

Introduction

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

About 10,000 new cases of acute myelogenous leukemia are diagnosed each year in the United States. Acute myelogenous leukemia may be called by several names, including: acute myelocytic leukemia, acute myeloblastic leukemia, acute granulocytic leukemia or acute nonlymphocytic leukemia. Before describing the disease and its management further, a brief description of normal blood and marrow is provided for background.

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

Normal Blood and Marrow

Blood is composed of plasma and cells suspended in plasma. The plasma is largely made up of water in which 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 vaccinations (e.g., polio virus antibodies). The cells include: *red cells, platelets, neutrophils, monocytes, eosinophils, basophils, and lymphocytes*.

The red cells make up half the volume of the blood. They are filled with hemoglobin, the protein that picks up oxygen in the lungs and delivers oxygen to the tissues. The platelets are small cells (one-tenth the size of red cells) that help stop bleeding if one is injured. For example, when one has a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of the vessel, clump together and plug up the bleeding. Later a firm clot forms. The vessel wall then heals at the site of the clot and returns to its normal state.

The neutrophils and monocytes are *white blood cells*. They are *phagocytes* (or eating cells) because they can ingest bacteria or fungi and kill them. Unlike the red cells and platelets, the white cells leave the blood and move into the tissues where they can ingest invading bacteria or fungi and help cure an infection. Eosinophils and basophils are two additional types of white cells that participate in allergic responses.

Most *lymphocytes*, another type of white blood cell, are in the *lymph nodes*, the *spleen*, and lymphatic channels, but some enter the blood. There are three major types of lymphocytes: T cells, B cells and natural killer (NK) cells.

The *marrow* is a 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 in adults. Blood passes through the marrow and picks up formed blood cells for circulation.

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 transform into the specific blood cells by a process of *differentiation* (see Figure 1). When the fully developed and functional cells are formed, they leave the marrow and enter the blood. In healthy individuals there are sufficient stem cells to keep producing new blood cells continuously.

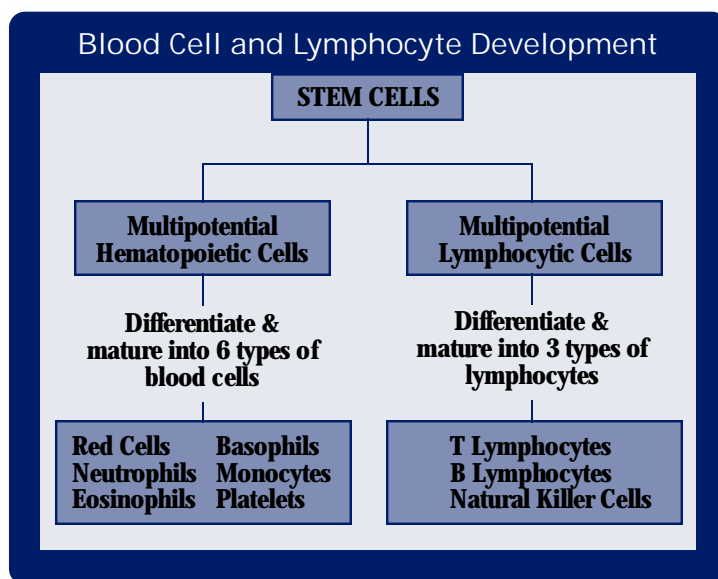


Figure 1. This figure depicts an abbreviated diagram of the process of hematopoiesis. This process involves the development of functional blood and lymphatic cells from stem cells.

Some stem cells enter the blood and circulate. They are present in such small numbers, they cannot be counted or identified in the usual type of blood counts. Their presence in the blood is important because they can be collected by special techniques and transplanted into a recipient if the donor is compatible and enough stem cells are harvested. This stem cell circulation from marrow to blood and back occurs in the fetus as well. This 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 an infection, such as pneumonia, and perform their other functions.

Acute Myelogenous Leukemia

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

The major forms of leukemia are divided into four categories: myelogenous and lymphocytic, each having an acute or chronic form. The terms myelogenous or lymphocytic denote the cell type involved. Acute leukemia is a rapidly progressing disease that affects mostly cells that are unformed or primitive (not yet fully developed or differentiated). These immature cells

cannot carry out their normal functions. Chronic leukemia progresses slowly and permits the growth of greater numbers of more developed cells. In general, these more mature cells can carry out some of their normal functions. Thus, the four major types of leukemia are: acute or chronic myelogenous and acute or chronic lymphocytic leukemia.

