removed by the liver can accumulate, leading to mental confusion and sleepiness.

### Infections

Intensive treatment is usually required to suppress immune function and kill tumor cells prior to transplant. The resulting suppression of white cells that normally prevent or combat infections leads to a very high risk of infection. Infections by bacteria, fungi, viruses, or other parasites are very likely. These organisms are present most often on the skin and in the mouth or the lower bowel. They are also found in uncooked food (salads, fresh fruits, and vegetables) and in the air.

When blood cell and immune cell levels are normal and when the skin and lining of the mouth and bowel are intact, the body easily fends off such microbes. These normal defenses are lost in transplant patients. For this reason, antibiotics and other antimicrobial drugs are sometimes administered to patients in anticipation of the nearly inevitable development of infection. The drugs are usually continued until the white cells reappear in the blood in sufficient numbers to make infections unlikely.

The term opportunistic microbes is applied to infectious agents that rarely cause infection unless severe immunodeficiency is present. A few such organisms are varieties of *Candida*, *Aspergillus*, *Pneumocystis*, or *Toxoplasma*.

Many precautions are taken to minimize the risk of infection. Measures to combat infection include the use of a single room with filtered air, limiting contact with visitors, use of masks, and meticulous hand washing by staff and visitors who enter the patient's room. *Indwelling catheter* sites must be kept clean. Uncooked fruits and vegetables, which carry surface bacteria or fungi, are prohibited. Unfortunately, several of these measures isolate the patient for the month or more that it takes for the donor stem cells to begin forming enough blood and immune cells to replenish the body's immune system.

### Graft Versus Host Disease

Graft versus host disease may be seen soon after the transplanted cells begin to appear in the recipient. This reaction occurs in many patients. It varies from barely perceptible to life-threatening and is most severe in older patients. With each advancing decade of age, the reaction occurs more frequently and severely.

An individual's immune cells recognize cells that are not genetically identical. The graft versus host reaction results when the donor's immune cells, especially the T lymphocytes, sense that the host cells are different from themselves. In the case of stem cell transplantation, the donor cells carefully measure the cells of the recipient's tissue for signs that they are different and attack them if they find significant variations. The differences may involve cell surface proteins that are not measured by HLA typing, or there may be subtle differences in HLA type that permit transplantation but not without engendering the reaction. With the exception of identical twins, some incompatibility will exist even though HLA test-

ing indicates sufficient similarity to permit a transplant to be successful. This difference is particularly evident if the donor and recipient are of the opposite sex. The severity of graft versus host disease depends on the type and degree of differences between patient and donor (see Table 3).

Acute graft versus host disease starts in the first 90 days after transplantation. The first signs are usually a rash and burning and redness of the skin that occur on the patient's palms or soles. The rash, along with the burning and redness, may spread to the patient's trunk and eventually develop over the entire body. Blistering can occur, and the exposed surface of the skin may flake off. Nausea, vomiting, abdominal cramps, and loss of appetite are signs of graft versus host disease in the gastrointestinal tract. Diarrhea is frequent. Jaundice and pain in the abdomen indicate that graft versus host disease has injured the liver, which also may be swollen. Acute graft versus host disease may be mild, moderate, or severe. It may be life-threatening if the manifestations are difficult to control.

Chronic graft versus host disease usually occurs after the third month post-transplant and may not develop for a year or more after the transplant. As is the case with the acute reaction, older patients are more likely to develop chronic graft versus host disease. It is more likely to occur in patients who previously have had acute graft versus host disease.

Most patients experience skin problems. A rash and itching may occur first. The skin may become scaly. If the reaction is severe, patches of skin may be lost. Patients' skin color may deepen and the texture become very hard. The skin may heal by scarring, and the motion of nearby joints, such as the fingers, may be restricted. Hair loss may accompany the skin injury.

