NON-HODGKIN LYMPHOMA

What is cancer?

Cancer develops when cells in a part of the body begin to grow out of control. Although there are many kinds of cancer, they all start because of out-of-control growth of abnormal cells.

Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide more rapidly until the person becomes an adult. After that, cells in most parts of the body divide only to replace worn-out or dying cells and to repair injuries.

Because cancer cells continue to grow and divide, they are different from normal cells. Instead of dying, they outlive normal cells and continue to form new abnormal cells.

Cancer cells develop because of damage to DNA. This substance is in every cell and directs all its activities. Most of the time when DNA becomes damaged the body is able to repair it. In cancer cells, the damaged DNA is not repaired. People can inherit damaged DNA, which accounts for inherited cancers. Many times though, a person’s DNA becomes damaged by exposure to something in the environment, like smoking.

Cancer usually forms as a tumor. Some cancers, like leukemia, do not form tumors. Instead, these cancer cells involve the blood and blood-forming organs and circulate through other tissues where they grow.

Often, cancer cells travel to other parts of the body, where they begin to grow and replace normal tissue. This process is called metastasis. Regardless of where a cancer may spread, however, it is always named for the place it began. For instance, breast cancer that spreads to the liver is still called breast cancer, not liver cancer.

Not all tumors are cancerous. Benign (non-cancerous) tumors do not spread (metastasize) to other parts of the body and, with very rare exceptions, are not life threatening.

Different types of cancer can behave very differently. For example, lung cancer and breast cancer are very different diseases. They grow at different rates and respond to different treatments. That is why people with cancer need treatment that is aimed at their particular kind of cancer.

Cancer is the second leading cause of death in the United States. Nearly half of all men and a little over one third of all women in the United States will develop cancer during their lifetimes. Today, millions of people are living with cancer or have had cancer. The risk of developing most types of cancer can be reduced by changes in a person's lifestyle, for example, by quitting smoking and eating a better diet. The sooner a cancer is found and treatment begins, the better are the chances for living for many years.

What Is Non-Hodgkin Lymphoma?

Non-Hodgkin lymphoma (also known as non-Hodgkin's lymphoma, NHL, or sometimes just lymphoma) is a cancer that starts in cells of the lymph system, which is part of the body's immune system. Lymph cells (called lymphocytes) are located mainly in the lymph nodes and other lymphoid tissues (such as the spleen or bone marrow). These will be described in more detail in the section The Lymph System and Lymphoid Tissue.

Other types of cancer -- lung or colon cancers, for example -- can spread to lymph tissue such as the lymph nodes or bone marrow. But cancers that start in these places and then spread to the lymph tissue are not lymphomas.

There are 2 main types of lymphomas. Hodgkin lymphoma (also known as Hodgkin's lymphoma, Hodgkin disease, or Hodgkin's disease) is named after Dr. Thomas Hodgkin, who first described it. *Hodgkin disease is discussed in a separate American Cancer Society document.* All other types of lymphoma are called non-Hodgkin lymphomas.

These 2 types of lymphoma can usually be distinguished from each other by looking at the cancer cells under a microscope. In some cases, sensitive lab tests may be needed to tell them apart.

The Lymph System and Lymphoid Tissue

To understand what lymphoma is, it helps to know about the body's lymph system.

The lymph system (also known as the lymphatic system) is composed mainly of lymphoid tissue, lymph vessels, and fluid called lymph (a clear fluid containing waste products and excess fluid from tissues). Lymphoid tissue is formed by several types of immune system

cells that work together to help the body fight infections. Lymphoid tissue is found in many places throughout the body (described below).

Lymphocytes

Most of the cells found in lymphoid tissue are lymphocytes, a type of white blood cell. The 2 main types of lymphocytes are *B lymphocytes* (B cells) and *T lymphocytes* (T cells). Both types can develop into lymphoma cells, but B-cell lymphomas are much more common than T-cell lymphomas in the United States.

Normal T cells and B cells do different jobs within the immune system.

B cells normally help protect the body against germs (bacteria or viruses) by making proteins called antibodies. The antibodies attach to the bacteria or viruses and attract other immune system cells that surround and digest the antibody-coated germs. Antibodies also attract certain blood proteins that can kill bacteria.

There are several types of T cells, each with a specialized job. Some normal T cells help protect the body against viruses, fungi, and some bacteria. They recognize specific substances found in virus-infected cells and destroy these cells. T cells can also release substances called cytokines that attract certain other types of white blood cells, which then digest the infected cells. T cells are also thought to destroy some types of cancer cells, as well as the cells of transplanted organs. Some types of T cells play a role in either boosting or slowing the activity of other immune system cells.

Lab tests identify B cells and T cells by certain substances on their surfaces. Some substances are found only on B cells, and others are found only on T cells. There are also several stages of B-cell and T-cell development (or maturation) that can be recognized by these lab tests.

This information is helpful because each type of lymphoma tends to resemble a particular subtype of normal lymphocytes at a certain level of development. Determining the type of lymphoma a person has is the first step in considering treatment options.

Organs That Contain Lymphoid Tissue

Because lymphoid tissue is in many parts of the body, lymphomas can start almost anywhere. The major sites of lymphoid tissue are:

Lymph nodes: Lymph nodes are bean-sized organs located throughout the body and connected by a system of lymphatic vessels. These vessels are like veins, except that instead of carrying blood, they carry lymph and immune system cells traveling between lymph nodes and other tissues.

Lymph nodes get bigger when they fight infection. Lymph nodes that grow in reaction to infection are called reactive nodes or hyperplastic nodes and are often tender to the touch. An enlarged lymph node is not usually a sign of a serious problem. Enlarged lymph nodes in the neck are often felt in people with sore throats or colds. But a large lymph node is also the most common sign of lymphoma. Lymph node enlargement is discussed more in the section, *How Is Non-Hodgkin Lymphoma Diagnosed?*

Spleen: The spleen is located under the lower part of the rib cage on the left side of the body. An average adult spleen weighs about 5 ounces. The spleen makes lymphocytes and other immune system cells to help fight infection. It also stores healthy blood cells and filters out damaged blood cells, bacteria, and cell waste.

Thymus gland: The thymus gland lies behind the upper part of the breastbone and in front of the heart. Before birth, the thymus plays a vital role in development of T lymphocytes. The thymus gland's size (about 1 ounce) and function diminish over the first 20 years of life. Despite this, the thymus continues to be active in immune system function throughout life.

Adenoids and tonsils: These are collections of lymphoid tissue located at the back of the throat. They help make antibodies against germs that are breathed in or swallowed. They are easy to see when they become enlarged during an infection or if they become cancerous.

Digestive tract: The stomach and intestinal tract as well as many other organs also contain lymphoid tissue.

Bone marrow: The bone marrow (the soft inner part of bones) makes red blood cells, blood platelets, and white blood cells. Red blood cells carry oxygen from the lungs to the rest of the body. Platelets plug up small holes in blood vessels caused by cuts or scrapes. White blood cells' main job is fighting infections. The 2 main types of white blood cells are granulocytes and lymphocytes. Bone marrow lymphocytes are primarily B cells. Lymphomas sometimes start from bone marrow lymphocytes.

Types of Non-Hodgkin Lymphoma

Classifying non-Hodgkin lymphoma can be quite confusing (even for many doctors) because there are so many types (around 30) and because several different systems have been used. The most recent system is the *World Health Organization (WHO)* classification. The WHO system uses the appearance of the lymphoma cells, the chromosome features of the cells, and the presence of certain chemicals on the surface of the cells. (Older systems classified lymphomas based only on their appearance under a microscope.)

This overview classifies the most common lymphomas according to whether they are B-cell or T-cell lymphomas and lists them by how common they are. Some rarer forms of non-Hodgkin lymphoma are not discussed here.

B-Cell Lymphomas

B-cell lymphomas make up most (about 85%) of non-Hodgkin lymphomas in the United States.

Diffuse Large B-cell Lymphoma

This is one of the more common types of non-Hodgkin lymphoma in the United States, accounting for about 1 out of every 3 cases. The cells are fairly large when viewed under the microscope.

Diffuse large B-cell lymphoma DLBCL can affect any age group but occurs mostly in older people (the average age of most patients is mid-60s). The usual symptoms are a quickly growing mass in an internal lymph node, such as in the chest or abdomen or in a lymph node that you can feel, for example, in the neck or armpit. Although this lymphoma usually starts in lymph nodes, it can grow in other areas such as the intestines, bone, and even the brain or spinal cord.

About 1 out of 3 of these lymphomas is confined to one part of the body (localized). When it is localized, this type of lymphoma is considered to be more curable than when it has spread to other parts of the body. Genetic tests have shown that there are different subtypes of DLBCL, even though they look the same under the microscope. These subtypes seem to have different outlooks (prognoses) and responses to treatment.

This is a fast growing lymphoma, but it often responds well to treatment with chemotherapy. Overall, about 3 out of 4 people will have no signs of disease after initial treatment, and about half of all people with this lymphoma are cured with therapy.

Follicular Lymphoma

About 1 out of 4 lymphomas in the United States are follicular lymphomas. The term follicular is used because the cells tend to grow in a circular, or nodular, pattern in lymph nodes.

The average age for people with this lymphoma is about 60. It is rare in very young people. Most of the time, this lymphoma occurs in many lymph node sites in the body, as well as in the bone marrow. In about 10% of cases, it only involves lymph nodes in one part of the body.

Although it is usually not considered curable by standard treatment, this is often a very slow-growing lymphoma, and the 5-year survival rate (the percentage of people surviving *at least* 5 years) is around 60% to 70%. Often these lymphomas are not treated when they are first diagnosed if the patient has no symptoms of the disease. Over time, out of 3 follicular lymphomas about 1 changes (transforms) into a fast-growing diffuse B-cell lymphoma.

