



Myeloma



**The Leukemia &
Lymphoma Society®**

Fighting Blood-Related Cancers



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Introduction

This booklet provides information about myeloma 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 and would welcome comments as to the clarity of the information provided and the omission of information that would have been helpful.

Each year, about 14,000 persons in the United States learn that they have myeloma. Myeloma may be called by several names, including plasma cell dyscrasia, plasma cell myeloma, myelomatosis, and multiple myeloma. The disease may be referred to as Kahler's disease, especially in Europe, in recognition of the physician who first published the most comprehensive description of myeloma. Before describing the disease and its management further, a brief description of normal blood and marrow is provided for background.

This publication is designed to provide general information in regard to the subject matter covered. It is distributed as a public service by The Leukemia & Lymphoma Society, with the understanding that The Leukemia & Lymphoma Society is not engaged in rendering medical or other professional services.

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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., poliovirus antibodies). The cells include *red cells*, *platelets*, *neutrophils*, *eosinophils*, *basophils*, *monocytes*, and *lymphocytes*.

The red cells make up half the volume of the blood. They are filled with hemoglobin, the protein that picks up oxygen in the lungs and delivers oxygen to the tissues. The platelets are small 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*, the *spleen*, and lymphatic channels, but some enter the blood. There are three major types of lymphocytes: T cells, B cells, and natural killer cells.

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 bone (vertebrae), hip and shoulder bones, ribs, breastbone, and skull contain marrow that is actively making blood cells.

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

When the fully developed and functional cells are formed, they leave the marrow and enter the blood. In healthy individuals there are sufficient

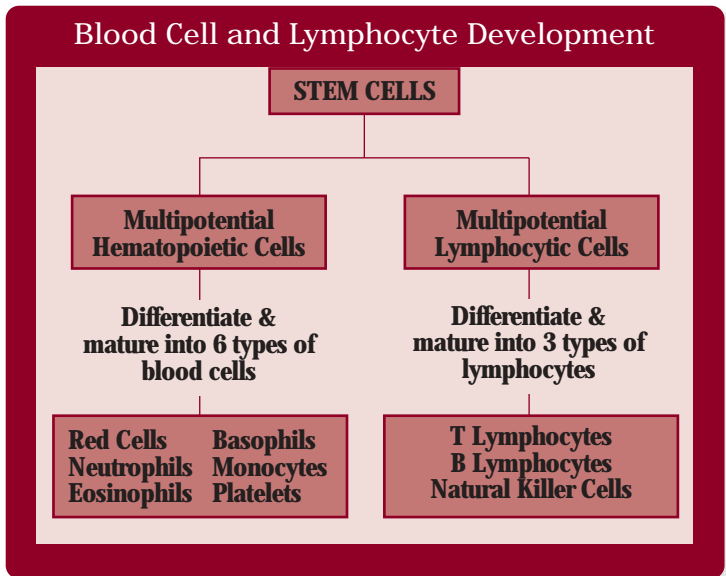


Figure 1. This figure depicts an abbreviated diagram of the process of hematopoiesis. This process involves the development of functional blood and lymphatic cells from stem cells.

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

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

History of Myeloma

Although bone abnormalities consistent with *myeloma* have been described in Egyptian mummies, physicians in England made the earliest clinical observations of myeloma in patients in the mid-19th century. By the turn of the 20th century, physicians had described the essential features of the disease: its appearance in the marrow as malignant plasma cells, its involvement in multiple sites in marrow, its destruction of bone, and its association with abnormal proteins in the urine and later the blood. In the late 19th century, the term “myeloma” was used to indicate the disease, which is derived from the Greek word “myel-,” meaning “marrow” and “-oma,” meaning “tumor.”

Types of Myeloma

Myeloma can be divided into several categories based on the distribution of the clinically apparent disease. Myeloma involving multiple marrow sites is by far the most common way in which the disease appears. Most cases (about 90 percent) have multiple sites involved at the time of diagnosis, and the term “multiple” is sometimes applied to the disease in its most common form. Various other terms are used to describe the disease in cases that appear to have a different distribution. These include solitary myeloma (only one site evident), localized myeloma (a few neighboring sites evident), or extramedullary myeloma (involvement of tissues other than the marrow, such as skin, muscle, or lung). Tumors of plasma cells outside the marrow are referred to as *plasmacytomas*. These categories allow the physician to decide what treatment works best for the particular type of disease presentation. Some cases of myeloma progress very slowly, and they may be referred to as smoldering or indolent myeloma.

Populations at Risk

Myeloma rarely occurs in people under the age of 40. Eighty percent of cases occur after the age of 60 (see Figure 2). Americans of African descent have a significantly higher rate of myeloma. Although myeloma increased somewhat in the Japanese people exposed to the highest doses of radiation after the atomic bomb blasts in Hiroshima and Nagasaki, exposure to radiation from diagnostic or therapeutic medical procedures does not cause myeloma.