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

Acute myelogenous leukemia (AML) results from acquired (not inherited) genetic damage to the DNA of developing cells in the *bone marrow*. The effects are: 1) the uncontrolled, exaggerated growth and accumulation of cells called “leukemic blasts” which fail to function as normal blood cells and 2.) the blockade of the production of normal marrow cells, leading to a deficiency of red cells (*anemia*), and platelets (*thrombocytopenia*) and normal white cells (especially neutrophils, i.e. *neutropenia*) in the blood.

Causes and Risk Factors

In most cases the cause of acute myelogenous leukemia is not evident. Several factors have been associated with an increased risk of disease. These include exposure to high doses of irradiation, as carefully studied in the Japanese survivors of atomic bomb detonations, exposure to the chemical benzene, usually in the work place, and exposure to *chemotherapy* used to treat cancers such as breast cancer, cancer of the ovary, or the lymphomas. Acute myelogenous leukemia is not contagious and is not inherited. Uncommon genetic disorders such as Fanconi anemia, Down syndrome and others are associated with an increased risk of AML. Older people are more likely to develop the disease. The risk increases about ten-fold

from age 30 (about 1 case per 100,000 people) to age 70 (about 1 case per 10,000 people) (see Figure 2).

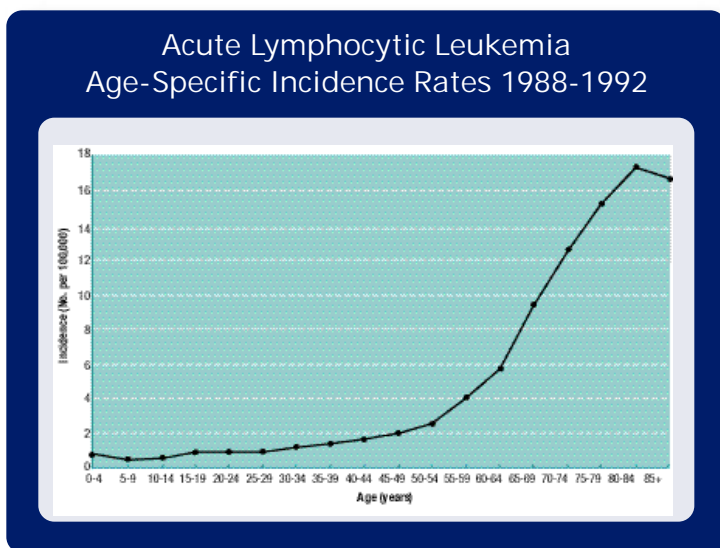


Figure 2. The horizontal axis shows 5 year age intervals. The vertical axis shows the frequency of new cases of AML per 100,000 in a given age group. (Data: National Cancer Institute SEER Program)

Subtypes of Acute Myelogenous Leukemia

Leukemia is a malignant disease (cancer) of the bone marrow and blood. Acute myelogenous leukemia can occur in a variety of ways: different types of cells may be seen by the physician in blood or marrow. Since most patients have one of eight different patterns of blood cell involvement, these patterns have formed a subclassification which is shown in the table (see Table 1).

Myeloblasts are undeveloped cells. If they are the dominant leukemia cells in the marrow at the time of diagnosis the leukemia is referred to as “myeloblastic” type. If there are many myeloblasts but there are some cells developing towards fully formed blood cells, the added designation “with maturation” is used. If there are cells that are developing features

Table 1. Acute Myelogenous Leukemia

Designation	Cell Subtype
M0	} Myeloblastic, without maturation
M1	
M2	Myeloblastic, with maturation
M3	Promyelocytic
M4	Myelomonocytic
M5	Monocytic
M6	Erythroleukemia
M7	Megakaryocytic

of monocytes (“monocytic” type) or red cells (“erythroleukemia” type), these designations are used and so forth.

Even though the leukemia cells look somewhat like blood cells, the process of their formation is incomplete. Normal, healthy blood cells are insufficient in quantity (see Figure 3).

The subclassification of the disease is important. Different types of therapy may be used and the course of the disease may be different. Additional features may be important in guiding the choice of therapy including: abnormalities of *chromosomes*, the cell *immunophenotype*, the age and the general health of the patient, and others.