Chronic Lymphocytic Leukemia /Small Lymphocytic Lymphoma

These related diseases account for about 1 out of 4 lymphomas. The same type of cell (known as a small lymphocyte) is involved in both chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL). The only difference is where the cancer occurs. In CLL it is mostly in the blood and bone marrow; in SLL, it is mainly in the lymph nodes.

Both are slow-growing diseases, although CLL, which is much more common, tends to grow slower. CLL and SLL are not considered curable with standard treatments, but depending on the stage and growth rate of the disease, most patients can live longer than 10 years. Occasionally over time, these slow-growing lymphomas transform into a more aggressive type of lymphoma.

For more detailed information, see the American Cancer Society document, *Leukemia -- Chronic Lymphocytic*.

Mantle Cell Lymphoma

Only about 5% of lymphomas are of this type. The cells are small to medium.

Men are affected most often. The average age of patients is in the early 60s. The lymphoma is usually widespread when it is diagnosed, involving lymph nodes, bone marrow, and, very often, the spleen.

Although this isn't a very fast growing lymphoma, it is hard to treat. Only about 1 in 5 patients survive at least 5 years. Newer, more aggressive treatments may be more effective than those used in the past, which may help improve the survival rates of patients now being diagnosed.

Marginal Zone B-cell Lymphomas

Marginal zone lymphomas account for about 4% of lymphomas. The cells in these lymphomas look small under the microscope. There are 3 main types of marginal zone lymphomas..

Extranodal marginal zone B-cell lymphomas (also known as mucosa-associated lymphoid tissue lymphomas): These lymphomas start in places other than the lymph nodes (hence the name extranodal)and are the most common type. Most mucosa-associated lymphoid tissue **(**MALT) lymphomas arise in the stomach and are thought to be related to an infection by the bacteria *Helicobacter pylori*, which is also the cause of stomach ulcers. Other possible sites of MALT lymphomas include the lung, skin, thyroid, salivary glands, and tissues surrounding the eye. Usually it is confined to the area where it begins and is not widespread. Many of these other MALT lymphomas have also been linked to infections with bacteria or viruses.

The average age of patients with this lymphoma is about 60. It is a slow-growing lymphoma and is often curable in its early stages. Doctors often use antibiotics as the first treatment for this type of lymphoma, especially MALT lymphoma of the stomach, as they may get rid of the *Helicobacter pylori* infection.

Nodal marginal zone B-cell lymphoma: This is a rare disease, found mainly in older women. Mostly lymph nodes are involved, although the cells can also sometimes be found in the bone marrow.

This tends to be a slow-growing lymphoma (although not usually as slow as MALT lymphoma), and many patients are cured if they are diagnosed in the early stages.

Splenic marginal zone B-cell lymphoma: This is a rare lymphoma. Most often the lymphoma is found only in the spleen and bone marrow.

Patients are often elderly and male and suffer from fatigue and discomfort caused by an enlarged spleen. Because the disease is slow-growing, treatment may not be needed unless the symptoms become troublesome.

Primary Mediastinal B-cell Lymphoma

This type accounts for about 2% of all lymphomas. The cells are large and resemble those of diffuse large B-cell lymphomas.

This lymphoma starts in the mediastinum (the area around the heart and behind the chest bone). It usually is localized at the beginning and rarely involves the bone marrow. It can cause trouble breathing because it often presses on the windpipe (trachea) leading into the lungs. It can also block the superior vena cava (the large vein that returns blood to the heart from the arms and head). This can cause the arms and face to swell.

About 2 out of 3 people with this lymphoma are women. Most are young -- in their 30s. It is a fast growing lymphoma but it is treatable. About half of patients can be cured.

Burkitt Lymphoma

This type makes up about 1% to 2% of all lymphomas. It is named after the doctor who first described this disease in African children and young adults. The cells are medium sized. Another kind of lymphoma, called Burkitt-like lymphoma, has slightly larger cells. Because this second kind of lymphoma is hard to tell apart from Burkitt lymphoma, the WHO classification combines them.

This is a very fast-growing lymphoma. In the African variety, it often starts as tumors of the jaws or other facial bones. In the more common types seen in the United States, the

lymphoma usually starts in the abdomen, where it forms a large tumor mass. It can also start in the ovaries, testes, or other organs, and can spread to the brain and spinal fluid.

Close to 90% of patients are male, and the average age is about 30. Although this is a fast-growing lymphoma, over half of patients can be cured by intensive chemotherapy.

Lymphoplasmacytic Lymphoma (Waldenstrom Macroglobulinemia)

This type is not common, accounting for 1% to 2% of lymphomas. The cells are small and found mainly in the bone marrow, lymph nodes, and spleen.

Most of the time the lymphoma cells make an antibody called immunoglobulin M (IgM), which is a very large protein. This antibody circulates in the blood in large amounts, and causes the liquid part of the blood to thicken, like syrup. This can lead to decreased blood flow to many organs, which can cause problems with vision (because of poor circulation in blood vessels in the back of the eyes) and neurological problems (such as headache, dizziness, and confusion) caused by poor blood flow within the brain. Other symptoms can include feeling tired and weak, and a tendency to bleed easily.

This lymphoma is slow growing. Although it isn't usually considered to be curable, most patients live longer than 5 years.

For more information, see the American Cancer Society document, *Waldenstrom Macroglobulinemia*.

Hairy Cell Leukemia

Despite the name, this is sometimes considered to be a type of lymphoma. This disease is rare -- about 1,000 people in the United States are diagnosed with this type each year. The cells are small B lymphocytes with projections around them that give them a "hairy" appearance. They are typically found in the bone marrow and spleen and circulating in the blood.

Patients tend to be older in general. Hairy cell leukemia is slow-growing, and some patients may never need treatment. An enlarging spleen or dropping blood counts (due to cancer cells invading the bone marrow) are the usual reasons to begin treatment, which is highly effective. Hairy cell leukemia is also described in the separate American Cancer Society document, *Leukemia--Chronic Lymphocytic*.

Primary Central Nervous System Lymphoma

This lymphoma usually involves the brain (called primary brain lymphoma), but it may also be found in the spinal cord and in tissues around the spinal cord and the eye. Over time, it tends to become widespread in the central nervous system. Although this was a rare tumor in the past, it has become more common in patients with acquired immune deficiency syndrome (AIDS). Most people develop headache and confusion. They can also have vision problems, paralysis of some facial muscles,, and even seizures in some cases.

The outlook for people with this condition has always been thought to be fairly poor, but about 30% to 50% of people can live at least 5 years with today's treatments.

T-Cell Lymphomas

T-cell lymphomas represent less than 15% of non-Hodgkin lymphomas in the United States.

Precursor T-lymphoblastic Lymphoma/Leukemia

This disease accounts for about 1% of all lymphomas. It can be considered either a lymphoma or leukemia, depending on how much of the bone marrow is involved (leukemias have more bone marrow involvement). The cancer cells are small-to-medium immature T-cells.

It often starts in the thymus gland (where many T cells are made) and can develop into a large tumor in the mediastinum (the area around the heart and behind the breast bone). This can cause trouble breathing if it presses on the windpipe (trachea) leading into the lungs. It can also block the superior vena cava (the large vein that returns blood to the heart from the arms and head), which can cause the arms and face to swell.

Patients are most often young adults, with males being affected more often than females.

This lymphoma is fast-growing, but if it hasn't spread to the bone marrow when it is first diagnosed, the chance of cure with chemotherapy is quite good. Once it is in the bone marrow, only about 40% to 50% of patients can be cured.

Peripheral T-cell Lymphomas

These lymphomas develop from more mature forms of T cells. There are several kinds of peripheral T-cell lymphomas, which in total account for about 5% of all lymphomas.

- **Cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome):** These T-cell lymphomas start in the skin. They are described in the American Cancer Society document, *Lymphoma of the Skin.*

- **Angioimmunoblastic T-cell lymphoma:** This lymphoma tends to occur in the lymph nodes and may affect the spleen or liver. Patients usually have fever, weight loss, and skin rashes and often develop infections. This lymphoma often progresses quickly, although some patients get better with cortisone-like drugs (corticosteroids) such as prednisone and/or chemotherapy. But it's not clear that this lymphoma can be cured, and intensive chemotherapy with a stem cell transplant is often used.

- **Extranodal natural killer/T-cell lymphoma, nasal type:** This type often involves the upper airway passages, such as the nose and upper throat, but it can also invade the skin and digestive tract. It is much more common in parts of Asia and South America. All ages can be affected. If the lymphoma is localized to the nasal passages, it can often be cured by chemotherapy and radiotherapy. But if it is widespread, then only a few patients are cured by very aggressive chemotherapy.

- **Enteropathy type T-cell lymphoma:** This lymphoma occurs in people with sensitivity to gluten, the main protein in wheat flour. The disease, called gluten-sensitive enteropathy, can progress to this lymphoma, which typically invades the walls of the intestines. Once it occurs, the patient's outlook is usually poor because of damage to the intestines.

- **Subcutaneous panniculitis-like T-cell lymphoma:** This rare lymphoma invades the deep layers of the skin, where it causes nodules to form. It is described further in the American Cancer Society document, *Lymphoma of the Skin.*

- **Anaplastic large cell lymphoma:** About 1% to 2% of lymphomas are of this type. The cells appear large under the microscope. The type of lymphoma is more common in young people, but it does occur in patients in their 50s and 60s. It usually starts in lymph nodes and can also spread to skin. There is also a form that begins in the skin. Although this type of lymphoma appears to be fast-growing, chemotherapy often works well. Many patients with this lymphoma are cured.

- **Peripheral T-cell lymphoma, unspecified:** This name is given to T-cell lymphomas that don't readily fit into any of the groups above. The tumor cells can be small or large. Most patients are in their 60s. As a group, these lymphomas tend to be widespread and grow quickly. Some cases respond well to chemotherapy, although few patients survive beyond 5 years.