Myeloma Age-Specific Incidence Rates 1995-1999

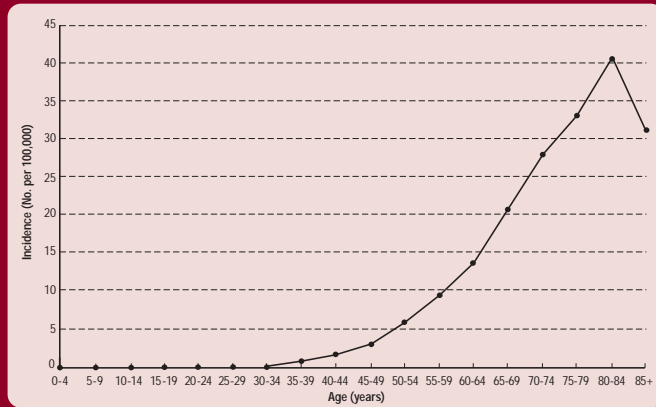


Figure 2. The horizontal axis shows the age at diagnosis of Americans who develop myeloma. Age is grouped into 5-year periods. The vertical axis represent the number of new cases of myeloma per 100,000 people in a particular 5-year age grouping. Thus, the risk of myeloma is 9 times (27 cases/100,000 persons) in those 70 to 74 years of age than in those 45 to 49 years of age (3 cases/100,000 persons). Data: National Cancer Institute SEER program.

Onset of the Disease

Myeloma results from an acquired injury to the DNA of a single cell in the lymphocyte development sequence that is destined to form plasma cells. Myeloma occurs in lymphocytes developing into B cells, as opposed to T cell development. As part of their normal function, B lymphocytes transform into plasma cells, which produce proteins called antibodies (see Figure 3). The B lymphocyte, if stimulated by a foreign antigen such as an infectious agent, transforms to a plasma cell. The latter produces antibodies that can attach to the infectious agent and make it susceptible to removal by other cells. In the disease myeloma, even though the malignant transformation takes place in a B lymphocyte, the change leads to an accumulation of malignant cells that has the appear-

ance of plasma cells. In most cases these malignant plasma cells are confined to the marrow. Their accumulation often interferes with normal blood cell production in the marrow.

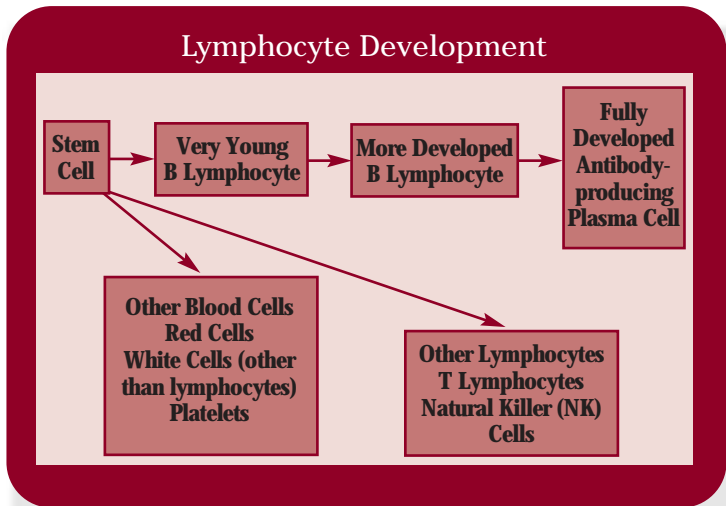


Figure 3. The malignant transformation in myeloma may occur in a more developed B lymphocyte. The affected lymphocytes are induced to complete step 3 and transform into malignant cells that have the appearance of plasma cells. The early events of lymphocyte development in the adult take place principally in the lymph nodes. The lymphocyte then migrates to the marrow (a major site of plasma cell development and function), where further development occurs. Thus, plasma cells including malignant forms like myeloma cells have an affinity for the marrow.

In the development of myeloma, a cell in the B lymphocyte development pathway transforms or becomes malignant. The cells resulting from the malignant transformation take the form of abnormal plasma cells, or myeloma cells. They sometimes look like normal plasma cells under the microscope. They may also have structural abnormalities that suggest they are malignant (cancer) cells. Special tests can identify them as malignant plasma cells.

Clinical Findings

Marrow

In normal marrow, plasma cells are relatively sparse. In patients with myeloma, plasma cells are often present in abnormally large numbers (see Figure 4). The *myeloma cells* accumulate in an uncontrolled manner, which is a sign of cancer, forming a tumor in the marrow. Sometimes, the myeloma cells collect in tissue and form a single mass, or tumor, called a plasmacytoma. In most cases, however, this tumor spreads, usually in many bones, including the ribs, backbone, pelvis, shoulder bones, breastbone, skull, and others

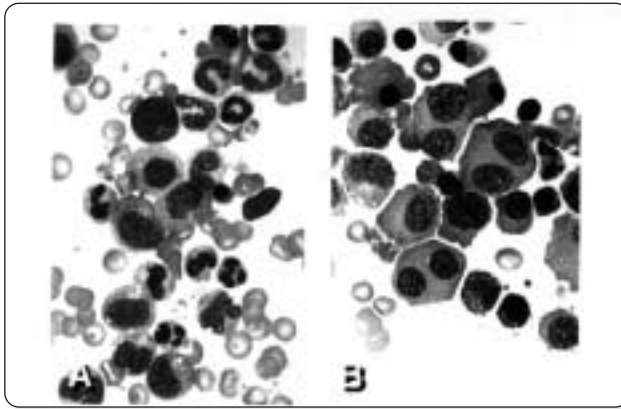


Figure 4. Panel A is a photograph of normal marrow cells. The variations in the shape and appearance of the cells are characteristic of the developmental stages of normal cells. Panel B is a photograph of marrow cells from a patient with myeloma. The shape and appearance of the cells are characteristic of plasma cells. Several cells have two nuclei, which may be one manifestation of abnormal plasma cells (myeloma cells).