The inside of the mouth and the esophagus (a tube that extends from the mouth to the stomach) may become excessively dry and damaged. Ulcers can result. The tendency to drying may lead to loss of tear formation and

Table 3. Graft Versus Host Disease

**Skin changes**  
•  
**Gastrointestinal tract malfunction**  
•  
**Liver injury**  
•  
**Other organ system impairment**

dryness of the vagina and other surfaces. The lungs also may suffer from the drying and scarring effects of the attack by the donor immune cells. Liver injury may result in failure of liver function and the flow of bile, which may not be overt but can be detected by blood chemical measurements. In severe cases, the bile may back up into the blood and cause jaundice. The chronic graft versus host reaction can be mild with later improvement, or more severe, persistent, and incapacitating.

Several drugs are used to prevent or minimize graft versus host disease (see Table 4). These drugs include methotrexate, glucocorticoid hormones (steroids), cyclosporine, and tacrolimus. Another technique used to reduce the severity and incidence of graft versus host disease is called T lymphocyte depletion. Since T lymphocytes are the primary effector cells in graft versus host disease, the donor's marrow can be depleted of T cells in an effort to minimize the immune attack (see T Lymphocyte Depletion on page 19).

### Leaving the Hospital

Some transplant centers perform autologous transplantation on an outpatient basis. Some patients may have a portion of either an autologous or allogeneic transplant performed on an outpatient basis.

By three to five weeks post-transplant, most patients have recovered sufficiently to leave the hospital. A patient is discharged when the bone mar-

row is producing a sufficient number of healthy red blood cells, white blood cells, and platelets and there are no treatment complications. There is variability from patient to patient in their recovery of blood cell counts and the severity of other associated complications, especially graft versus host disease.

When blood cells return, a sense of well being begins to return. Mouth sores and diarrhea lessen or disappear. Appetite may improve. Before leaving the hospital, it is important that patients are able to eat and drink to get sufficient fluid and nourishment. The absence of fever, vomiting, and diarrhea are also important considerations. Before discharge, both the physician and patient should feel comfortable that there are no remaining needs that require very close surveillance or hospital-based resources.

## Aftercare

In general, recovery from autologous transplantation is more rapid. Some of the difficulties and restrictions described below are applicable principally to allogeneic transplantation.

After being discharged from the hospital, the patient continues recovery at home. Patients and families are instructed in the continuing care needed at home. They learn what signs, such as fever, pain, diarrhea, and others, should prompt rapid contact with the physicians responsible for care. Home visits by nurses or physicians and patient visits to the ambulatory care center permit appropriate follow-up and adjustment of activities and medications, in most cases. These visits may be frequent at first. After several months, if all is going as anticipated, the indwelling venous catheters can be removed and the frequency of patient visits can be decreased.

It takes six to 12 months (or somewhat longer) to recover nearly normal blood cell levels and immune cell function. During this time the patient

Table 4. Some Drugs Used to Treat Graft Versus Host Disease

<b>Anti-T cell antibodies</b>	<b>Cyclosporine</b>
<b>Antithymocyte globulin</b>	<b>Methotrexate</b>
<b>Azathioprine</b>	<b>Prednisone</b>
<b>Cyclophosphamide</b>	<b>Tacrolimus</b>

should avoid contact with crowds, such as at shopping centers, religious services, parties and concerts, to reduce the risk of infection. Patients also may be advised to avoid contact with children who have had recent immunization with live viruses. The immunity that the patient had from previous vaccinations may be decreased and reimmunization with vaccines made from inactivated organisms may be useful.

If the patient was treated with total body radiation during conditioning, the lenses of the eyes would have become irradiated and there is the possibility that cataracts may develop prematurely. Irradiation of the gonads leads to sterility in men and premature menopause in women. In the former case, hormone replacement is usually not necessary. In women so treated, estrogen and progesterone replacement therapy is invariably needed indefinitely. Children may have a slowed growth rate and may require growth hormone treatment and replacement of other hormones. In very young patients, puberty may be delayed and hormonal therapy required. Radiation may decrease thyroid function and require that thyroid hormone be administered orally. The severity of chronic graft versus host disease has a major impact on the long-term course. If this immune reaction is present, the patient is susceptible to troublesome infections.