Symptoms and Signs

Most patients feel a loss of well-being. They tire more easily, may feel short of breath when physically active. They may have a pale complexion from anemia. Several signs of bleeding caused by a very low *platelet* count may

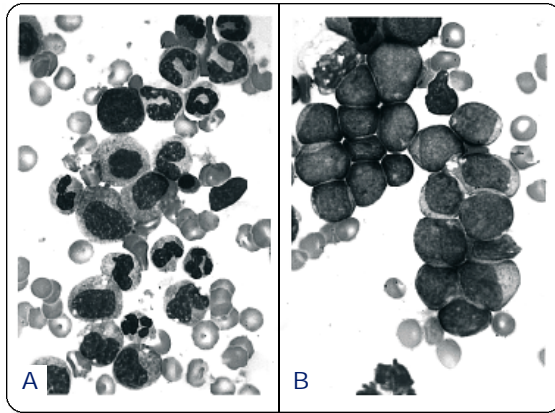


Figure 3. Panel A shows a photograph taken through a microscope of normal marrow cells. The differences in appearance among the cells reflect their different developmental stages. Panel B shows a photograph taken through a microscope of acute myelogenous leukemia blast cells. The monotonous appearance of these cells, which are “frozen” in an earlier stage of development, is in contrast to the normal cells in panel A.

be noticed. They include black and blue marks or bruises occurring for no reason or because of a minor injury, the appearance of pin-head sized spots under the skin, called *petechiae*, or prolonged bleeding from minor cuts. Mild fever, swollen gums, frequent minor infections like pustules or perianal sores, slow healing of cuts, or discomfort in bones or joints may occur.

Diagnosis

To diagnose the disease the blood and marrow cells must be examined. In addition to low red cell and platelet counts, examination of the stained (dyed) blood cells with a light microscope will usually show the presence of leukemic blast cells. This is confirmed by examination of the marrow which invariably shows leukemic *blast cells*. The blood and/or marrow cells are also used for studies of the number and shape of chromosomes (*cytogenetic* examination), *immunophenotyping*, and other special studies, if required.

Treatment

Nearly all patients with acute myelogenous leukemia require treatment as soon after diagnosis as possible. The principal goal of treatment is to bring about a *remission* in which there is no evidence of leukemic blast cells in the blood or marrow. Normal blood cell production is restored and blood cell counts return to normal levels.

In most patients intensive chemotherapy is required to achieve complete remission. At least two drugs are combined to treat patients initially. Approaches to treatment are undergoing intensive study throughout the world and there are variations on the general descriptions given here. Thus, a patient may receive either a different number of drugs, sequence of drugs, or types of drugs than described here and be receiving appropriate and effective treatment. It is, however, important to seek treatment in a center where physicians are experienced in the care of patients with acute leukemia.

In order to prepare the patient for treatment, an *indwelling catheter* is placed in a vein in the upper chest to allow ready access for infusion of drugs, blood cells and the removal of blood samples for cell counts and chemical tests. In some patients, if the white cell count is very high, a drug called allopurinol is given to minimize the build up of blood uric acid. Uric acid is a breakdown product of cells. It enters the blood and is excreted in the urine. If many cells are killed simultaneously by therapy, the amount of uric acid in the urine can be so high that uric acid kidney stones can form which may seriously interfere with the flow of urine.

Chemotherapy

Induction Therapy

This is the initial phase of specific treatment. In most cases an anthracycline antibiotic (e.g. daunorubicin, doxorubicin, or idarubicin) is combined with cytarabine (syn. cytosine arabinoside, Ara-C) (see Table 2). Both drugs act in different ways to prevent DNA synthesis of leukemia cells, stopping

their growth and leading to their death. The anthracycline antibiotic is given, usually, in the first three days of treatment. Cytarabine is started at the same time but is given for seven to 10 days of treatment. Both drugs are dissolved in fluids and injected into a vein.

The goal of induction therapy is to rid the blood and marrow of visible leukemic blast cells. If blast cells are still evident, a second course of chemotherapy may be required to rid the marrow of blasts. Usually the same drugs are used for each course.

When chemotherapy is effective, developing blood cells as well as leukemia cells are eliminated from the marrow, resulting in a severe deficiency of red cells (anemia), *phagocytes* (neutropenia and monocytopenia) and platelets (thrombocytopenia) in the blood. Transfusion of red cells and, often, platelets may be required. The deficiency of phagocytes (microbe-eating cells) permits bacteria and fungi, normally present on skin, in the nose, mouth or large bowel (colon), or transferred from other persons or the environment, to establish infection during this period. Because of this, antibiotic therapy is frequently required.

In most patients, after several weeks normal blood cell production will return and transfusion of cells and antibiotics will no longer be needed. Blood cell counts gradually approach normal, well-being returns and leukemia cells cannot be identified in blood or marrow. This is a remission. In this state, residual leukemic cells are inactive. They do not interfere with normal blood cell development but have the potential to regrow and cause a *relapse* of the leukemia. For this reason, additional therapy in the form of chemotherapy with or without *autologous stem cell infusion* or *allogeneic stem cell transplantation* is usually advised.