What Are the Key Statistics About Non-Hodgkin Lymphoma?

In the United States, about 66,120 people (35,450 men and 30,670 women) are expected to be diagnosed with non-Hodgkin lymphoma in 2008. These statistics include both adults and children. It is the fifth most common cancer in both men and women in this country (not counting skin cancers), accounting for about 4% of all cancers.

The average American's risk of developing non-Hodgkin lymphoma during his or her lifetime is about 1 in 50. This risk may be altered for any individual by certain risk factors (listed in the next section).

Since the 1970s, incidence rates for non-Hodgkin lymphoma have nearly doubled. Some of this increase is due to AIDS-related non-Hodgkin lymphoma, but for the most part the reason for the rise is not known. In recent years, the increase in non-Hodgkin lymphoma cases has been mainly in women.

Although some types of non-Hodgkin lymphoma are among the more common childhood cancers, over 95% of cases occur in adults. The type of non-Hodgkin lymphoma seen in children is often very different from that seen in adults. There is a separate American Cancer Society document on non-Hodgkin lymphoma in children.

The average age at diagnosis is in the 60s and around half of patients are older than 65. The risk of developing non-Hodgkin lymphoma increases throughout life, and the elderly have the highest risk. The aging of the American population is likely to lead to an increase in non-Hodgkin lymphoma cases during the coming years.

Non-Hodgkin lymphoma is more common in men than in women. African Americans and Asian Americans are less likely than whites to develop non-Hodgkin lymphoma.

The American Cancer Society estimates that approximately 19,160 people in the United States (9,790 men and 9,370 women) will die of non-Hodgkin lymphoma in 2008. Survival rates vary widely based on the type of lymphoma and stage of disease at the time of diagnosis. However, the overall 5-year relative survival rate for people with non-Hodgkin lymphoma is 63%, and 10-year relative survival is 51%.

The 5-year survival rate refers to the percentage of patients who live *at least* 5 years after their cancer is diagnosed. Although many of these patients live much longer than 5 years after diagnosis, 5-year rates are used to produce a standard way of discussing prognosis. Five-year *relative* survival rates are calculated in ways that exclude the effect of diseases other than cancer on survival. Of course, 5-year survival rates are based on patients first diagnosed and treated more than 5 years ago. Recent improvements in treatment often result in a better outlook for newly diagnosed patients.

What Are the Risk Factors for Non-Hodgkin Lymphoma?

A risk factor is something that affects your chance of getting a disease such as cancer. Different cancers have different risk factors. For example, unprotected exposure to strong sunlight is a risk factor for skin cancer. But risk factors are not absolute. Having a risk factor, or even several risk factors, does not mean that you will get the disease. And many people who get the disease may not have had any known risk factors.

Researchers have found several factors that may affect a person's chance of getting non-Hodgkin lymphoma. There are many types of lymphoma, and some of these factors have been linked only to certain types.

Age

Getting older is a strong risk factor for this disease, with most cases occurring in people in their 60s or older.

Exposure to Certain Chemicals

Some studies have suggested that chemicals such as benzene and certain herbicides and insecticides (weed- and insect-killing substances) may be linked with an increased risk of non-Hodgkin lymphoma. Research to clarify these possible links is still in progress.

Some chemotherapy drugs used to treat other cancers can increase the risk of developing leukemia or non-Hodgkin lymphoma many years later. For example, patients who have been treated for Hodgkin disease have an increased risk of later developing non-Hodgkin lymphoma. But it's not totally clear if this is related to the disease itself or if it may be an effect of the treatment.

Radiation Exposure

Studies of survivors of atomic bombs and nuclear reactor accidents have shown they have an increased risk of developing several types of cancer, including leukemia, thyroid cancer, and non-Hodgkin lymphoma. Patients treated with radiation therapy for some other cancers, such as Hodgkin disease, have a slightly increased risk of developing non-Hodgkin lymphoma later in life. This risk is greater for patients treated with both radiation therapy and chemotherapy.

Immune System Deficiency

People with weakened immune systems have an increased risk for non-Hodgkin lymphoma. For example, patients who receive organ transplants (kidney, heart, liver) are treated with drugs that suppress their immune system to prevent it from attacking the new organ. These patients have a higher risk of developing non-Hodgkin lymphoma. The exact risk depends on which drugs and at what doses they are used.

The human immunodeficiency virus (HIV) can also weaken the immune system, and people infected with HIV are at increased risk of non-Hodgkin lymphoma.

Several genetic diseases can cause children to be born with a deficient immune system. Along with the risk of getting serious infections because of reduced immune defenses, these children also have an increased risk of developing non-Hodgkin lymphoma. Although these inherited immune deficiency diseases can be passed on to children, people with non-Hodgkin lymphoma who do not have these inherited diseases do not pass an increased risk of lymphoma on to their children.

Autoimmune Diseases

In autoimmune diseases, the immune system becomes abnormal and sees the person's own tissues as foreign, and tries to destroy them, as it would a germ. Some autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE, or lupus), and others have been linked with an increased rate of non-Hodgkin lymphoma.

Certain Infections

Lymphocytes (the types of cells from which lymphomas start) are part of the body's immune defenses. Several types of infections may raise the risk of non-Hodgkin lymphoma in different ways.

Infections that Directly Transform Lymphocytes

Some viruses can directly affect the DNA of lymphocytes, helping to transform them into cancer cells. The human T-cell leukemia/lymphoma virus (HTLV-1) and the Epstein-Barr virus (EBV) seem to work in this way.

Infection with HTLV-1 increases a person's risk of developing certain types of T-cell non-Hodgkin lymphoma. This virus is most common in some parts of Japan and in the Caribbean region, but is now found throughout the world. In the United States, it causes less than 1% of lymphomas. HTLV-1 spreads through sexual intercourse and contaminated blood and can be passed to children through breast milk from an infected mother.

In areas of Africa where Burkitt lymphoma is common, infection with the Epstein-Barr virus (EBV) is an important risk factor for this disease. In developed countries such as the United States, EBV is more often associated with lymphomas in patients infected with HIV. It has also been linked with developing nasal T-cell lymphoma and post-transplant lymphoma.

Infections that Weaken the Immune System

Infection with human immunodeficiency virus (HIV), also known as the AIDS virus, commonly causes immune system deficiency. HIV infection is a risk factor for developing certain types of non-Hodgkin lymphoma, such as Burkitt lymphoma and diffuse large B-cell lymphoma.

Infections that Cause Chronic Immune Stimulation

Some long-term infections may increase the risk of lymphoma by forcing a person's immune system to be on constant alert. As more lymphocytes are made to fight the infection, there is a greater chance that genetic mistakes can occur, which might eventually lead to lymphoma.

A type of bacteria, *Helicobacter pylori*, known to cause stomach ulcers, has also been linked to some lymphomas mucosa-associated lymphoid tissue (MALT lymphoma) of the stomach. The body's immune reaction to this infection increases the risk of non-Hodgkin lymphoma. The importance of this recent discovery is that antibiotics can help in treating some patients who have already developed lymphomas of the stomach due to *H. pylori*.

The hepatitis C virus (HCV) can also cause long-term infections. Recent reports have found that infection with HCV seems to be a risk factor for developing certain types of lymphoma.

Body Weight and Diet

Several studies have suggested that being overweight or obese may increase your risk of non-Hodgkin lymphoma. Some studies have also suggested that a diet high in vegetables may lower risk, although more research is needed to confirm this. In any event, maintaining a healthy weight and eating a healthy diet have many known health benefits outside of the possible beneficial effects on lymphoma risk.

Do We Know What Causes Non-Hodgkin Lymphoma?

Although researchers have found that non-Hodgkin lymphoma is linked with a number of risk factors, most patients with non-Hodgkin lymphoma do not have any known risk factors, and the causes of their cancers are unknown. This is complicated by the fact that lymphomas are actually a diverse group of cancers.

Still, scientists have made a lot of progress in understanding how certain changes in DNA can cause normal lymphocytes to become lymphoma cells. Normal human cells grow and function mainly based on the information contained in each cell's chromosomes. Human DNA is packaged in 23 pairs of chromosomes, which are long molecules of DNA in each cell. DNA is the chemical that makes up our genes - the instructions for how our cells

function. We resemble our parents because they are the source of our DNA. But DNA affects more than how we look.

Some genes contain instructions for controlling when cells grow and divide. Certain genes that speed up cell division are called *oncogenes*. Others that slow down cell division or cause cells to die at the right time are called *tumor suppressor genes*.

Each time a cell prepares to divide into 2 new cells, it must make a new copy of the DNA in its chromosomes. This process is not perfect, and errors can occur that may affect genes within the DNA. Cancers can be caused by DNA mutations (defects) that turn on oncogenes or turn off tumor suppressor genes.

Some people with certain types of cancer have DNA mutations they inherited from a parent that increased their risk for the disease. But non-Hodgkin lymphoma is not one of the cancer types often caused by these inherited mutations. In other words, there is no increased risk of lymphoma in the children of patients with lymphoma.

DNA mutations related to non-Hodgkin lymphoma are usually acquired after birth, rather than being inherited. Acquired mutations may result from exposure to radiation, cancer-causing chemicals, or infections, but often these mutations occur for no apparent reason. They seem to happen more often as we age, and lymphomas for the most part are a cancer of older people.

Translocations are a type of DNA change that can cause non-Hodgkin lymphoma to develop. A translocation means that DNA from one chromosome breaks off and becomes attached to a different chromosome. When this happens, oncogenes can be turned on or tumor suppressor genes can be turned off. Some lymphomas are characterized by specific chromosomal defects that may lead to the development of lymphoma. For example, most cases of follicular lymphoma have a translocation between chromosomes 14 and 18, which results in the turning on of the BCL2 oncogene. This stops the cell from dying at the right time.