## Social and Emotional Aspects

Transplantation for leukemia, lymphoma, or myeloma is a daunting personal challenge. How the challenge will be met depends on different individuals' ability to endure the risks and hardships involved. The patient is faced with the risk of disease recurrence or progression and death if transplantation is not chosen or a possibility of an earlier death, severe side effects, or recurrence of the disease if transplantation is chosen. These challenges are counterbalanced by the hope of recovery and cure and the likelihood that new and better methods may make success more probable and the side effects less disabling.

The decision to undertake transplantation often is made under intense pressure, usually because of a medical crisis. Also, there are the mixed emotions created by whether or not a donor will be found and what is in store should one be found. If the transplant center is not nearby, the patient and family are placed under additional strains and are detached from support systems in their home community. The loss of autonomy, the isolation, the separation from work, school, friends, colleagues, and outside interests have to be endured.

There is disruption of family relationships as well. Children may worry about the outcome of a parent's illness and the separation from father or mother. Parents suffer the uncertainty of the outcome of a child's treatment and the strain put on siblings and other family members and friends. The cost of the procedure and relocation of family, if necessary, is usually in the range of several hundred thousand dollars. Although much of this cost may be recovered from insurance, some will not.

The challenges of a long hospital stay, much of this in isolation, loss of well-being, and many potential, very uncomfortable, painful or disfiguring side effects add up to a very trying experience. Patients require grit and

the hope that better days are ahead. Even with great personal strength, the support of loved ones, nurses, physicians, and others is vitally important. Family can be the key to sustaining and supporting the patient through the ordeal. Several other techniques can be brought to bear on supporting the patient as he or she recovers strength and well-being and begins a return toward normal activities. For many patients, perhaps most, the experience is psychologically challenging and will result in changes in self-image and interpersonal relationships. For many, however, a successful outcome and a return to vitality and their school, job, or other roles and relationships is very satisfying to patient, family, and healthcare providers.

There are programs to help ease the emotional and economic strain created by leukemia, lymphoma or myeloma. 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 about The Leukemia & Lymphoma Society's programs and services for patients, call your local chapter or call the public information resource line at (800) 955-4572. You may also visit our Web site at [www.leukemia-lymphoma.org](http://www.leukemia-lymphoma.org)

## Allogeneic Human Stem Cell Transplantation

The transfer of stem cells from one person to another who is not an identical twin. In the setting of allogeneic transplantation, an evaluation aims to find a donor who is very similar in tissue type to the recipient. The closer the similarity the higher the probability that the transplant will be a success and that harmful immune reactions will be minimized. Siblings of the same sex are the most likely to be closely matched, but other family members and unrelated matched donors can be similar enough to achieve a successful transplant if the optimal match is not available and the severity of illness justifies the risk.

## Alloreactivity

The immune reaction between the immune cells of one individual and those of another individual. In stem cell transplantation, this immune reaction can occur in two directions because, unlike solid organ transplants, the donor “organ” contains many lymphocytes and later the donor stem cells will eventually make lymphocytes. The classic alloreactive direction is the host or recipient lymphocytes attacking the transplanted organ, so called “host versus graft disease” or more commonly called “graft rejection.” The other direction is graft versus host disease in which the donor lymphocytes admixed with the other cells infused attack the recipient’s tissues (see Graft Versus Host Disease).

## 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 (see *Immune Globulins, Gamma Globulins*). These antibodies can be used to identify specific cells and improve the classification of leukemia or lymphoma (see *Immunophenotyping*).

### Antigen

A foreign substance that enters the body and stimulates the production of complementary antibodies by B lymphocytes. A foreign substance may stimulate the response of T lymphocytes as well. When bacteria infect a tissue, the immune system recognizes them as foreign and causes the B lymphocytes to create antibodies against them. These antibodies attach to the antigen. This attachment of antibodies to their antigen facilitates the ingestion of bacteria by bacteria-eating neutrophils (*phagocytes*). Transplanted cells can act to stimulate an immune response of a different type in which T lymphocytes of the recipient attack the cells perceived as foreign from the donor (see Rejection or Host Versus Graft Disease) or T lymphocytes in the cell suspension from the donor can attack the tissue cells perceived as foreign in the recipient (see Graft Versus Host Disease).