One exception to this pattern is the treatment of the acute promyelocytic subtype of AML. In this subtype, the cells that accumulate in the marrow can be identified as promyelocytes, the next step in blood cell formation after the myeloblast. As a part of the expression of this form of AML the

leukemia cells are stalled at this stage of development. A derivative of vitamin A, retinoic acid, is administered before chemotherapy. Retinoic acid is capable of inducing the leukemic promyelocytes to develop into mature cells (neutrophils). It markedly decreases the concentration of leukemic blast cells in the marrow and a remission frequently ensues. For the remission to be long-lasting, chemotherapy must follow. But retinoic acid often minimizes the side effects of chemotherapy because blood cell counts may be improved and the number of primitive leukemia cells is decreased when chemotherapy is started.

Arsenic trioxide, like retinoic acid, can induce remission of acute promyelocytic leukemia. Studies are in progress to learn how best to use these drugs in combination with chemotherapy.

Post-Remission Therapy

Since residual leukemic cells that cannot be detected by the blood or marrow examination remain after a remission, the optimal treatment of AML usually requires additional intensive therapy after remission has been achieved. There is no consensus as to the best approach, in part, because individual factors such as age of the patient, the ability to tolerate intensive treatment, cytogenetic findings, the availability of a stem cell donor and others may influence the approach used. If chemotherapy is to be used, the best results occur if intensive treatment is applied. One current approach is to use very high doses of cytarabine given intravenously soon after remission occurs.

Therapy can be further intensified in patients who do not have a histocompatible donor by giving very intensive chemotherapy and reinfusing the patient's own marrow to restore blood cell production, which otherwise would be profoundly impaired by this amount of chemotherapy. The marrow is harvested from the patient shortly after remission is induced and frozen (cryopreserved) until it is thawed for use. Special techniques are required to keep marrow cells from being damaged during the freezing and thawing process.

Table 2. Some Drugs Used in the Treatment of Acute Myelogenous Leukemia

Most anti-leukemic drugs interact with the genetic material in the cell, the DNA or deoxyribonucleic acid.

Antitumor Antibiotics

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

- daunorubicin (daunomycin, rubidomycin, Cerabidine)
- doxorubicin (Adriamycin, Rubrex)
- mitoxantrone (Novantrone)
- idarubicin (Idamycin)

Antimetabolites

These are chemicals that are very similar to natural building blocks of DNA or RNA, but they are changed sufficiently from the natural chemical. When they substitute for it, they block the cell's ability to form RNA or DNA, preventing the cell from growing.

- 5-azacytidine (Mylosar)
- cytarabine (cytosine arabinoside, Ara-C, Cytosar)
- 2-chlorodeoxyadenosine (Cladribine)
- fludarabine (Fludara)
- hydroxyurea (Hydrea)
- 6-mercaptopurine (Purithenol)
- methotrexate (Mexate)
- 6-thioguanine (Thioguanine)

DNA Repair Enzyme Inhibitors

These drugs act on certain proteins (enzymes) which help to repair injury to DNA. These drugs prevent the enzymes from working and make the DNA more susceptible to injury.

- etoposide (VP-16, VePesid)
- teniposide (VM-26, Vumon)
- topotecan (Hycamtamine)

DNA Synthesis Inhibitors

The drug reacts with DNA to alter it chemically and keep it from permitting cell growth.

- carboplatin (Paraplatin)

Cell Maturing Agents

- *all-trans* retinoic acid
- arsenic trioxide

Patients between the age of approximately 1 and 50 years who are in remission and have a histocompatible donor are candidates for allogeneic *stem cell transplantation*. The decision to do a transplant depends on the features of the leukemia, the age of the patient and the patient's understanding of the potential benefits and risks. For example, a younger patient with cytogenetic findings that are associated with a higher probability of relapse would be a candidate for allogeneic stem cell transplantation.

Older Patients

Acute myelogenous leukemia occurs more frequently with advancing age. At least half the patients are over 65 years of age when the disease occurs. At this time other medical problems including heart disease, lung disease, diabetes mellitus or others may be present. The intensity of treatment requires consideration of these factors and the drugs, doses and frequency of treatment are often individualized to consider the features of the leukemia, the health of the patient and the patient's anticipated tolerance of therapy.