Scientists are learning much about the exact genes involved in lymphoma. This information is already being used to develop new and more accurate tests to detect and classify certain types of non-Hodgkin lymphoma. Hopefully, these discoveries will soon be used in developing new treatments.

Even though researchers have found many of the key DNA changes that cause lymphoma and are beginning to understand how these changes develop in people with certain risk factors, they still do not know why most lymphomas develop in people with no apparent risk factors.

Lymphocytes (the cells from which lymphomas start) are immune system cells, so it's not surprising that changes in the immune system seem to play an important role in many cases of lymphoma.

- People with immune deficiencies (due to inherited conditions, drug treatment, organ transplants, or HIV infection) have a much higher chance of developing lymphoma than people without an immune deficiency.
- People with certain autoimmune diseases (where the immune system constantly attacks a certain part of the body) have an increased risk of getting lymphoma.
- People with certain chronic infections are also at increased risk, probably because the immune system is constantly making new lymphocytes to fight the infection, which increases the chances for mistakes in DNA.

Can Non-Hodgkin Lymphoma Be Prevented?

Most people with non-Hodgkin lymphoma have no known risk factors, so there was no way to prevent their lymphomas from developing. For now, the best way to reduce the risk for non-Hodgkin lymphoma is to try to prevent known risk factors such as immune deficiency.

The most preventable cause of immune deficiency is human immunodeficiency virus (HIV) infection. Medical advances have nearly eliminated contaminated blood as a source of HIV infections. HIV is spread among adults mostly through unprotected sex and among injection drug users through sharing contaminated needles. Preventing the spread of HIV would prevent many deaths from non-Hodgkin lymphoma. Treating HIV with anti-HIV drugs also seems to lower the chance of developing non-Hodgkin lymphoma significantly.

Preventing the spread of the human T-cell leukemia/lymphoma virus (HTLV-1) could have a great impact on non-Hodgkin lymphoma prevention in areas of the world where this virus is common, such as Japan and the Caribbean region. The virus is rare in the United States but seems to be increasing in some areas. The same strategies used to prevent HIV spread could also help control HTLV-1.

The recent discovery of the link between *Helicobacter pylori* infection and some lymphomas of the stomach offers a potential opportunity for prevention, but the benefit of this strategy has not been proven yet. Most people with *H. pylori* infection have no symptoms, and some have only mild heartburn. Finding the best way to detect and treat this infection in people without symptoms will require more research.

Some non-Hodgkin lymphomas are caused by treatment of cancers with radiation and chemotherapy or the use of immune system-suppressing drugs to avoid rejection of transplanted organs. Doctors are trying to find ways to treat cancer and organ transplant patients in ways that do not increase the risk of lymphoma as much. But for now, the life-threatening nature of the diseases requiring these treatments still usually outweighs the small risk of developing non-Hodgkin lymphoma many years later.

Can Non-Hodgkin Lymphoma Be Found Early?

At this time, no special tests are available that can find non-Hodgkin lymphoma early. The best strategy for early diagnosis is prompt attention to the signs and symptoms of this disease, which are discussed in the next section.

People with known risk factors for non-Hodgkin lymphoma (such as HIV infections, organ transplants, or prior cancer treatment) should receive careful, regular medical checkups. These people do not commonly develop lymphoma, but they and their doctors should be familiar with possible symptoms and signs of lymphoma.

How Is Non-Hodgkin Lymphoma Diagnosed?

If signs or symptoms suggest that a patient has non-Hodgkin lymphoma, exams and tests are done to find out for certain if this disease is present and, if so, to determine the exact type of lymphoma.

Signs and Symptoms of Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma may cause many different signs and symptoms, depending on its location in the body. In some cases it may not cause any symptoms until it grows quite large.

Lymph Nodes Near the Skin

Non-Hodgkin lymphoma can affect lymph nodes close to the surface of the body (such as on the sides of the neck, in the groin or underarm areas, or above the collar bone), which are easily seen or felt as lumps under the skin. These are often found by the patient, a family member, or a health care professional. Enlarged lymph nodes are more often caused by infections than by non-Hodgkin lymphoma.

Abdomen

When the lymphoid tissue inside the abdomen is involved, the abdomen can become tender, painful, and/or swollen. This may be due to either a tumor or to large collections of fluid. When lymphoma causes swelling near the intestines, the passage of feces may be blocked, which may lead to discomfort or abdominal pain. The pressure or blockage can also cause nausea or vomiting.

Lymphomas of the stomach often cause pain in the stomach, nausea, and reduced appetite.

Chest

When lymphoma starts in the thymus or lymph nodes in the chest, it may irritate or compress the nearby trachea (windpipe), which can cause coughing or trouble breathing.

The superior vena cava (SVC) is the large vein that carries blood from the head and arms back to the heart. It passes near the thymus and lymph nodes inside the chest. Lymphomas in this area may push on the SVC, which can cause the blood to back up in the veins. This is known as *SVC syndrome*. It can cause swelling in the face and arms and a bluish-red coloration of the head, arms, and upper chest. It can also cause trouble breathing and a change in consciousness if it affects the brain. The SVC syndrome can be life-threatening, and requires treatment right away.

Brain

Lymphomas of the brain, called *primary brain lymphomas*, can cause headache, trouble thinking and moving parts of the body, personality changes, and sometimes seizures.

Skin

Lymphomas of the skin can be seen and felt. They often appear as extremely itchy, red to purple lumps or nodules under the skin. (For more details, see the separate document *Lymphoma of the Skin*.)

General symptoms

Along with symptoms and signs resulting from local effects of cancer growth, non-Hodgkin lymphoma can produce generalized symptoms, such as:

- unexplained weight loss
- fever
- drenching night sweats (enough to soak clothing)
- severe itchiness

Doctors sometimes call these generalized effects *B symptoms*. The presence of B symptoms is often related to the presence of more rapidly growing lymphoma cells.

Diagnosing Non-Hodgkin Lymphoma by a Biopsy

The diagnosis of lymphoma may be delayed because enlarged lymph nodes are more often caused by infections than by non-Hodgkin lymphoma. Because of this, doctors often wait a few weeks to see if they remain large. Sometimes they prescribe antibiotics to see if the antibiotics cause the nodes to shrink.

If the node continues to grow or stays the same size, either a small piece of the node or, more commonly, the entire node is removed for viewing under the microscope and for other lab tests. This procedure is called a biopsy.

A biopsy may be needed imediately if the size, texture, or location of the node or the presence of other symptoms strongly suggests cancer is present. But there is no evidence that a delay in diagnosis of a few weeks is harmful in most instances. The exception to this would be a very rapidly growing lymphoma.

Types of Biopsies Used to Diagnose Non-Hodgkin Lymphoma

A biopsy is the only way to diagnose non-Hodgkin lymphoma. There are several biopsy procedures, and the doctor's choice is based on the unique aspects of each person's situation.

Excisional or incisional biopsy: This is the most common type of biopsy. In this procedure, a surgeon cuts through the skin to remove either the entire node (excisional biopsy) or a small part of a large tumor (incisional biopsy). If the node is near the skin surface, this is a simple operation that can be done with local anesthesia (numbing medicine). But if the node is inside the chest or abdomen, general anesthesia is used (where the patient is asleep). This method almost always provides enough of a sample to diagnose the exact type of non-Hodgkin lymphoma. It is preferred, if it can be done without too much discomfort to the patient.

Fine needle aspiration biopsy: In a fine needle aspiration (FNA) biopsy, the doctor uses a very thin needle attached to a syringe to withdraw (aspirate) a small amount of tissue from a tumor mass. For an enlarged node near the surface of the body, the doctor can aim the needle while feeling the node. If the tumor is deep inside the body, the doctor can guide the needle while viewing a computed tomography (CT) scan (see discussion of imaging tests later in this section).

The main advantage of FNA is that it does not require surgery. The disadvantage is that in many cases the thin needle cannot remove enough of a sample to make a definite diagnosis. But advances in lab tests (discussed later in this section) and the growing experience of many doctors with FNA have improved the accuracy of this procedure.

Most doctors will use FNA in patients already diagnosed with lymphoma to confirm that an enlarged lymph node or organ in another area also contains lymphoma. FNA is also very useful in diagnosing cancers that spread to nodes from other organs and in identifying nodes swollen by infection that don't need to be removed.

Other Types of Biopsies

These procedures may be done to diagnose lymphoma, but they are more often done to help stage (determine the extent of) a lymphoma that has already been diagnosed.

Bone marrow aspiration and biopsy: Bone marrow samples are obtained from a bone marrow aspiration and biopsy -- two tests that are often done at the same time. The samples are usually taken from the back of the pelvic (hip) bone, although in some cases they may be taken from the sternum (breastbone) or other bones.

In bone marrow *aspiration*, you lie on a table (either on your side or on your belly). After cleaning the area, the skin over the hip and the surface of the bone are numbed with local anesthetic, which may cause a brief stinging or burning sensation. A thin, hollow needle is then inserted into the bone and a syringe is used to suck out a small amount of liquid bone marrow (about 1 teaspoon). Even with the anesthetic, most patients still have some brief pain when the marrow is removed.

A bone marrow *biopsy* is usually done just after the aspiration. A small piece of bone and marrow (about 1/16 inch in diameter and 1/2 inch long) is removed with a slightly larger needle that is twisted as it is pushed down into the bone. The biopsy may also cause some brief pain. Once the biopsy is done, pressure will be applied to the site to help stop any bleeding.

These tests can be used for the initial diagnosis and for staging (to see how far the cancer has spread).

Lumbar puncture (spinal tap): This test looks for lymphoma cells in the cerebrospinal fluid (CSF), which is the liquid that bathes the brain and spinal cord.

For this test, the patient may lie on their side or sit up. The doctor first numbs an area in the lower part of the back near the spine. A small needle is then placed between the bones of the spine to withdraw some of the fluid.