Abnormal Proteins (monoclonal immunoglobulins)

In myeloma, large amounts of a single type of protein, called monoclonal immunoglobulin, is made and secreted into the blood. The term “monoclonal” indicates the protein is derived from one cell population (the

malignant plasma cells) and is being made without the purpose of responding to an antigen, such as an infectious agent. Normally, many types of proteins, called polyclonal immunoglobulins, are made by plasma cells for the purpose of providing immunoglobulins (also called antibodies) to protect the body against infection by invading viruses, bacteria, or other agents.

Monoclonal immunoglobulin can be measured in the blood, and its amount correlates approximately with the extent of the myeloma process. Changes in the amount of this protein usually parallels progression (increasing monoclonal immunoglobulin concentration in the blood) or regression (decreasing immunoglobulin concentration in the blood) of the myeloma.

The intact immunoglobulin is composed of two larger pieces (heavy chains) and two smaller pieces (light chains) attached to each other (see Figure 5). This whole immunoglobulin, made of the four chains, is too large to pass through the filtering apparatus of the kidney, and thus is present in the blood but not the urine. In most cases of myeloma, one of the small pieces of the immunoglobulin (the light chain) is also made by the malignant plasma (myeloma) cells. This piece of immunoglobulin enters the blood but is excreted rapidly in the urine. The light chain is often called Bence Jones protein, since the English physician Henry Bence Jones associated its excretion in the urine with myeloma. When excreted in large amounts, Bence Jones protein (immunoglobulin light chains) can cause renal injury and kidney failure.

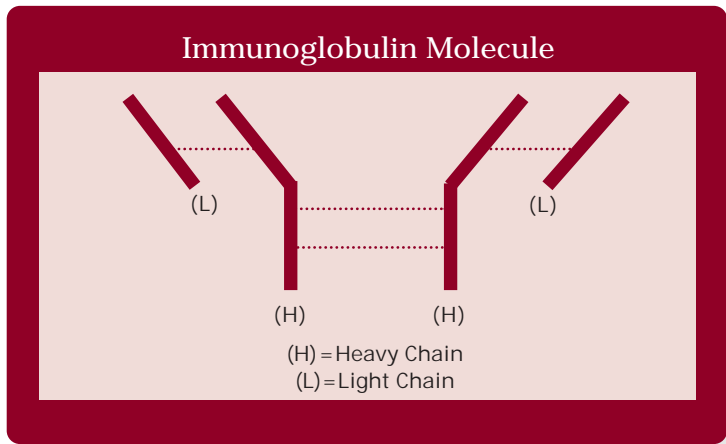


Figure 5. The monoclonal immunoglobulin in myeloma, like normal immunoglobulin, is made up of two heavy chains and two light chains attached to each other. In many cases the coordination of making and attaching light chains and heavy chains in the malignant plasma cells is lost and light chains leave the cell unattached. They are also referred to as Bence Jones protein. They are small enough to pass through the kidney and enter the urine, where they can be detected.

Bone Destruction

Another special feature of malignant plasma (myeloma) cells is that they secrete chemicals (*cytokines*) that stimulate other cells that dissolve bone. Bone is remodeled continuously. This remodeling is a coordinated effect of cells that dissolve bone (osteoclasts) and cells that lay down new bone (osteoblasts). The chemicals secreted by plasma cells stimulate the bone-dissolving cells into marked overactivity. The bone-forming cells cannot keep up. Holes (lytic spots) develop in the bone. Bone is thinned (osteoporosis) and can be weakened sufficiently to break (fracture) with normal stresses of walking or lifting. Slightly increased stresses of coughing and minor falls or injuries can also break the bones when thinned by the effects of myeloma.

Symptoms and Signs

Bone pain is the most common early symptom of myeloma. Most patients feel pain in the back or the ribs, but it can occur in any bone.

The pain is usually made worse by movement. Patients fatigue more easily and often feel weak. They may have a pale complexion from *anemia*, which is a common medical problem for patients with myeloma and may contribute to the fatigue. If the disease progresses, the concentration of other normal cells in the blood, e.g., the white cells and platelets, may also decrease. Patients may have repeated infections because antibodies to invading viruses, bacteria, or other disease agents are not made efficiently or in adequate amounts. A urinary tract, bronchial, lung, skin, or other site of infection may be the first sign of the disease. In addition, recurrent infections may complicate the course of the disease.

Diagnosis

Myeloma may be discovered during a “routine” medical examination, before patients have symptoms of the disease. The diagnosis of myeloma depends on three principal findings. 1) Increased numbers of malignant plasma cells (myeloma cells) are found when a bone marrow aspiration and biopsy are performed (usually from the hipbone). 2) Monoclonal immunoglobulin and Bence Jones (light chain) proteins are found in the blood or urine, respectively (see Figure 6). 3) Imaging studies of the bones identify the thinning, holes, or fractures of the bones that characterize myeloma. Magnetic resonance (MR) imaging can detect bone changes earlier than conventional x-ray studies. Taken together, these three findings make it possible for physicians to diagnose myeloma in a patient.

In most patients with myeloma at least small amounts of monoclonal light chains can be detected in the urine. In some patients, the myeloma cells are so disordered that they do not make a complete monoclonal immunoglobulin molecule with two heavy and two light chains (see page 9 and Figure 5); their myeloma cells make only light chains. In these cases of myeloma, referred to as “light chain disease,” the examina-

tion of serum will not show the characteristic increase or “spike” of monoclonal immunoglobulin, but the urine will have large amounts of monoclonal light chains.