Special Treatments

In some types of leukemia, particularly acute lymphocytic leukemia, the leukemic blast cells may invade the lining of the spinal cord or brain. With the exception of one subtype, monocytic leukemia, this does not usually occur with AML. When the lining of the spinal cord or brain is involved, treatment requires that chemotherapy be given into the spinal canal. A spinal tap (lumbar puncture) is a commonly used medical procedure, performed under local anesthesia, in which a needle is placed into the spinal canal. The spinal fluid is removed and examined for leukemia cells and the fluid is replaced with fluid containing appropriate drugs, usually cytarabine or methotrexate.

Occasionally, radiation therapy may be used to treat a localized accumulation of leukemia cells in a troublesome site. This type of problem is infrequent.

Side Effects of Treatment and Their Management

Acute myelogenous leukemia decreases the production of normal blood cells, but the levels are further decreased by the added effects of chemotherapy. The intensity of chemotherapy required to destroy sufficient leukemia cells to permit a remission leads to even more severe decreases in red cells, phagocytes, and platelets. Severe anemia, the risk of bleeding from a low platelet count, and a high likelihood of infection result. Red cell and *platelet transfusions* are usually effective in providing sufficient amounts of those cells until the beneficial effects of treatment occur several weeks later and blood cell counts return toward normal. Practical methods for transfusion of phagocytes are not currently available and antibiotic therapy is used when the earliest signs of infection develop.

A rise in temperature or chills may be the only signs of infection in a patient with a very low blood white cell concentration. In this setting, persistent coughing, tenderness at a site prone to infection like the area surrounding the anus or facial sinuses, sore throat, pain on urination or frequent loose stools, also may be signs of an infection. Efforts to decrease the risk of infection by vigorous hand washing by all visitors and medical personnel and meticulous care of indwelling catheter sites are important. Care of the gums, a site of bacterial accumulation, also is an important area of infection prevention.

The use of blood cell *growth factors* which stimulate the production of phagocytes can shorten the period during which the white cell count is low. Those used most frequently are *granulocyte-colony stimulating factor* (G-CSF) and *granulocyte-macrophage colony stimulating factor* (GM-CSF).

Chemotherapy affects tissues that require a high rate of cell birth (cell division) to keep them functional. The lining of the mouth, the lining of the intestines, the skin and the hair follicles are such tissues. This explains why mouth ulcers, diarrhea and hair loss are common after chemotherapy. Skin rashes also may occur.

Nausea and vomiting can be distressing features of chemotherapy. The causes can be complex. The effects are the result of actions on the intestines and on centers of the brain which, when triggered, lead to vomiting. Fortunately, drugs which counteract the nausea and vomiting can relieve these distressing side effects, if they occur.

Refractory Leukemia and Relapsed Leukemia

Some patients, even after intensive treatment, have residual leukemic cells in their marrow. This circumstance is referred to as “refractory leukemia.” Some patients, who have had a remission of leukemia after therapy, have a return of leukemia cells in the marrow and a decrease in normal blood cells. This situation is referred to as “relapse.” In the case of refractory leukemia, different approaches, such as drugs not used in the first course of treatment or stem cell transplantation, may be used in an effort to induce remission. In patients who relapse, the duration of the remission, their age and the cytogenetic findings in the leukemia cells influence the approach to therapy. Drugs similar to those initially used, different drugs or stem cell transplantation may be used to treat the leukemia.

Several areas are under intensive study in an effort to develop approaches to increase the proportion of patients who have a remission and to increase the duration of remission and the frequency of cures.

Social and Emotional Aspects

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

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

Children may feel frightened and helpless and may be too young to fully understand the nature of the problem. They have to reconcile lost schooling, separation from friends, inability to participate in everyday activities, such as sports, at least for a time. Children may direct their anger and fear of being hurt toward medical staff. Reengagement in as many activities as possible is one of the best ways to soothe and reassure the child and minimize disruptions in the child's development.

Parents of children with acute leukemia may be confused, angry and fearful. Time commitments and financial burdens of the illness may cause disagreements within the family. Siblings of the patient may also be affected. They may fear the disease will strike them. They may feel guilty that something they did or said caused their brother's or sister's illness. They may feel guilty that they are healthy and the sibling is ill. They may receive less time from parents who must devote extra time to their ill child.

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

and emotional aspects of the disease, you may request a copy of the following Society publication: *Coping With Survival*, a booklet dealing with the psychosocial aspects of the disease for leukemia patients.

There are programs to help ease the emotional and economic strain created by leukemia. To order publications or obtain information, call your local Society chapter or call the public information resource line at (800) 955-4572. You may visit our website at www.leukemia-lymphoma.org to view publications and obtain more information about The Leukemia & Lymphoma Society programs and services.