Lab Tests Used to Diagnose and Classify Non-Hodgkin Lymphoma

All biopsy samples and fluids are looked at under a microscope by pathologist (a doctor with special training in recognizing cancer cells). The pathologist looks at the appearance, size, and shape of the cells and how the cells are arranged. This may reveal not only if the person has a lymphoma, but also what type of lymphoma it is. Because the diagnosis of lymphoma can be tricky, it helps if the pathologist is trained and experienced in diagnosing lymphomas.

Pathologists who specialize in diagnosing lymphoma can often tell which kind of lymphoma a patient has, but sometimes this exam does not provide a definite answer. In these cases, one or more of the following lab tests may be needed.

Immunohistochemistry

In this test, a part of the biopsy sample is treated with special antibodies (man-made versions of immune system proteins) that attach only to specific molecules on the cell surface. These antibodies cause color changes, which can be seen under a microscope. This test may be helpful in distinguishing different types of non-Hodgkin lymphoma from one another and from other diseases.

Flow Cytometry

Like immunohistochemistry, this test looks for certain substances on the outside surface of cells that help identify what types of cells they are. But this test can look at many more cells than immunohistochemistry.

For this test, a sample of cells is treated with special antibodies that stick to the cells only if these substances are present on their surfaces. The cells are then passed in front of a laser beam. If the cells now have antibodies attached to them, the laser will cause them to give off light, which can be measured and analyzed by a computer. Groups of cells can be separated and counted by these methods.

This is the most commonly used test for *immunophenotyping* -- classifying lymphoma cells according to the substances (antigens) on their surfaces. Different types of lymphocytes have different antigens on their surface. These antigens may also change as each cell matures.

Flow cytometry can help determine whether lymph node swelling is due to non-Hodgkin lymphoma, some other cancer, or a non-cancerous disease. It has also become very useful in helping doctors determine the exact type of non-Hodgkin lymphoma so that they can select the best treatment.

Cytogenetics

This technique allows scientists to evaluate the chromosomes (long strands of DNA) in the lymphoma cells. Scientists look at cells under a microscope to see if the chromosomes have any translocations (where part of one chromosome has broken off and is now attached to another chromosome), as happens in certain types of lymphoma. In addition to translocations, some lymphoma cells may have too many chromosomes, too few chromosomes, or other abnormalities of the chromosome. These changes can be used to help identify the type of lymphoma.

Molecular Genetic Studies

Tests of lymphoma cell DNA can detect most changes that are visible under a microscope in cytogenetic tests, as well as others that can't be seen.

Fluorescent in situ hybridization (FISH) is similar to cytogenetic testing. It can find most translocations that are visible under a microscope in standard cytogenetic tests, as well as some translocations too small to be seen with usual cytogenetic testing. It uses special fluorescent dyes that only attach to specific parts of chromosomes. FISH can be used to look for specific changes in chromosomes. It can be used on regular blood or bone marrow samples. It is very accurate and can usually provide results within a couple of days, which is why this test is now used in many medical centers.

Very sensitive DNA tests such as polymerase chain reaction (PCR) can also find translocations too small to be seen under a microscope, even if there are very few lymphoma cells present in a sample.

These tests can also detect certain genes that have been "turned on" and are contributing to the lymphoma cells' abnormal growth. In the future, as researchers learn more about lymphomas, these may become the most useful tests for determining what kind of lymphoma is present.

Other Lab Tests

Blood tests may be used to measure the amounts of certain types of cells and chemicals in the blood. While they are not used to diagnose lymphoma, they can be helpful in deciding how advanced the lymphoma is. In patients already known to have lymphoma, if the blood counts are low, it might indicate that the lymphoma is growing in the bone marrow and damaging normal blood cell production. Results of another blood test that measures levels of lactate dehydrogenase (LDH), will often be abnormally high in the blood of patients with fast-growing lymphomas.

Other blood tests can help detect liver or kidney problems caused by the spread of lymphoma cells or due to the side effects of certain chemotherapy drugs. Blood tests can also help determine if treatment is needed to correct low or high blood levels of certain minerals. Tests may also be done to make sure blood is clotting properly.

Imaging Tests

Imaging tests are used to find and look at tumors inside the body. These tests are an important part of staging (determining if and how much the cancer has spread) non-Hodgkin lymphoma.

Chest X-ray

X-rays of the chest are often done to look for enlarged lymph nodes in this area.

Computed Tomography

The computed tomography (CT) scan is a type of x-ray that produces detailed, cross-sectional images of your body. Unlike a regular x-ray, CT scans can show the detail in soft tissues (such as internal organs). This scan can help tell if any lymph nodes or organs in your body are enlarged. A CT scan is useful for looking for lymphoma in the abdomen, pelvis, chest, head, and neck.

Instead of taking one picture, as does a regular x-ray, a CT scanner takes many pictures as it rotates around you. A computer then combines these pictures into detailed images of the part of your body that is being studied.

Often after the first set of pictures is taken, you will receive an intravenous (IV) injection of a dye, or radiocontrast agent, which helps better outline structures in your body. You may also be asked to drink 1 to 2 pints of a solution of contrast material. This helps outline the intestine so that it is not mistaken for tumors if your doctor is looking for abnormal areas in your abdomen. A second set of pictures is then taken.

The IV injection of contrast dye can cause some flushing (a feeling of warmth, especially in the face). Some people are allergic and get hives or, rarely, more serious reactions like trouble breathing and low blood pressure. Be sure to tell the doctor if you have ever had a reaction to any contrast material used for x-rays.

CT scans take longer than regular x-rays. You need to lie still on a table while they are being done. During the test, the table moves in and out of the scanner, a ring-shaped machine that completely surrounds the table. You might feel a bit confined by the ring you have to lay in when the pictures are being taken.

In some cases, CT can be used to guide a biopsy needle precisely into a suspicious area. For this procedure, called a *CT-guided needle biopsy*, you remain on the CT scanning table while a radiologist moves a biopsy needle through the skin and toward the location of the mass. CT scans are repeated until the needle is within the mass. A fine needle biopsy sample (tiny fragment of tissue) or a core needle biopsy sample (a thin cylinder of tissue about ½-inch long and less than 1/8-inch in diameter) is then removed to be looked at under a microscope.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) scans use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed by the body and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern

into a very detailed image of parts of the body. A contrast material might be injected, just as with CT scans, but is used less often.

MRI scans are very helpful in looking at the brain and spinal cord. MRI scans take longer than CT scans -- often up to an hour. You may have to lie inside a narrow tube, which is confining and can upset people who are afraid of enclosed spaces. Newer, open MRI machines can help with this if needed. The MRI machine makes loud buzzing noises that you may find disturbing. Some places provide headphones to block this out.

Positron Emission Tomography

Positron emission tomography (PET) scans involve injecting glucose (a form of sugar) that contains a radioactive atom into the blood. Because cancer cells in the body grow rapidly, they absorb large amounts of the radioactive sugar. A special camera can then create a picture of areas of radioactivity in the body.

PET scans can help tell if an enlarged lymph node contains lymphoma or is benign. The picture is not finely detailed like a CT or MRI scan, but it provides helpful information about your whole body.

PET scans can be used to tell if a lymphoma is responding to treatment. Some doctors will repeat the PET scan after 1 or 2 courses of chemotherapy. If the chemotherapy is working, the lymph nodes will no longer take up the radioactive glucose. PET scans can also be used after treatment in helping decide whether an enlarged lymph node still contains lymphoma or is merely scar tissue.

Recently, newer devices have been developed that combine the PET scan with a CT scan. PET/CT scans can help pinpoint the exact location of the lymphoma.

Gallium Scan

During this procedure, the radiologist injects a small dose of radioactive gallium into a vein. It is attracted to lymph tissue in the body. A special camera can then detect the radioactivity, showing the location of the gallium. These tests can find tumors that might be non-Hodgkin lymphoma in bones and other organs.

The gallium scan will not detect most slow-growing lymphomas but will recognize many fast-growing (aggressive) lymphomas. It was used before PET scans were available and can still be useful in finding lymphoma deposits that the PET scan may miss. It is also useful in distinguishing infections from lymphomas when the diagnosis is not clear.

Bone Scan

For bone scans, a different radioactive substance is used. After it is injected, it travels to areas of the bone that are damaged. Lymphoma often causes bone damage , and a bone scan will find it. But a bone scan will also pick up non-cancerous problems, such as arthritis and fractures. This test is not generally used in the early staging process for non-Hodgkin lymphoma.

Ultrasound

Ultrasound uses sound waves and their echoes to produce a picture of internal organs or masses. For this test, a small, microphone-like instrument called a transducer is placed on the skin (which is first lubricated with a gel). It emits sound waves and picks up the echoes as they bounce off the organs. The echoes are converted by a computer into a black and white image that is displayed on a computer screen.

Ultrasound can be used to look inside your abdomen for enlarged lymph nodes or organs such as the liver and spleen. It can also detect kidneys that have become swollen because the outflow of urine has been blocked by enlarged lymph nodes. (It can't be used to look at organs or lymph nodes in the chest because the ribs block the sound waves.)

This is an easy test to have done, and it uses no radiation. You simply lie on a table, and a technician moves the transducer over the part of your body being looked at.

How Is Non-Hodgkin Lymphoma Staged?

Once non-Hodgkin lymphoma is diagnosed, tests are done to determine the stage (extent of spread) of the disease. The treatment and prognosis (outlook) for a patient with non-Hodgkin lymphoma depend on both the exact type and the stage of the lymphoma.