### Autologous Blood or Marrow Stem Cell Transplantation (Infusion)

This technique involves the harvesting of a patient's blood or marrow stem cells, which are often frozen for later use. The patient then is 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 marrow. This procedure uses autologous blood stem cells with increasing frequency because marrow stem cells circulate in the blood and can be recovered there by hemapheresis (see Hemapheresis).

### B Lymphocytes

One of three specialized lymphocyte types. They produce antibodies in response to any foreign substances, but to bacteria, viruses, and fungi in particular. These lymphocytes are a vital part of the immune system and are important to our defense against infection. The B lymphocytes mature into plasma cells, which are the principal antibody producing cells.

### 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.

## Blast Cells

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 up to 80 percent of all marrow cells. In acute myelogenous leukemia, myeloblasts accumulate; in acute lymphocytic leukemia or some lymphomas, lymphoblasts accumulate. The distinction between leukemic myeloblasts and lymphoblasts sometimes can be made by microscopic examination of stained marrow cells. Often, immunophenotyping or 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 back bones, ribs, breast bone, pelvis, shoulders, and skull is most active in blood cell formation.

## Bone Marrow Transplantation (see Stem Cell Transplantation)

## Cellular Immunity

That portion of the immune system that protects the individual from infection by the action of T lymphocytes. Deficiency in this portion of the immune system produces an immunodeficiency that can permit infection by microbes such as the bacillus of tuberculosis, cytomegalovirus, and many others that might be fended off more easily in a healthy individual. T lymphocytes also cooperate with B lymphocytes to increase the effectiveness of antibody formation (see *Humoral Immunity*).

## 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. The cells of the marrow, the intestinal tract, the skin, and hair follicles are most sensitive to these drugs. Effects on these organs, mouth sores, diarrhea, rashes, and hair loss are common side effects of chemotherapy.

## 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 a 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, which 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)

## Conditioning Treatment

Intensive therapy with cytotoxic drugs or drugs and total body radiation before allogeneic stem cell transplantation. The therapy serves three purposes. First, it severely depresses the lymphocytes that are the key cells in the immune system. This action helps to prevent the rejection of the stem cell graft. Second, it markedly decreases the marrow cells. This may be important in order to open up the special niches that transplanted stem cells lodge themselves in order to engraft. Third, if the patient is being transplanted for a hematologic malignancy, this intensive therapy serves to greatly reduce any remaining tumor cells.

## Cryopreservation

A technique used to keep frozen cells intact and functional for many years. Blood or marrow cells, including stem cells, can be stored for very long periods and remain functional if they are suspended in a fluid that contains a chemical that prevents cellular injury during freezing or thawing. This chemical is referred to as a cryoprotective agent. Glycerol is one of the most commonly used agents. The freezing temperature is much lower (colder) than that of a household freezer.

## Cultures

If an infection is suspected, it is helpful to know both the principal site and the type of bacterium, fungus, or other microorganism involved so that the most specific antibiotic can be selected as treatment. To determine the site and organism, samples of body fluids such as sputum, blood, and urine and swabs of the inside of the nose, throat, and 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 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 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 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 of patients after chemotherapy. Cytokines that stimulate cell division 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.

## Engraftment

The process of transplanted stem cells homing to the recipient's marrow and producing blood cells of all types. This occurrence is first evident when new white cells, red cells, and platelets begin to appear in the recipient's blood following transplantation.

## Eosinophils

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

## Erythrocytes

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

## Fractionation of the Dose

In order to minimize the significant side effects of total body irradiation conditioning therapy, the dose of radiation required is given in several daily smaller doses rather than one larger dose. This approach has decreased the adverse effects of this treatment.

## 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 they are made by immune cells, specifically B lymphocytes and their derivatives, plasma cells. 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.