Follow-Up

Patients who are in remission continue to be examined regularly by their physicians. After the induction of remission and the completion of post-remission therapy, careful periodic assessment of the patient's state of health, blood cell counts and, if necessary, marrow is required. As time progresses, the interval between assessments may be lengthened but should continue indefinitely.

The Future

The proportion of patients with AML who enter remission, stay in remission for years or are cured has increased significantly over the past 25 years. Several areas of research have contributed to this progress.

Drug Resistance

The leukemia cells of some patients are not as easily killed by drugs as those of other patients. This may lead to a failure of current treatment. Research has uncovered mechanisms in the leukemia cell that protect it from the effects of chemotherapy. As these mechanisms are defined, ways of reversing drug resistance are also being developed. New drugs that facilitate the effects of chemotherapy are being tested.

Oncogenes

Understanding the precise damage (*mutations*) in DNA that causes a normal cell to be transformed into a leukemia cell should permit new therapies to be developed. These therapies may block the effects of cancer-causing genes (*oncogenes*) and the cancer-causing proteins that the genes direct to be made.

Transplantation

The use of stem cells from blood and from cord blood may make transplantation easier. These stem cells can be frozen and stored in a manner similar to a blood bank, making them available to potential recipients who do not have related (sibling) donors with similar tissue types.

New Drug Treatments

Extensive testing is being conducted to synthesize new drugs or find them from natural (botanical) sources. These drugs are first tested for their usefulness in the laboratory. Then, through the method of clinical trials, they are used with patients. Researchers are also investigating new combinations of existing drugs for their usefulness in the treatment of leukemia, lymphoma, Hodgkin's disease and myeloma.

Immunotherapy

Research is being conducted on several approaches that may enhance the body's natural defenses. The goal is to kill or prevent the growth of leukemia cells. Radioimmunotherapy is an example of immunotherapy. This approach combines antibodies with attached isotopes that emit irradiation. These antibodies can be made in the laboratory. They can be made so they attach leukemia cells, specifically. They are injected into the patient to destroy leukemia cells. Another approach uses normal lymphocytes which can attack leukemia cells because the lymphocytes have been immunized to recognize the leukemia cells as foreign or abnormal.

Cytokines

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

Leukemia-Type Specific Therapy

Increasingly, clinical studies are identifying leukemia by more specific criteria than the appearance of the leukemia cells. These additional factors include the type of chromosome abnormality, the presence of *multidrug resistance* characteristics, the immunophenotype and others. New and different drug regimens are being tested in situations that are likely to be unresponsive to the usual chemotherapy.

Minimal Residual Disease.

Sensitive molecular techniques permit the identification of small amounts of residual leukemia cells at times when blood and marrow appear normal. This approach can be used if the leukemia cell has a detectable molecular abnormality. Additionally, it can permit more sensitive follow-up of patients in remission and can help determine whether small numbers of leukemia cells remain and if additional treatment is necessary.

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

Anemia

A decrease in the number of red blood 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 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. Antibodies can be used to identify specific cells and improve the classification of leukemia or lymphoma (see Immunophenotyping).

Apheresis

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

Autologous Stem Cell Infusion

This technique, often referred to as transplantation, involves harvesting the patient's stem cells from blood or marrow. The stem cells are often frozen for later use. The patient is then given intensive therapy and the stem cells are reinfused via an indwelling catheter. The blood or marrow may be obtained from a patient with a disease of the marrow (for example, acute myelogenous leukemia) when in remission or when the marrow and blood 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 person (recipient). The purpose of the procedure is to restore blood cell production from the preserved and reinfused stem cells after intensive therapy has severely damaged the patient's remaining marrow. This procedure was usually performed using marrow but increasingly autologous blood stem cells are used.

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 distinctive features, allowing better distinctions to be made among them.

Basophil

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

Blast Cells

This term refers to the earliest marrow cells identified by the light microscope. Blasts represent about 1 percent of normally developing marrow cells. They are largely myeloblasts, which are cells that will develop into neutrophils. In normal lymph nodes, blasts are usually lymphoblasts, that is, cells that are part of lymphocyte development. In the acute leukemias, blast cells, similar in appearance to normal blast cells, accumulate in large numbers, perhaps up to 80 percent of all marrow cells. In acute myelogenous leukemia, myeloblasts accumulate and in acute lymphocytic leukemia,

lymphoblasts accumulate. Sometimes the distinction can be made by examination through the microscope of stained marrow cells. Often, immunophenotyping or use of special staining of marrow cells is required to be sure of the distinction.

Bone Marrow

The bones are hollow and their central cavity is occupied by marrow, a spongy tissue which plays a major role in the development of blood cells. After puberty, the marrow in the spine, ribs, breast bone, hip, shoulders, and skull is most active in blood cell formation.