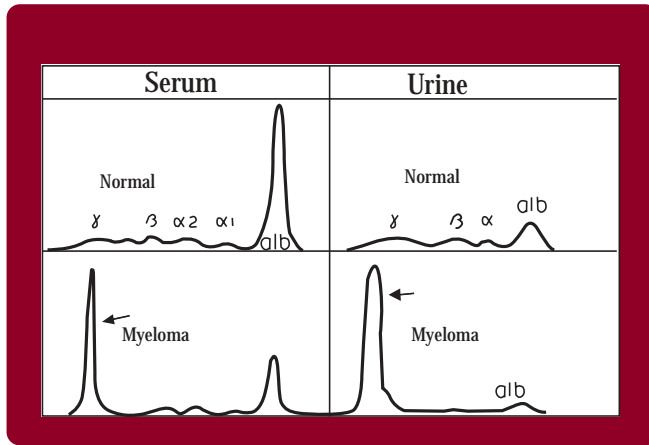


Figure 6. This figure represents the graphs of the readout of the serum protein measurement as performed in a clinical laboratory. The differences between normal serum and urine and those of a patient with myeloma are shown. The upper left panel displays the distribution of normal human serum proteins. There are two major types of proteins, albumin (alb) and globulin. The Greek symbols alpha (α), beta (β), and gamma (γ) are used to denote the different types of globulins. In the lower left panel is the serum protein readout of a patient with myeloma. The characteristic findings are the lower amount of albumin in the far right peak and the markedly increased amount of gamma globulin in the far left peak (see arrow). The upper right panel displays the proteins in a concentrated urine. Characteristically only very small amounts of protein are detected. The amounts are magnified here since the urine was concentrated 100-fold before the proteins were measured. In the lower right panel is the urine from a patient with myeloma with very large excretion of light chains (Bence Jones protein) shown by the far left peak (see arrow). Virtually all patients with myeloma have a protein peak either in serum or urine or both.

Other Tests of Blood and Urine

Physicians will also obtain other informative blood tests that measure red cell, white cell, and platelet concentrations in the blood (complete blood count). The latter measurements indicate the degree to which the

myeloma cells in the marrow are affecting normal blood cell development. Blood calcium is measured because the bone destruction causes calcium to leave bone and raise the blood levels. High calcium can be injurious. The concentration of three proteins in the blood, lactic dehydrogenase, beta-2 microglobulin, and C-reactive protein, are obtained. These proteins are each an indirect measure of the size and growth rate of the myeloma tumors. Tests that reflect kidney function (urea nitrogen and creatinine) and a urine examination (urinalysis) are usually performed, since impaired kidney function can result from the affects of the abnormal protein on the kidney and metabolic changes, such as elevated blood calcium.

Cytogenetic studies of the chromosomes in the nucleus of myeloma cells in the marrow often display abnormalities in chromosome structure. These alterations can give a clue to the likelihood of the disease being more or less rapidly progressive and may contribute to the decision on the best approach to treatment.

Complications

Infections

Infections are one of the most troublesome medical problems for patients with myeloma. Patients with myeloma may not be able to fight infections efficiently because their B lymphocytes do not make antibodies in response to microbes that enter the body. The effects of *chemotherapy* or radiation therapy on blood cell production also cause further deficits in white blood cells, which contributes to the risk of infection.

Pain

Bone pain may occur because of the expansion of myeloma tumors; successful treatment may relieve such pain. Patients also may experience pain that radiates from the back when the back bones (vertebrae) collapse and impinge on nerves. Fractures of bones may also result in pain.

Kidney Impairment

Myeloma patients may have serious problems with their kidney function for two principal reasons. One reason is the excretion of large amounts of Bence Jones protein in the urine. This excess protein can damage the kidney filtration apparatus and the channels or tubules that are important in urine formation. Another reason is that patients with myeloma often have high levels of calcium in the blood (*hypercalcemia*). When bones are damaged, calcium is released into the blood. High blood concentration of calcium can damage the kidneys, as well.

Masses of Myeloma Cells (plasmacytomas)

Extramedullary myeloma is the term applied to masses of myeloma cells that develop outside the marrow. These may involve organs like lymph nodes, the respiratory tract, the gastrointestinal tract, or the skin. In the skin, they are evident as small tumors often with a purple discoloration. In some cases, the spinal cord may be injured, due to myeloma masses that extend from bone and press on the cord.

Impaired Blood Flow

Occasionally, the abnormal protein (monoclonal immunoglobulin) concentration in the blood is so great that it interacts with the red cells to produce a sludging of blood flow, which is referred to as hyperviscosity. The circulation of the oxygen-carrying red cells is slowed, and the work of the heart is increased by the resistance of the blood to being pumped through the circulation. This complication can lead to headaches, dizziness, weakness, fatigue, sleepiness, oozing from cuts, and other symptoms. Rarely, some myeloma monoclonal immunoglobulins may congeal in the cold and lead to poor circulation, especially if the body is exposed to cold temperatures. These immunoglobulins are referred to as cryoglobulins (from the Greek word “kryos,” meaning “cold”).