Tests used to gather information for staging include:

- physical exam
- blood tests
- imaging tests, including a chest x-ray and CT or MRI scan of the chest/abdomen/pelvis (other tests such as a PET scan may also be used)
- bone marrow aspiration and biopsy (often but not always done)
- lumbar puncture (spinal tap - this is not often done)

These tests are described in the section, *How Is Non-Hodgkin Lymphoma Diagnosed?*

Ann Arbor Staging System

The staging system most often used to describe the spread of non-Hodgkin lymphoma in adults is called the Ann Arbor staging system. The stages are described by Roman numerals I through IV (1-4). Lymphomas that affect organs outside of the lymph system (extranodal organs) have E added to their stage (for example, stage IIE), while those affecting the spleen have an S added.

Stage I

If either of the following is present it means the disease is stage I:

- The lymphoma is in a lymph node or nodes in only 1 region, such as the neck, groin, underarm, and so on.
- The cancer is found only in 1 area of a single organ outside of the lymph system (IE).

Stage II

If either of the following is present it means the disease is stage II:

- The lymphoma is in 2 or more groups of lymph nodes on the same side of (above or below) the diaphragm (the muscle that aids breathing and separates the chest and abdomen). For example, this might include nodes in the underarm and neck area but not the combination of underarm and groin nodes.
- The lymphoma extends locally from a single group of lymph node(s) into a nearby organ (IIE). It may also affect other groups of lymph nodes on the same side of the diaphragm.

Stage III

If either of the following is present it means the disease is stage III:

- The lymphoma is found in lymph node areas on both sides of (above and below) the diaphragm.
- The cancer may also have spread into an area or organ next to the lymph nodes (IIIE), into the spleen (IIIS), or both (IIIE, S).

Stage IV

If either of the following is present it means the disease is stage IV:

- The lymphoma has spread outside of the lymph system into an organ that is not right next to an involved node.
- The lymphoma has spread to the bone marrow, liver, brain or spinal cord, or the pleura (thin lining of the lungs).

Along with the Roman numeral, each stage is also assigned an A or B. The letter A is added if the person doesn't have any symptoms of lymphoma. The letter B is added (stage IIIB, for example) if any of the following symptoms are present:

- unexplained weight loss (more than 10% of weight)
- soaking night sweats
- unexplained fever > 100°

Although the type and stage of the lymphoma provide useful information about a person's prognosis, for some types of lymphomas (especially fast-growing ones) the stage is not too helpful on its own. Other factors are looked at to help overcome this.

International Prognostic Index

The International Prognostic Index (IPI) was first developed to help determine the outlook for people with fast-growing lymphomas. However, it has proven useful for most other lymphomas as well (other than slow-growing follicular lymphomas, which are discussed below). The index depends on 5 factors:

- a person's age
- the stage of the lymphoma
- whether or not it is in organs outside the lymph system
- a person's performance status (PS) -- how well the person can complete normal daily activities
- the blood (serum) level of lactate dehydrogenase (LDH) -- this level goes up in the presence of fast-growing tumors

Good Prognostic Factors	**Poor Prognostic Factors**
Age 60 or below	Age above 60
Stage I or II	Stage III or IV
No lymphoma outside of lymph nodes, or lymphoma in only 1 area outside of lymph nodes	Lymphoma present in more than 1 organ of the body outside of lymph nodes
PS: Able to function normally	PS: Needs a lot of help with daily activities
Serum LDH is normal	Serum LDH is elevated

Each poor prognostic factor, is assigned 1 point. People without any poor prognostic factors would have a score of 0, while those with all of the poor prognostic factors would have a score of 5. The index divides people with lymphomas into 4 risk groups:

- low (0 or 1 poor prognostic factors)
- low intermediate (2 poor prognostic factors)
- high intermediate (3 poor prognostic factors)
- high (4 or 5 poor prognostic factors)

In the studies used to develop the index, about 75% of people in the lowest risk group lived longer than 5 years, whereas only about 30% of people in the highest group lived 5 years or longer. While these numbers show the difference the index scores can make, newer treatments have been developed since then, so current survival rates are likely to be higher.

This prognostic index is important because it allows doctors to plan treatment better than they could from just the pathology report and staging information. This has become more important as new, more effective treatments have been developed that sometimes have more side effects. The index helps doctors figure out whether these treatments are needed. It also gives patients information about the outlook for their future.

Follicular Lymphoma International Prognostic Index

Although the IPI is useful for most lymphomas, it is not as helpful for follicular lymphomas, which tend to be slower growing. Doctors have developed the Follicular Lymphoma International Prognostic Index (FLIPI) specifically for this type of lymphoma. It uses slightly different prognostic factors than the IPI.

Good Prognostic Factors	**Poor Prognostic Factors**
Age 60 or below	Age above 60
Stage I or II	Stage III or IV
Blood hemoglobin 12 g/dL or above	Blood hemoglobin level below 12 g/dL
4 or fewer lymph node areas affected	More than 4 lymph node areas affected
Serum LDH is normal	Serum LDH is elevated

Patients are assigned a point for each poor prognostic factor. People without any poor prognostic factors would have a score of 0, while those with all poor prognostic factors would have a score of 5. The index then divides people with follicular lymphoma into 3 groups:

- low risk: no or 1 poor prognostic factor(s)
- intermediate risk: 2 poor prognostic factors
- high risk: 3 or more poor prognostic factors

The study used to develop the FLIPI included a group of about 1,800 patients and was reported in 2004. It yielded the following survival rates:

Risk Group	**5-year Survival Rate**	**10-year Survival Rate**
low-risk	91%	71%
intermediate-risk	78%	51%
high-risk	53%	36%

These rates reflect the number of people who lived for *at least* 5 or 10 years after being diagnosed – many people lived longer than this.

How Is Non-Hodgkin Lymphoma Treated?

This information represents the views of the doctors and nurses serving on the American Cancer Society's Cancer Information Database Editorial Board. These views are based on their interpretation of studies published in medical journals, as well as their own professional experience.

The treatment information in this document is not official policy of the Society and is not intended as medical advice to replace the expertise and judgment of your cancer care team. It is intended to help you and your family make informed decisions, together with your doctor.

Your doctor may have reasons for suggesting a treatment plan different from these general treatment options. Don't hesitate to ask him or her questions about your treatment options.

This section starts by describing the types of treatments used for non-Hodgkin lymphoma. This is followed by a discussion of the typical treatment options based on the type of lymphoma, as well as the stage (extent) and other prognostic factors when these are important.

Some General Comments About Treatment

In recent years, there has been much progress in treating non-Hodgkin lymphoma. The treatment options for people with lymphoma depend on the type of lymphoma and its stage, as well as the other prognostic factors of the lymphoma. Of course, no 2 patients are exactly alike, and standard options are often tailored to each patient's unique situation.

It is important to understand all treatment options. It is often a good idea to seek a second opinion. This can provide additional information and help you feel more confident about the treatment plan that is chosen.

Several different types of treatment can be used against non-Hodgkin lymphoma.

Surgery

Surgery is often used to obtain a tissue sample to diagnose and classify a lymphoma, but it is rarely used as a treatment option.

In rare cases it may be used to treat lymphomas that start in certain organs outside of the lymph system, such as the thyroid or stomach, and that have not spread beyond these organs. But for treating lymphoma that is completely confined to one area, radiation therapy is usually preferred over surgery.

Radiation Therapy

Radiation therapy uses high-energy rays to kill cancer cells. Radiation focused on a cancer from a source outside the body is called *external beam radiation*. This is the type of radiation therapy most often used to treat non-Hodgkin lymphoma. Radiation might be used as the main (primary) treatment of early (stage I or II) non-Hodgkin lymphomas because these tumors respond very well to radiation. But more often, it is used along with chemotherapy.

Radiation therapy can also be used to ease (palliate) symptoms caused by lymphoma that has spread to internal organs, such as the brain or spinal cord, or when a tumor is causing pain because it is pressing on nerves.

Possible Side Effects

Immediate side effects of radiation therapy may include mild skin problems or fatigue. Radiation of the abdomen may cause upset stomach and diarrhea. Often these effects go away after a short while.

Longer-term side effects of radiation can sometimes be a bigger problem.

- Chest radiation therapy may cause lung damage and lead to trouble breathing. Lung cancer can also occur after lung radiation, particularly in smokers, though it is not common.

- Side effects of brain radiation therapy may include headaches and trouble thinking. When they happen, they usually become most serious 1 or 2 years after treatment.

- Other types of cancer can form in the area that received radiation. Although a person's risk of this happening is not high, because so many people with lymphoma are cured, this is a major problem. Some studies estimate the incidence of new cancers in areas receiving radiation may be as high as 1% per year.

Radiation may also make the side effects of chemotherapy worse.

Chemotherapy

Chemotherapy is the use of anti-cancer drugs that are injected into a vein or a muscle or taken by mouth. These drugs enter the bloodstream and reach almost all areas of the body, making this treatment very useful for lymphoma. In some patients, chemotherapy is given by injection into the spinal fluid (intrathecal injection) to treat lymphoma cells on the surface of the brain and spinal cord. Depending on the type and the stage of the lymphoma, chemotherapy may be used alone or in combination with radiation therapy.

Many drugs are useful in treating lymphoma patients. Often, several drugs are combined. The treatments all have different schedules, but they are usually repeated several times in cycles given 3 or 4 weeks apart. Most chemotherapy treatments are given on an outpatient basis (in the doctor's office or clinic or hospital outpatient department) but some require a hospital stay.

The most common combination of drugs is called CHOP. This includes the drugs cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin) and prednisone. Another common combination leaves out doxorubicin and is called CVP. Other commonly used chemotherapy drugs are chlorambucil (which is a pill), fludarabine, and etoposide. For information, see the American Cancer Society documents on these drugs.

Sometimes a patient may take one chemotherapy combination for several cycles and later switch to a different one if the first combination doesn't seem to be working. This is usually determined by imaging tests such as CT scans or by physical exam (for example, if an enlarged lymph node has not shrunk).

Possible Side Effects

Chemotherapy drugs work by attacking cells that are dividing quickly, which is why they work against lymphoma cells. But other cells in the body, such as those in the bone marrow, the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells are also likely to be affected by chemotherapy, which can lead to side effects.