### Graft Versus Host Disease

The immune attack by lymphocytes in the donor's marrow or blood cell suspension (the graft) against the tissues of the recipient (the host). The immune cells most engaged in this reaction are donor T lymphocytes, which are present in the donor's blood or marrow, the source of stem cells. The principal sites of injury are the skin, the liver, and the gastrointestinal tract. The reaction does not occur in identical twin transplants. The reaction may be minimal in closely matched individuals or severe in less well matched individuals. These reactions are mediated in part by antigens that are not in the HLA system and cannot be matched prior to transplant. For example, in the case of a female stem cell donor and a male recipient, factors that are produced by genes on the Y chromosome may be seen as foreign by the female donor's cells, which do not share the genes on the Y chromosome. This fact does not prohibit female donors and male recipients, but it makes the risk of immune reaction higher.

### Graft Versus Leukemia Effect

The immune reaction of transplanted T lymphocytes not only has the potential to attack the recipient's normal tissues (graft versus host) but to recognize and attack the malignant cells of the recipient. This effect was noted when: 1) leukemia recurrence after transplant was seen to be more likely if the donor and recipient were identical twins than if they were nonidentical siblings; 2) the more prominent the graft versus host disease the less likely was leukemia recurrence; and 3) the removal of donor T lymphocytes decreased graft versus host disease but also resulted in a higher frequency of leukemia relapse. Each of these observations could be explained best by an immune attack by donor lymphocytes against

recipient leukemia cells that collaborated with the intensive conditioning treatment to keep the leukemia in check. This effect seems to be most active in myelogenous leukemia, although it may occur in patients with myeloma as well.

### 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.

**Granulocyte-colony Stimulating Factor** (see Cytokines)

**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, 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 siblings), 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).

### Haplotype

The tissue type contributed by either the mother or father to his or her offspring. It is implied that it represents the genes on one parental chromosome. When a transplant procedure is between a donor and recipient

that are haplotype identical, it means that the tissue type or HLA type of each is identical in respect to mother or father but not identical to the other. In some situations, if the discrepancy is not too great, the transplant may still be possible if the underlying disease makes the risk of partial compatibility warranted. Conditioning of the recipient and lymphocyte depletion of the donor stem cell suspension are steps taken to mitigate the risk of immune cell activation by the tissue type differences.

### Hemapheresis

The process of removing a component of a donor's blood and returning the unneeded components. The process uses continuous circulation of blood from a donor through an apparatus and then back to the donor. This process makes it possible to remove a desired element from large volumes of blood. Platelets, red cells, white cells, or plasma can be removed selectively. For example, this technique permits the harvesting 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, which can be frozen, stored, and later used for stem cell transplantation.

### 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 replaced 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.

### Host

The recipient of the transplant who is playing “host” to the transplanted stem cells.

### 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. Often, the lymphomas are complicated by common or unusual infections because of the susceptibility of HIV-infected individuals. “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 the marked deficiency of T lymphocytes caused by HIV infection.

## Humoral Immunity

The portion of the immune system that produces antibodies. This portion of the system is represented by the various types of B lymphocytes that make antibodies and are scattered throughout the lymph nodes, other lymphatic tissue, and the bone marrow. B lymphocytes mature into plasma cells that produce antibodies (see *Cellular Immunity*).

## Iliac Crest

The edge of the hip bone 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 cellular antigens to determine the specific types of cells in a sample of blood cells, marrow cells, or lymph node cells. A tag is attached to antibodies that react with specific antigens in the cells. 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.

## Immunosuppression

A state in which the immune system does not function properly and its protective functions are inadequate. The patient is more susceptible to infections including those from microbes that are usually not highly infectious (see *Opportunistic Infection*). This can occur as a result of intensive

chemotherapy and radiation therapy, especially as used for conditioning of a patient for transplantation. It also can occur because of disease states. Human immunodeficiency virus infection is one such disease. Graft versus host disease creates an immunosuppressive state in that immune protection against infection is inadequate. In the transplant patient the conditioning regimen and severe graft versus host disease can result in overwhelming infection.