Acute Myelogenous Leukemia

There is a heightened risk among myeloma patients of developing acute myelogenous leukemia, especially after treatment with certain cytotoxic drugs. This complication occurs in a small proportion of patients.

Treatment

Chemotherapy With or Without Stem Cell Infusion

Chemotherapy has been the mainstay of treatment for myeloma. Chemotherapy uses drugs to kill the malignant plasma (myeloma) cells. Table 1 lists the drugs most commonly used. Often, two or three drugs are used simultaneously. As many as six drugs are combined in some intensive treatment programs.

Table 1. Drugs Used in Treatment of Myeloma

- cyclophosphamide (Cytosan)
- dexamethasone (Decadron, Dexacort)
- doxorubicin (Adriamycin, Rubex)
- idarubicin (Idamycin)
- interferon alfa (Roferon-A, Intron-A)
- melphalan (Alkeran)
- pamidronate (Aredia)
- prednisone
- thalidomide (Thalomid)
- vincristine (Oncovin)
- zoledronic acid (Zometa)

Some patients are diagnosed with minimal disease and little evidence of progression. This circumstance has been referred to as smoldering myeloma. In such cases, watchful waiting may be preferable to early chemotherapy. In most such cases, *therapy* will eventually be required.

Chemotherapy for myeloma has led to sustained *remissions* in some patients. Temporary cessation or marked slowing of the disease may occur for a time. Achieving complete remission for long periods has been

infrequent. Thus, “conventional” chemotherapy with one, two, or three drugs has given way to more intensive treatment. Since myeloma occurs principally in individuals between 60 and 80 years of age, the ability to tolerate intensive therapy must be judged on an individual basis.

High-dose chemotherapy or high-dose chemotherapy and radiotherapy followed by autologous stem cell infusion has proved more successful in inducing remissions than conventional therapy. In the small proportion of patients between ages 30 and 50 who have myeloma, consideration can be given to allogeneic *stem cell transplantation* from an HLA-matched donor. This approach, in the aggregate, may not be significantly better than *autologous stem cell infusion* because it has very high risk.

Thalidomide is a drug that is very useful in some patients with myeloma. It can be used alone or in combination with other drugs. It is given orally. Newer forms under development are more potent and may have broader antimyeloma effects.

Bisphosphonates are potent inhibitors of bone resorption. Pamidronate (Aredia) or zoledronic acid (Zometa) are bisphosphonates that can alleviate bone disease, decreasing pain and the likelihood of fracture and decreasing the high blood calcium associated with bone destruction. The drugs may also facilitate the effect of chemotherapy.

In some patients with severe anemia, the administration of an engineered form of the red blood cell growth factor, erythropoietin, may improve the anemia or decrease the need for blood transfusions.

Radiation therapy uses high-energy rays (x-rays) to kill malignant plasma (myeloma) cells and may be used to treat myeloma patients in select circumstances. Radiation therapy is the main treatment for localized myeloma, such as a solitary myeloma or an accumulation of myeloma

cells outside the marrow (plasmacytoma). Patients sometimes receive radiation therapy in preparation for stem cell transplantation. Carefully selected patients whose bone pain does not respond to chemotherapy may receive radiation therapy as well. Because the disease may be widespread, radiation therapy may be impractical if there are widely distributed sites of painful bone involvement.

Other Related Diseases

Essential Monoclonal Gammopathy

This common condition is usually found in older persons and increases in frequency in the 6th through 9th decades of life. It is manifested by the appearance of a pathological (monoclonal) protein in the blood analogous to that which characterizes myeloma (see Figure 6 on page 12). However an increase in plasma cells is not apparent in the marrow, and anemia, bone damage, recurrent infections and other features of myeloma are not present. The disorder usually does not affect the well being of the patient although occasionally the monoclonal protein may interact with normal tissues and lead to symptoms depending on the tissue affected. The significance of the disorder is that it evolves into a progressive B lymphocyte malignancy, such as myeloma or lymphoma, in about 30 percent of those affected over 20 years of observation. The disorder has received many names including “benign monoclonal gammopathy” and “monoclonal gammopathy of unknown significance (MGUS).” The significance of the disorder, that is the risk of evolution to myeloma or lymphoma, is now well recognized, however.

Macroglobulinemia

This disease has similarities to myeloma in that it is a malignancy of B lymphocytes that produce a monoclonal immunoglobulin that can be measured in the blood. The malignant B lymphocytes replace the normal marrow cells and may cause anemia and other blood cell deficiencies by

preventing the normal marrow cells from making blood cells efficiently. Macroglobulinemia also occurs in older individuals, as does myeloma. It differs from myeloma in that it usually does not progress as rapidly and does not lead to bone destruction and fractures. The monoclonal immunoglobulin produced by the malignant B lymphocyte is a very large type, referred to as macroglobulin (large globulin). This feature has given the disease its designation “macroglobulinemia.” Jan Waldenström, a Swedish *hematologist*, first described the disease, and his name is sometimes associated with the designation, as “Waldenström macroglobulinemia.”

Primary Amyloidosis

An uncommon disease process is associated with the deposit of the material called *amyloid* (from the French word meaning “starch”) in tissues such as the heart, gastrointestinal tract, the nerves, the skin, and other sites. Although there are several types of amyloid, one type is caused by the deposit of immunoglobulin light chains (see Figure 5 on page 10) in the tissues. In some patients with myeloma, the light chains made by their plasma cells can result in the formation of amyloid and its deposition in tissues. This type of amyloidosis can occur with or without overt myeloma. In patients with myeloma-associated amyloid, the involvement of the heart, intestines, or nerves can produce dysfunction in those organs, and significantly complicates the management of the myeloma. In other patients, the marrow may not have increased numbers of plasma cells and the bones may not be affected. The malignant B cells, which make the light chains that deposit in the tissues and form the amyloid, are too few to be identified by a marrow biopsy.