The side effects of chemotherapy depend on the type and dose of drugs given and the length of time they are taken. These side effects can include:

- hair loss
- mouth sores
- loss of appetite
- nausea and vomiting
- increased chance of infections (due to low white blood cell counts)
- easy bruising or bleeding (due to low blood platelet counts)
- fatigue (due to low red blood cell counts)

These side effects are usually short-term and go away after treatment is finished.

There are often ways to lessen these side effects. For example, drugs are usually given to help prevent or reduce nausea and vomiting.

Drugs known as growth factors (G-CSF or GM-CSF, for example) are sometimes given to help the white blood cells recover from the effects of chemotherapy and thus reduce the chance of infection. Antibiotics may also be given before signs of infection appear, but they are usually given at the earliest sign of an infection, such as a fever.

If your white blood cell counts are very low during treatment, you can help reduce your risk of infection by carefully avoiding exposure to germs. During this time, your doctor may advise you to:

- Wash your hands often.
- Avoid fresh, uncooked fruits and vegetables and other foods that might carry germs.
- Avoid fresh flowers and plants because they may carry mold.

- Make sure other people wash their hands before they come in contact with you.
- Avoid large crowds and people who are sick (wearing a surgical mask offers some protection in these situations).

Because many of the side effects of chemotherapy are caused by low white blood cell counts, some people find it helpful to keep track of their counts. If you are interested in doing this, ask your doctor or nurse about your blood cell counts and what these numbers mean.

If your platelet counts are very low, you may be given drugs or platelet transfusions to help protect against bleeding. Fatigue caused by anemia (very low red blood cell counts) can be treated with drugs or with red blood cell transfusions.

Organs that could be directly damaged by certain chemotherapy drugs include the bone marrow, kidneys, liver, testes, ovaries, brain, heart, and lungs. If serious side effects occur, chemotherapy may have to be reduced or stopped, at least for a short time. Careful monitoring and adjustment of drug doses are important because some side effects to organs can be permanent. If the patient is monitored carefully, however, these side effects rarely occur.

Tumor lysis syndrome is a possible side effect caused by the rapid killing of large numbers of lymphoma cells that are very sensitive to chemotherapy. When the cells are killed, they break open and release their contents into the bloodstream. This can overwhelm the kidneys, which cannot get rid of all of these substances at once. Excess amounts of certain minerals may also affect the heart and nervous system. This side effect can be prevented by giving the patient extra fluids and certain drugs, such as sodium bicarbonate, allopurinol, and rasburicase.

Chemotherapy can also cause side effects that can last over time or that might not occur until years after treatment. One of these is damage to bone marrow cells that can eventually result in leukemia. Also, some drugs can damage heart muscle. Other drugs can sometimes cause damage to the kidneys or nerves.

Biological Therapy (Immunotherapy)

Biological therapies use man-made versions of substances normally made by the immune system. These substances may kill lymphoma cells, slow their growth, or activate the patient's own immune system to more effectively fight the lymphoma.

Monoclonal Antibodies

Antibodies are proteins normally made by the immune system to help fight infections. Man-made versions, called monoclonal antibodies, can be designed to attack a specific target, such as a substance on the surface of lymphocytes (the cells in which lymphomas start).

Several monoclonal antibodies are now being used to treat lymphoma.

Rituximab (Rituxan) is an antibody that recognizes and attaches to a substance called CD20 found on the surface of some types of lymphoma cells. This attachment seems to cause the lymphoma cell to die. Patients usually get intravenous (IV) infusions each week for 4 weeks. The treatments can be given in the doctor's office or clinic. Common side effects are usually mild but may include chills, fever, nausea, rashes, fatigue, and headaches. Even if these symptoms occur during the first rituximab infusion, it is very unusual for them to recur with later doses.

Newer forms of monoclonal antibodies are similar to rituximab but have radioactive molecules attached to them, which may help them work better.

- Ibritumomab tiuxetan (Zevalin) is another antibody directed at CD20, but this one has radioactive yttrium attached to it.
- Tositumomab (Bexxar), which is also an antibody directed at CD20, although this one has radioactive iodine attached to it.

While these drugs may eventually prove to be more powerful than rituximab, they are somewhat harder for doctors to give (because of the radiation dosing involved). Another limitation is that they cannot be used with chemotherapy because they also lower blood counts. At this time they are generally used if chemotherapy and/or rituximab are no longer working.

Alemtuzumab (Campath) is an antibody directed at the CD52 antigen. It is useful in some cases of chronic lymphocytic leukemia (CLL) and also some types of peripheral T-cell lymphomas.

Interferon

Interferon is a hormone-like protein made by white blood cells to help the immune system fight infections. Some studies have suggested that giving man-made interferon can cause some types of non-Hodgkin lymphomas to shrink or stop growing.

The side effects of this treatment include fatigue, fever, chills, headaches, muscle and joint aches, and mood changes. Because of these side effects, interferon is not used very often. It may be given to some patients in addition to chemotherapy.

Bone Marrow or Peripheral Blood Stem Cell Transplant

Stem cell transplants are sometimes used to treat lymphoma patients who are in remission or who have a relapse during or after treatment. Although only a small number of patients with

NHL are treated with this therapy, this number is growing. About 4,000 non-Hodgkin lymphoma patients in the US and Canada receive a stem cell transplant each year.

The usual doses of chemotherapy drugs can cause serious side effects to quickly dividing tissues such as the bone marrow. Even though higher doses of these drugs might be more effective in treating the lymphoma, they are not given because the severe damage to bone marrow cells would cause lethal shortages of blood cells, and other vital organs would likely be damaged as well.

A stem cell transplant (SCT) allows doctors to use higher doses of chemotherapy and sometimes radiation therapy. After treatment is finished, the patient receives a transplant of blood-forming stem cells to restore the bone marrow.

Blood-forming stem cells used for a transplant are obtained either from the blood (for a peripheral blood stem cell transplant, or PBSCT) or from the bone marrow (for a bone marrow transplant, or BMT). Peripheral blood stem cells are obtained from a procedure similar to a blood donation, while bone marrow donation is usually done in an operating room under general anesthesia (while the donor is asleep). Bone marrow transplants were more common in the past, but they have largely been replaced by PBSCTs.

Types of Transplants

There are 2 main types of stem cell transplants. They differ with regard to the source of the blood-forming stem cells.

Allogeneic stem cell transplant: In this type of transplant, the stem cells come from someone else -- usually a donor whose tissue type is almost identical to the patient's. Tissue type is based on certain substances present on the surface of cells in the body. These substances can cause the immune system to react against the cells. Therefore, the closer a tissue match is between the donor and the recipient, the better the chance the transplanted cells will "take" and begin making new blood cells.

The donor may be a brother or sister or a matched unrelated donor (MUD). The stem cells from an unrelated donor come from volunteers whose tissue type has been stored in a central registry and matched with that of the patient. Sometimes umbilical cord stem cells are used. These cord blood stem cells come from blood drained from the umbilical cord and placenta after a baby is born and the umbilical cord is cut.

Allogeneic transplants have limited usefulness in treating lymphoma because it is often hard to find a matched donor. Another drawback is that side effects of this treatment are often too severe for people over 55 years old. About 1 out of 4 transplants for lymphoma is of this kind.

Autologous stem cell transplant: In this type of transplant, a patient's own stem cells are removed from his or her bone marrow or peripheral blood. They are collected on several occasions in the weeks before treatment. The cells are stored while the person gets treatment (high-dose chemotherapy and/or radiation) and then are reinfused into the patient's blood.

With some types of lymphoma that tend to spread to the bone marrow or blood, an autologous transplant may not be possible because it may be hard to get stem cells free of lymphoma cells. Even after purging (treating the stem cells in the lab to kill or remove lymphoma cells), returning some lymphoma cells with the stem cell transplant is possible.

With either type of transplant, the blood-forming stem cells are carefully frozen and stored before treatment. The patient then receives high-dose chemotherapy and sometimes whole body radiation treatment as well. (Radiation shields are used to protect the lungs, heart, and kidneys from damage during radiation therapy.)

This destroys remaining cancer cells, but it also kills all or most normal cells in the bone marrow. After therapy, the frozen stem cells are thawed and returned to the body like a blood transfusion. The stem cells settle into the patient's bone marrow over the next several days and start to grow and make new blood cells.

The Transplant Procedure

The patient getting the stem cell transplant may be admitted to the bone marrow transplant (BMT) unit of the hospital or receive treatment as an outpatient depending on a number of factors.

If treated as an inpatient, the patient is usually admitted to the hospital on the day before chemotherapy begins. He or she will usually stay in the hospital (BMT unit) until after the high-dose chemotherapy and the stem cells have been given, and until the stem cells have started making new blood cells again (see below).

If this is done as an outpatient procedure, patients and their families must be able to spot complications requiring their doctor's attention. Unless they live close to the transplant center, they will be asked to stay in a nearby hotel.

After the proper education, the patient starts high-dose chemotherapy and may be given high-dose whole body radiation. The chemotherapy and radiation treatments are meant to destroy any remaining cancer cells. They also kill the normal cells of the bone marrow and the immune system. This prevents the stem cell transplant (graft) from being rejected. Once treatment is complete, the stem cells (autologous or allogeneic) are given through a vein or venous access line, just like a blood transfusion. The stem cells migrate to the bone marrow.

In an allogeneic SCT, the person getting the transplant is given drugs such as cyclosporine, methotrexate, tacrolimus, or prednisone to prevent acute graft-versus-host-disease (GVHD; see the section Graft Versus Host Disease for a more thorough description). In GVHD, the immune cells in the donor's marrow or cord blood (the graft) attack the patient's body (the host).