Bone Marrow Transplantation (see Stem Cell Transplantation).

Chemotherapy

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

Chromosome

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 2000 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 (cancers), benign and malignant are derived from a single cell with an injury to DNA (mutated) and, thus, are clonal. The mutated cell has an alteration in its DNA which forms an oncogene and leads to its transformation into a cancer-causing cell. The cancer is the total accumulation of cells that grow from the single mutated cell. Leukemia, lymphoma and myeloma are examples of cancers which are clonal, that is, derived from a single abnormal cell.

Colony Stimulating Factor (CSF) (see Cytokines).

Computed Tomography (CT) scan

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

Cultures

If an infection is suspected, it is helpful to know the principal site involved and the type of bacterium, fungus or other microorganism involved so that the most specific antibiotics can be selected for treatment. To determine the site and organism, samples of body fluids such as sputum, blood 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 determine 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 determine which antibiotic kills the organism. This process determines the “antibiotic sensitivity” of the organism.

Cycle

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

Cytogenetics

This is 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*." Chemicals derived from lymphocytes that act on other white blood cells are called "*interleukins*," that is, they interact between two types of leukocytes. Some cytokines can be made commercially and used in the treatment of leukemia. Granulocyte-colony stimulating factor (G-CSF) is one such cytokine. It stimulates the production of neutrophils and shortens the period of low neutrophil counts in the blood after chemotherapy. Cytokines that stimulate cell growth are sometimes referred to as "growth factors."

Differentiation

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

Eosinophils

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

Erythrocytes

A synonym for red cells. (see Red Cells)

Granulocytes

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

Growth Factors (see Cytokines).

HLA

The acronym for human leukocyte antigens. These proteins are on the surface of most tissue cells and give an individual his or her unique tissue type. 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 on the surface of cells act as antigens when donated (transplanted) to another individual, the bone marrow or stem cell recipient. If the antigens on the donor cells are identical (e.g. identical twins) or very similar (e.g. HLA matched sibling) the transplantation (donated marrow or cells) are more likely to survive in the recipient (engraft). In addition, the recipient’s body cells are less likely to be attacked by the donated cells (graft versus host disease).

Hematologist

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

Hematopoiesis

This term describes the process of blood cell development in the marrow. The most undeveloped cells in the marrow are stem cells. They start the

process of blood cell development. The stem cells begin to develop into young or immature blood cells like red cells or white cells of various types. This process is called “differentiation.” The young or immature blood cells then further develop into fully functional blood cells. This process is called “maturation.” The 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 because most blood cells live for short periods and must be continuously replaced. Red cells die in four months, platelets in 10 days and most neutrophils in two or three days. About five hundred billion blood cells are made each day. 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.

Iliac Crest

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

Immunophenotyping

A method that uses the reaction of antibodies with antigens to determine a specific type of cell in a sample of blood cells, marrow cells or lymph node cells. A tag is attached to antibodies that react with specific antigens in the cell. The tag can be identified by the laboratory equipment used for the test. As cells carrying their array of antigens are tagged with specific antibodies they can be identified; for example, myelogenous leukemic cells can be distinguished from lymphocytic leukemic cells. This method helps to subclassify cell types which may, in turn, help to decide on the best treatment to apply in that type of leukemia or lymphoma.

Indwelling Catheter

Several types of catheters (e.g. Hickman, Broviac, others) are available for 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 external end of the catheter can be used to administer medications, fluids, or blood products or to withdraw blood samples. With meticulous care, catheters can remain in place for long periods of time (many months), if necessary.

Interleukin (see Cytokine).

Karyotype

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

Leukocytes

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

Leukopenia

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

Lymph nodes

Small structures, the size of beans, that contain large numbers of lymphocytes and are connected with each other by small channels called lymphatics. These nodes are distributed throughout the body. In patients with lymphoma, Hodgkin's disease, and some types of lymphocytic leukemia, the malignant lymphocytes grow and expand the lymph nodes so that they may be enlarged in size. This enlargement of lymph nodes can be seen, felt or measured by *computed tomography (CT) scan* or *magnetic resonance (MR) imaging* depending on the degree of enlargement and location.

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 natural killer cells that can attack virus-infected cells or tumor cells.

Lymphokine (see Cytokines).

Magnetic Resonance (MR) Imaging

This technique provides detailed images of body structures. It differs from a CT scan in that the patient is not exposed to X-rays. The signals generated in the tissues in response to the magnetic field are converted by computer into images of body structures such as lymph nodes. Thus, the size and any changes in size of tumor masses or organs such as the liver and spleen can be measured.