Heavy Chain Disease

Heavy Chain disease is rare disease of B lymphocytes, so named because the protein made by the malignant lymphocytes is an incomplete immunoglobulin (the heavy chain of the immunoglobulin), (see Figure 5). It is similar to myeloma in that it is a malignancy of B lymphocytes that secrete a characteristic immunoglobulin, but its clinical features are quite different. For example, there is no bone disease.

POEMS Syndrome

POEMS syndrome is very uncommon marrow disorder related to myeloma. The name of the syndrome is derived from its five most common features: P (peripheral neuropathy), O (organ enlargement), E (endocrine gland dysfunction), M (monoclonal plasma cell tumors and monoclonal immunoglobulin), S (skin changes). The nerve injury is often the most disabling element and can include progressive weakness of arms or legs. The bone alterations related to the marrow accumulation of plasma cells takes on a different character than that in classic myeloma. It looks denser rather than less dense than normal. Thyroid or sex hormone deficiencies may require replacement therapy. Therapy can benefit several features of the disease.

Social and Emotional Aspects

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

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

Family members or loved ones may have questions about chemotherapy and alternative methods of treatment. It is best to speak directly with physicians regarding specific medical questions. Family members or

loved ones should discuss any problems or reactions they may have. Nurses and other health professionals understand the complexity of emotions and the special ongoing needs of those living with myeloma. They also will spend much time with patients becoming their confidants and can be very helpful in their emotional support. For more information about the social and emotional aspects of the disease, you may request a copy of the Society publication, *Coping With Survival*, a booklet dealing with the psychosocial aspects of the disease for leukemia and myeloma patients.

There are programs to help ease the emotional and economic strain created by myeloma and 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 also want to visit our web site at www.leukemia-lymphoma.org to view publications and obtain more information about The Leukemia & Lymphoma Society programs and services.

The Future

Anticytokines

Researchers continue to look for better ways to diagnose and treat myeloma, and our knowledge is growing. Scientists believe that the cytokine interleukin-6 may be an important stimulator of myeloma cell growth. Techniques to block the action of interleukin-6, using inhibitors of its action, are being studied in the laboratory.

Immunotherapy

Various forms of immunotherapy are also under study. The malignant plasma (myeloma) cells express highly specific targets for immune attack. Vaccines are being studied that could contain the immune cells of treated patients so as to attack their myeloma cells. These vaccines and other

types under study are not preventive treatments as in the case of most vaccines for infectious diseases. They would reduce the myeloma tumors or suppress the growth of residual myeloma tumors after other forms of therapy have reduced their size.

Counteracting Cell Resistance Factors

Myeloma cells are inherently resistant to current chemotherapy. In part, this is related to the presence of multidrug resistance factors in the cell that prevent drugs from acting on the cell. Several new approaches to counteracting these drug resistance factors are under study and could be used in the future to enhance the effectiveness of drugs.

New Drugs

New more potent forms of thalidomide are under study. These are pills taken orally that have broad actions against myeloma. They kill myeloma cells and alter their environment to impair their accumulation. Drugs useful in other cancers have shown some positive effects in the treatment of myeloma. Two examples are arsenic trioxide and topotecan.

Targeted Radiotherapy

A radioactive isotope that attaches to bone is being studied to determine if its myeloma-killing radiation can be used to treat the disease prior to autologous transplantation.

Proteasome Inhibitors

Proteasomes are structures in cells that are responsible for breaking down proteins that are no longer needed. This process of recycling proteins is important for normal cell function and survival. Inhibitors of this process can kill malignant cells since they require this function for survival. A proteasome inhibitor is being studied to see if it can kill myeloma cells and not severely affect normal cells. One such inhibitor has shown effectiveness in early studies.

Stabilizing Damaged Bones

New surgical techniques are being employed to inject a chemical cement into damaged vertebrae so that they reconstitute themselves and alleviate disabling back pain and in some cases restore height lost by vertebral collapse.

These and other new approaches, some of which are being supported by the research programs of the Society, hold the promise of increasing the rate of remission and finding a cure for myeloma.

Amyloid

A term meaning “starchlike.” In myeloma, amyloid develops when parts of the immunoglobulin molecule, referred to as light chains, deposit in tissues. In the type of amyloid that occurs in myeloma or closely related diseases, organ failure can occur as a result of amyloid deposits in the heart, gastrointestinal tract, and other systems.

Anemia

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

Antibodies

Proteins released by plasma cells that recognize and bind to the specific foreign substances. These foreign substances are called antigens. Plasma cells are derived from B lymphocytes. Antibodies coat, mark for destruction, or inactivate foreign particles like bacteria, viruses, or foreign chemicals like harmful toxins. Antibody binds specifically to its antigen. One, also, can make antibodies in the laboratory in two ways. If one injects material from one species into another, the latter will recognize it as foreign and make antibodies to it. Human cells injected into rabbits, for example, allows one to prepare rabbit antibodies directed against the human cell that acted as the antigen. These antibodies are usually polyclonal antibodies. A technique known as a hybridoma can be used to get immune cells in a laboratory flask to generate a specific antibody called a monoclonal antibody. These antibodies can be used in several important ways. They can be used to identify and classify human leukemias and lymphomas or can be altered to make them useful in antibody-mediated immunotherapy.