### 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 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)

### Interstitial Pneumonitis

A severe inflammation in the lungs that can occur as a toxic effect of total body irradiation in the conditioning regimen. The small airways and intervening spaces between air sacs get congested, swollen, and exchange of oxygen can be compromised. Typically, no infection is present although a similar reaction can occur as a result of infection.

### Intrathecal

The space between the covering or lining of the central nervous system and the brain or spinal cord. The lining is called the meninges. In some situations drugs have to be administered directly into the spinal canal

when leukemia or lymphoma cells are in the meninges. This is called intrathecal therapy.

### 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 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.

### 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)

**Mini Transplants**

A term applied to new, investigational procedures that condition older, less tolerant patients with lower doses of drugs before infusing allogeneic stem cells. These transplants have been used in patients with chronic leukemias.

**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.

**Monocytes (macrophages)**

A type of white blood cell that assists in fighting infection. The monocyte, along with the neutrophil, are 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 (scavenging).

**Mucous Membranes**

The inner lining of cavities such as the mouth, nose, and sinuses. These linings require new cells to be made to replace those that drop off. This replacement is a normal process and keeps the lining intact and moist. Radiation therapy or chemotherapy drugs that block cells from dividing prevent the replacement of lost cells. The linings become dry, defective, and may ulcerate in patients who receive such treatment. This change can

be painful, such as when mouth or anal ulcers develop. The loss of what is referred to as the barrier function of mucous membranes permits microbes to enter the tissue or blood and often leads to infection.

### 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. They each are determined by genes that govern how the cell will respond to the chemical agents. 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 prevents 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 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 infection. 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” (for polynuclear) or “seg” (for segmented nucleus).

## 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. This person is usually an internist who treats adults or a pediatrician who treats 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.

## Opportunistic Infection

Infection by a microbe that is usually unable to cause disease in a healthy individual but can produce serious infections in persons with immune deficiency, like those undergoing allogeneic stem cell transplantation.

## Pancytopenia

A decrease below normal in the concentration 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 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 suppresses 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 a 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 hemapheresis. 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.

### 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 nonleukemia cells. PCR requires a specific DNA abnormality or marker, like an oncogene, in the leukemia or lymphoma cells for its use.

### Purging

The process by which tumor cells are removed from the marrow or blood cell suspension that is to be used for an autologous transplant. The stem cells used in an autologous transplant are obtained from the patient with leukemia, lymphoma or myeloma. An attempt is made to treat the patient and induce a remission before the stem cells are harvested, but some inapparent tumor cells are probably always present. Purging is used to try to further minimize returning tumor cells to the patient with the stem cells after intensive, and hopefully curative, cytotoxic treatment is given.

### Red Blood Cells

Blood cells that carry 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 or Recurrence

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

## Remission

The 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 resist 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 causing 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 more subtle and requires more sensitive tests to identify the oncogene.

## Spleen

An organ of the body that is in the left upper portion of the abdomen just under the left side of the diaphragm. 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 since most of its functions can be performed by other organs, such as the lymph nodes and liver.

### Stem Cells

These are primitive cells in marrow that are important in making red blood cells, white blood cells, and platelets (see Hematopoiesis). 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 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 developed, 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 an unrelated donor who has a tissue type that matches that of a patient. This approach requires screening tens of thousands of unrelated individuals of similar ethnicity to the patient.

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 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 hemapheresis. The stem cells also circulate in large numbers in fetal blood and can be recovered from placental and umbilical cord blood after childbirth. The harvesting, freezing, and storing of “cord blood” provide

another source of stem cells for transplantation. Since blood 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. Thus, there is no genetic or, therefore, immune disparity and no likelihood of a host versus graft (rejection) or a graft versus host reaction. 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 a large volume screening program 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 Lymphocyte Depletion

A process to decrease the number of immune cells that cause graft versus host disease. Usually antibodies against T lymphocytes are used to draw them out of the stem cell sample to be used for transplant. The decreased presence of T lymphocytes in the transplant minimizes the intensity of graft versus host disease. Since T lymphocytes help stem cells engraft and can suppress residual tumor cells in the recipient some T cells are useful in the transplanted cells.