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 (scavenger).

Multidrug Resistance

A characteristic of cells that makes them resistant 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 eject several drugs out of cells. The cell wall rapidly ejects chemicals 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 concentration of neutrophils, a type of white blood cell.

Neutrophils

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

Oncologist

A physician who diagnoses and treats patients with cancer. They are usually internists, who treat adults, or pediatricians, who treat children. Radiation

oncologists specialize in the use of radiation to treat cancer and surgical oncologists specialize in the use of surgical procedures to treat cancer. These physicians cooperate and collaborate to provide the best treatment plan (surgery, radiation therapy or chemotherapy) for the patient.

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).

Pancytopenia

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

Petechiae

Pin-head 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 radiotherapy and/or chemotherapy that suppresses blood cell production in the bone marrow.

Platelets

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

Platelet Transfusion

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

Polymerase Chain Reaction (PCR)

A technique to expand trace amounts of DNA or RNA so that the specific type of the DNA or RNA can be determined. This technique has become useful in detecting a very low concentration of residual leukemic cells, too few to be seen using a microscope. The technique can detect the presence of one leukemic cell among five hundred thousand to one million non-leukemic cells. PCR requires a specific DNA (or RNA) abnormality or marker, like an oncogene, in the leukemic or lymphomatous cells for its use.

Red 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

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

Remission

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

Resistance to Treatment

The ability of cells to live and divide despite their exposure to a chemical that ordinarily kills cells or inhibits their growth. This is the cause of refractory leukemia, whereby a proportion of leukemic cells resist the damaging effects of a drug or drugs. Cells have several ways to develop drug resistance. (see Multidrug Resistance)

Somatic Mutation

This event is 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 in the left upper portion of the abdomen just under the left side of the diaphragm. It contains clusters of lymphocytes like lymph nodes do and also filters the blood of old or worn out blood cells. It is often affected in leukemia, especially the lymphocytic leukemias, lymphoma and Hodgkin's disease. Enlargement of the spleen is referred to as “splenomegaly.” Removal of the spleen by surgery is referred to as

“splenectomy.” Removal of the spleen can be done since its function 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”). Generally, the stem cells are largely found in the marrow but some leave the marrow and circulate in the blood. Using special techniques, the stem cells in blood can be collected, preserved by freezing and, later, thawed and used for therapy.

Stem Cell Transplantation

This is a technique which was developed to restore the marrow of patients who had lethal injury to that site. Such injury can occur because of primary marrow failure, destruction of marrow by disease, or intensive chemical or radiation exposure. As first designed, the source of the transplant was the marrow of a healthy donor who had the same tissue type (HLA type) as the patient. Usually, the source was a brother or sister. Donor programs have been established to identify unrelated donors who have a matching tissue type. This approach requires screening tens of thousands of unrelated individuals of similar ethnicity.

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

If the donor is an identical twin, the transplant is called “syngeneic,” the medical term for genetically identical. If the donor is a non-identical sibling, the transplant is called “allogeneic,” indicating it is from the same species and in practice nearly always matching in tissue type. The term “matched unrelated” is applied to the donor recruited from large volume screening programs searching for the rare individual who is very similar in tissue type to the patient.

Unfortunately, the important technique of harvesting a patient’s marrow, freezing it and returning it to them after they have received intensive chemotherapy and or radiotherapy for their underlying disease has been referred to as autologous (self) or auto-transplantation. This term is a well-entrenched misnomer since transplantation implied transferring tissue from one individual to another. This technique would better be referred to as autologous marrow infusion (see Autologous Stem Cell Infusion).

Therapy

The treatment of AML has different segments. *Induction therapy* refers to the methods used to destroy visible leukemic cells in blood and marrow to cause or “induce” a remission, which results in return of normal blood cells. *Consolidation therapy* is additional treatment given after remission is induced. Often high doses of chemicals are used in several short periods of treatment. The goal is to further decrease the concentration of residual leukemic cells. The greater the reduction in leukemic cells, the higher the probability that natural defenses will suppress the disease and result in a long-term remission. *Maintenance or continuation therapy* refers to the administration of chemicals periodically for a long period of time (months or years) usually in lower doses than consolidation therapy. This approach as previously practiced has shown little efficacy in the treatment of acute myelogenous leukemia and has been largely replaced by consolidation therapy.

Thrombocytopenia

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

Translocation

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

Tumor Suppressor Gene (antioncogene)

A gene which 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 occurred.

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 this booklet.

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* Medical textbook

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