Apheresis (see Hemapheresis)

Autologous Stem Cell Infusion

This technique, often referred to as transplantation, involves 1) harvesting the patient's stem cells from blood or marrow, 2) freezing them for later use, and 3) thawing and infusing them via an indwelling catheter after the patient has been given intensive chemotherapy or radiation therapy. 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 are not overtly abnormal (for example, lymphoma). Technically, this procedure is not transplantation, which implies taking tissue from one individual (donor) and giving it to another person (recipient). The purpose of this 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 can be performed using marrow or blood stem cells. The latter can be harvested by *hemapheresis*. (see the Society booklet, "*Blood and Marrow Stem Cell Transplantation*")

Basophil

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

Bisphosphonates

A class of drugs that include pamidronate (Aredia) and zoledronic acid (Zometa). They prevent the thinning of bone. They probably act by preventing cells that dissolve bone, osteoclasts, from doing so. In myeloma, bone thinning (osteoporosis) and fracture are major problems. These drugs have been very helpful in preventing or minimizing the bone loss.

Bone Marrow

The bones are hollow and their central cavity is occupied by marrow, a spongy tissue that is the site of blood cell formation. By puberty, the marrow in the spine, ribs, breastbone, hip, shoulders, and skull is most active in blood cell formation. In the adult, the bones of the hands, feet,

legs, and arms do not contain marrow in which blood cells are made. In these sites the marrow is filled with fat cells. When marrow cells have matured into blood cells they enter the blood that passes through the marrow and are carried throughout the body.

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 normal cells of the marrow, the intestinal tract, the skin, and hair follicles are most sensitive to these chemicals, injury to these organs cause the most common tissue effects of chemotherapy (i.e., low blood cell counts, mouth sores, diarrhea, and hair loss).

Cytokines

These are cell-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 treatment. Granulocyte colony-stimulating factor (G-CSF) is one such cytokine. It stimulates the production of neutrophils and shortens the period of low neutrophil counts in the blood after chemotherapy. Cytokines that stimulate cell growth are sometimes referred to as “growth factors.”

Differentiation

The process by which stem cells transform from cells without a specific structural or functional characteristic into functional cells of a single blood cell line. The process of differentiation of stem cells forms the red blood cells, platelets, neutrophils, monocytes, eosinophils, basophils and lymphocytes.

Eosinophil

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

Growth Factors (see Cytokines)

Hemapheresis

The process of removing a donor's blood to extract a specific component 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 a platelet transfusion from one donor (rather than six to eight separate donors). In so doing, the recipient of the platelets is exposed to the blood of fewer donors or can be given HLA-matched platelets from a single related donor. This technique is also used to remove circulating blood stem cells that can be frozen, stored, and later used instead of marrow stem cells for transplantation. The system of hemapheresis is closed and sterile.

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 continuous activity is that most blood cells live for short periods and must be continuously replaced. After release from the marrow, red cells are removed in four months, platelets in ten days, and most neutrophils in one to 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 that occurs when the marrow is injured by replacement with leukemia, lymphoma, or myeloma cells.

Hypercalcemia

An abnormally high concentration of calcium in the blood. In myeloma, the breakdown of bone, which is rich in calcium, is the main cause of high blood and urine calcium. The high calcium can contribute to weakness, loss of appetite, nausea, confusion, lethargy, and other symptoms.

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 and some types of lymphocytic leukemia, the malignant lymphocytes grow and expand the lymph nodes so that they may be enlarged. 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 is the essential cell type 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 (NK) cells that can attack virus-infected cells or tumor cells.

Monocytes

A type of white cell that represents about five to ten percent of the cells in normal human blood. 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, can ingest dead cells (scavenger), and can assist lymphocytes in their immune functions.

Myeloma

A neoplasm of B lymphocytes that manifests itself as the derivative cells referred to as plasma cells. The disease usually starts in the marrow, which is replaced by malignant plasma cells. The malignant plasma cells make a monoclonal immunoglobulin, the detection of which may be very helpful in diagnosis. The cells secrete chemicals that stimulate the overactivity of bone-dissolving cells, called osteoclasts, leading to osteoporosis and brittle bones that fracture easily.

Myeloma Cells

These are malignant plasma cells that are the hallmark of myeloma. Their appearance may be similar to normal plasma cells, but they are present in increased numbers.

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. A severe deficiency of neutrophils increases the patient's susceptibility to infection. A neutrophil may be called a "poly" (polymorphonuclear neutrophil) or "seg" (segmented neutrophil) because its nucleus has several lobes.

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 are neutrophils and monocytes. They emigrate out of the blood and into tissues in which an infection has developed. A severe decrease in the blood level of these cells is the principal cause of susceptibility to infection in patients treated with intensive radiotherapy and/or chemotherapy. The latter treatments suppress blood cell production in the marrow resulting in deficiencies of these phagocytic cells.

Plasmacytoma

A localized tumor of malignant plasma cells either in a bone or in the other tissues of the body. If there is only one such area of bone involved it is called solitary plasmacytoma. An area outside of bone may be referred to as extramedullary plasmacytoma.