## 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 (see Cycle 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 blood platelets.

## Tolerance

A very important event in the long-term success of transplantation. After a time, usually a year or so, the prior host and donor T lymphocytes die off and new lymphocytes are formed from the donor's engrafted stem cells. These "adapt" to the new host and stop attacking the recipient's cells. If tolerance is present, the immune system is no longer distracted and can serve the patient by working efficiently to protect against microbes. Risk of infection returns toward that of a healthy person. Immunosuppressive therapy can be stopped.

## 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.

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

# Further Readings

## Society Patient Booklets

*Blood Transfusion.* The Leukemia & Lymphoma Society, 2001.

Understanding Blood Cell Counts Fact Sheet. The Leukemia & Lymphoma Society, 2000.

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*I'm Having a Bone Marrow Transplant.* The Leukemia & Lymphoma Society, 1997. A coloring book for young patients.

## Nontechnical Resources

*Autologous Stem Cell Transplants: A Handbook for Patients.* SK Stewart, 2000. BMT Information Network, Highland Park, IL.

*Bone Marrow Transplants.* SK Stewart, 1992. BMT Information Network, Highland Park, IL. A book of basics for patients.

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*A Resource Guide For Bone Marrow/Stem Cell Transplant.* C Slotkin, 2001. National Bone Marrow Transplant Link, Southfield, MI.

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### Technical

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*Hematology. Basic Principles and Practice*. Edited by R Hoffman, EJ Benz, SJ Shattil, B Furie, HJ Cohen, LE Silverstein, P McGlave. Churchill Livingstone, 3rd Edition, 2000. Chapters 84-97.





# 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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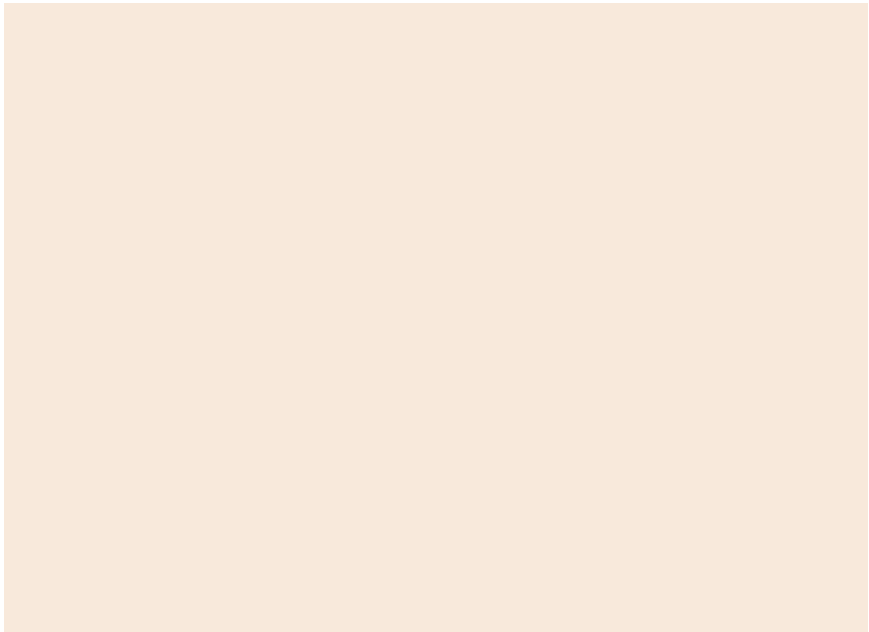
*Home Office The Leukemia & Lymphoma Society  
1311 Mamaroneck Avenue – Suite 310  
White Plains, NY 10605*

*Free Literature: (800) 955-4572  
[www.leukemia-lymphoma.org](http://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



*Fighting Leukemia, Lymphoma,  
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