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. Thrombocyte is a synonym for platelet and is often used as the prefix in terms describing disorders of platelets, such as thrombocytopenia or thrombocythemia.

Red Cells

Blood cells that contain hemoglobin. Hemoglobin binds oxygen when red cells pass through the lungs and releases it to the tissues of the body. The red cells make up a little less than half the volume of blood in healthy individuals.

Relapse or Recurrence

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

Remission

A disappearance of evidence 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. Long-term benefit usually requires a complete remission, especially in acute leukemia or progressive lymphomas.

Spleen

An organ of the body in the left upper portion of the abdomen under the left side of the diaphragm. It contains clusters of lymphocytes and also filters the blood of old or worn-out cells. It is often affected in lymphocytic leukemias and lymphomas. Enlargement of the spleen is referred to as “splenomegaly.” Removal of the spleen by surgery is referred to as “splenectomy.” Removal of the spleen is used to treat certain diseases. Other organs, such as the lymph nodes and liver, can perform most of the functions of the spleen.

Stem Cell

These are primitive cells in marrow that are required to make red cells, white cells, and platelets (see “hematopoiesis”). Generally, the stem cells are largely found in the marrow but some leave the marrow and circulate in the blood. Using special techniques, the stem cells in blood can be collected, preserved by freezing, and later thawed and used for stem cell therapy.

Stem Cell Transplantation

This is a technique that was developed to restore the marrow of patients who had lethal injury to that site. Such injury can occur because of primary marrow failure, destruction of marrow by disease, or intensive chemical or radiation exposure. As first designed, the source of the transplant was the marrow cells of a healthy donor who had the same

tissue (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 a very small fraction of the marrow cells called “stem cells.” These stem cells not only reside in the marrow but also circulate in the blood. They can be harvested from the blood of a donor by treating the donor with an agent or agents that cause a release of larger numbers of stem cells into the blood and collecting them by hemapheresis. 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. 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 implies transferring tissue from one individual to another. This technique would better be referred to as autologous marrow infusion (see “autologous stem cell infusion”).

Therapy

The treatment of leukemia and lymphoma has different segments. Induction therapy refers to the methods used to destroy visible malignant cells in blood, marrow, or lymph nodes to cause or “induce” a remission, which results in disappearance of abnormal cells and a return of normal blood cells. Consolidation therapy is additional treatment given after remission is induced. Often, high doses of drugs are used in several short periods of treatment. The goal is to further decrease the concentration of residual malignant cells. The greater the reduction in malignant 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.

White Blood Cells

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

Society Patient Booklets:

Acute Myelogenous Leukemia, The Leukemia & Lymphoma Society, 2002.

Blood and Marrow Stem Cell Transplantation, The Leukemia & Lymphoma Society, 2002.

Understanding Drug Therapy and Managing Side Effects, The Leukemia & Lymphoma Society, 2002.

Coping With Survival, The Leukemia & Lymphoma, 2000.

Cancer Clinical Trials Fact Sheet, The Leukemia & Lymphoma Society, 2002

Choosing and Communicating With a Cancer Specialist Fact Sheet, The Leukemia & Lymphoma Society, 2002

Technical Sources:

Williams Hematology. Edited by E. Beutler, M.A. Lichtman, B. Coller, T.J. Kipps. McGraw Hill Co, 6th Edition, 2001.

Hematology: Basic Principles and Practice. Edited by R. Hoffman., New York: Churchill Livingstone, 3rd Edition, 2000.

Chapters and Free Information

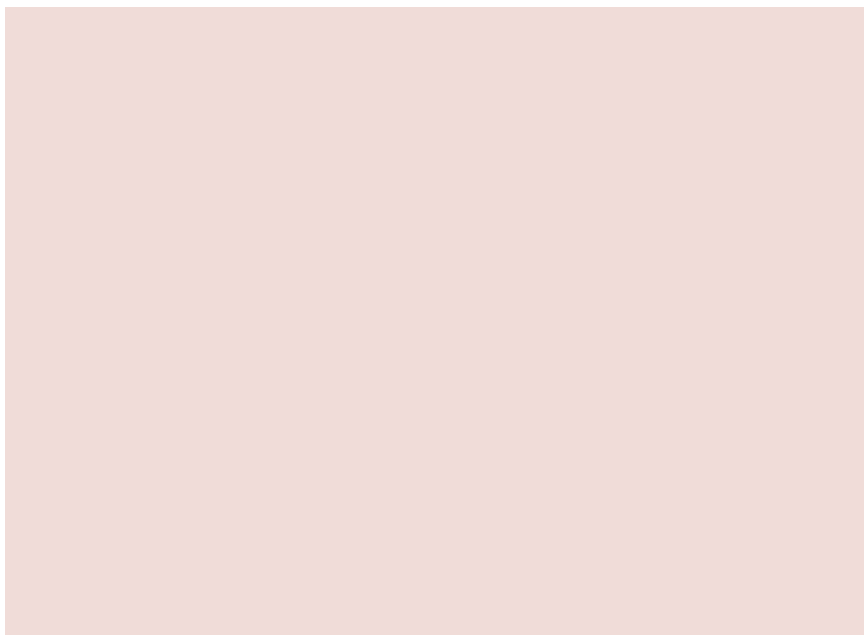
Information about leukemia, lymphoma, and myeloma is available from The Leukemia & Lymphoma Society's offices located in the states and cities listed below. Please refer to your telephone directory for local address and telephone number, or call 800-955-4572.

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