For the next 3 to 4 weeks the patient is given as much supportive therapy as needed. This can include IV nutrition; antibiotics to treat bacteria, viral, and fungal infections; red blood cell and/or platelet transfusions; or other medicines as needed.

Usually around 2 to 3 weeks after the stem cells have been infused , they begin making new white blood cells. This is followed by the new platelet production and, several weeks later, by new red blood cell production. Because of the high risk of serious infections right after treatment, patients remain in protective isolation (where exposure to germs is kept to a minimum) until a measure of their white blood cells-- the absolute neutrophil count (ANC)-- rises above 500. They can usually leave the hospital when their ANC nears 1,000.

Patients then typically make regular visits to the outpatient transplant clinic for about 6 months, after which time their care is continued by their regular oncologist or internist. At this point, they only come back to the clinic for regular exams or if they have symptoms that should be checked by their doctor.

Practical Points

Bone marrow or peripheral blood SCT is a complex treatment. If the doctors think a patient may benefit from a transplant, it should be done at a hospital where the staff has experience with the procedure and with managing the recovery phase. Some stem cell transplant programs may not have experience in certain types of transplants, especially transplants from unrelated donors.

SCT is very expensive (more than $100,000) and often requires a lengthy hospital stay. Because some insurance companies may view it as an experimental treatment, they may not pay for the procedure. Find out what your insurer will cover before deciding on a transplant so you will have an idea of what you might have to pay.

Possible Side Effects

Side effects from a stem cell transplant are generally divided into early and long-term effects. The early complications and side effects are basically the same as those caused by any other type of high-dose chemotherapy (see the Chemotherapy section of this document), and are caused by damage to the bone marrow and other quickly growing tissues of the body. They can include low blood cell counts (with increased risks of infection and bleeding), nausea, vomiting, loss of appetite, mouth sores, and hair loss.

Complications and side effects that can persist for a long time or that may occur many years after the transplant include:

- graft-versus-host disease (GVHD), which occurs only in allogeneic (donor) transplants
- infertility and premature menopausal symptoms in female patients (caused by damage to the ovaries)
- infertility in male patients
- damage to the thyroid gland that can cause problems with metabolism
- cataracts (damage to the lens of the eye that can affect vision)
- damage to the lungs, causing shortness of breath
- bone damage called aseptic necrosis (if damage is severe, the patient may need to have part of the affected bone and the joint replaced)
- possible development of leukemia several years later

Graft-versus-host disease: This is one of the most serious complications of allogeneic (donor) stem cell transplants. It occurs because the immune system of the patient is taken over by that of the donor. The donor immune system then may recognize the patient's own body tissues as foreign and may react against them. Symptoms can include severe skin rashes with itching, mouth sores (which can affect eating), nausea, and severe diarrhea. Liver damage may cause yellowing of the skin and eyes (jaundice). The lungs may also be damaged. The patient may also become easily fatigued and develop muscle aches.

Graft versus host disease (GVHD) is often described as either acute or chronic, based on how soon after the transplant it begins. Sometimes GVHD can become disabling, and if it is severe enough, it can be fatal. Usually, immune suppressing drugs can be used to control GVHD.

On the positive side, the graft-versus-host disease also leads to "graft-versus-lymphoma" activity. Any lymphoma cells remaining after the chemotherapy and radiation therapy are often killed by immune reactions of the donor cells since the lymphoma cells are seen as foreign by the donor's immune system as well. Mild graft-versus-host disease can be a good thing.

Non-myeloablative Transplant (Mini-transplant)

Most patients over the age of 55 can't tolerate a standard allogeneic transplant that uses high doses of chemotherapy. Some, however, may be able to have a non-myeloablative transplant (also known as a mini-transplant or reduced-intensity transplant), where they receive lower doses of chemotherapy and radiation that do not completely destroy the cells in their bone marrow. They then receive the allogeneic (donor) stem cells. These cells enter the body and establish a new immune system, which sees the lymphoma cells as foreign and attacks them (a "graft-versus-lymphoma" effect).

Doctors have learned that if they use small doses of certain chemotherapy drugs and low doses of total body radiation, an allogeneic transplant can still work with much less toxicity. In fact, a patient can receive a non-myeloablative transplant as an outpatient.

The major complication is graft-versus-host disease, which may damage the patient's body tissue. Researchers are looking for ways to eliminate the graft-versus-host response while keeping the graft-versus-lymphoma effect.

For more information on these procedures, see the American Cancer Society document, *Bone Marrow and Peripheral Blood Stem Cell Transplants.*

Clinical Trials

You have had to make a lot of decisions since you've been told you have cancer. One of the most important decisions you will make is deciding which treatment is best for you. You may have heard about clinical trials being done for your type of cancer. Or maybe someone on your health care team has mentioned a clinical trial to you. Clinical trials are one way to get state-of-the art cancer care. Still, they are not right for everyone.

Here we will give you a brief review of clinical trials. Talking to your health care team, your family, and your friends can help you make the best treatment choice for you.

What Are Clinical Trials?

Clinical trials are carefully controlled research studies that are done with patients. These studies test whether a new treatment is safe and how well it works in patients, or they may test new ways to diagnose or prevent a disease. Clinical trials have led to many advances in cancer prevention, diagnosis, and treatment.

The Purpose of Clinical Trials

Clinical trials are done to get a closer look at promising new treatments or procedures in patients. A clinical trial is only done when there is good reason to believe that the treatment, test, or procedure being studied may be better than the one used now. Treatments used in clinical trials are often found to have real benefits and may go on to become tomorrow's standard treatment.

Clinical trials can focus on many things, such as:

- new uses of drugs that are already approved by the US Food and Drug Administration (FDA)
- new drugs that have not yet been approved by the FDA

- non-drug treatments (such as radiation therapy)
- medical procedures (such as types of surgery)
- herbs and vitamins
- tools to improve the ways medicines or diagnostic tests are used
- medicines or procedures to relieve symptoms or improve comfort
- combinations of treatments and procedures

Researchers conduct studies of new treatments to try to answer the following questions:

- Is the treatment helpful?
- What's the best way to give it?
- Does it work better than other treatments already available?
- What side effects does the treatment cause?
- Are there more or fewer side effects than the standard treatment used now?
- Do the benefits outweigh the side effects?
- In which patients is the treatment most likely to be helpful?

Phases of Clinical Trials

There are 4 phases of clinical trials, which are numbered I, II, III, and IV. We will use the example of testing a new cancer treatment drug to look at what each phase is like.

Phase I clinical trials: The purpose of a phase I study is to find the best way to give a new treatment safely to patients. The cancer care team closely watches patients for any harmful side effects.

For phase I studies, the drug has already been tested in lab and animal studies, but the side effects in patients are not fully known. Doctors start by giving very low doses of the drug to the first patients and increase the doses for later groups of patients until side effects appear or the desired effect is seen. Doctors are hoping to help patients, but the main purpose of a phase I trial is to test the safety of the drug.

Phase I clinical trials are often done in small groups of people with different cancers that have not responded to standard treatment, or that keep coming back (recurring) after treatment. If a drug is found to be reasonably safe in phase I studies, it can be tested in a phase II clinical trial.

Phase II clinical trials: These studies are designed to see if the drug works. Patients are given the best dose as determined from phase I studies. They are closely watched for an effect on the cancer. The cancer care team also looks for side effects.

Phase II trials are often done in larger groups of patients with a specific cancer type that has not responded to standard treatment. If a drug is found to be effective in phase II studies, it can be tested in a phase III clinical trial.

Phase III clinical trials: Phase III studies involve large numbers of patients -- most often those who have just been diagnosed with a specific type of cancer. Phase III clinical trials may enroll thousands of patients.

Often, these studies are randomized. This means that patients are randomly put in one of two (or more) groups. One group (called the control group) gets the standard, most accepted treatment. Another group (or more than one group) will get the new treatment being studied. All patients in phase III studies are closely watched. The study will be stopped early if the side effects of the new treatment are too severe or if one group has much better results than the others.

Phase III clinical trials are usually needed before the FDA will approve a treatment for use by the general public.

Phase IV clinical trials: Once a drug has been approved by the FDA and is available for all patients, it is still studied in other clinical trials (sometimes referred to as phase IV studies). This way more can be learned about short-term and long-term side effects and safety as the drug is used in larger numbers of patients with many types of diseases. Doctors can also learn more about how well the drug works, and if it might be helpful when used in other ways (such as in combination with other treatments).

What It Will Be Like to Be in a Clinical Trial

If you are in a clinical trial, you will have a team of experts taking care of you and watching your progress very carefully. Depending on the phase of the clinical trial, you may receive more attention (such as having more doctor visits and lab tests) than you would if you were treated outside of a clinical trials. Clinical trials are specially designed to pay close attention to you.

However, there are some risks. No one involved in the study knows in advance whether the treatment will work or exactly what side effects will occur. That is what the study is designed to find out. While most side effects go away in time, some may be long-lasting or even life threatening. Keep in mind, though, that even standard treatments have side effects. Depending on many factors, you may decide to enter (enroll in) a clinical trial.

Deciding to Enter a Clinical Trial

If you would like to take part in a clinical trial, you should begin by asking your doctor if your clinic or hospital conducts clinical trials. There are requirements you must meet to take part in any clinical trial. But whether or not you enter (enroll in) a clinical trial is completely up to you.

Your doctors and nurses will explain the study to you in detail. They will go over the possible risks and benefits and give you a form to read and sign. The form says that you understand the clinical trial and want to take part in it. This process is known as giving your informed consent. Even after reading and signing the form and after the clinical trial begins, you are free to leave the study at any time, for any reason.

Taking part in a clinical trial does not keep you from getting any other medical care you may need.

To find out more about clinical trials, talk to your cancer care team. Here are some questions you might ask:

- Is there a clinical trial that I could take part in?
- What is the purpose of the study?
- What kinds of tests and treatments does the study involve?
- What does this treatment do? Has it been used before?
- Will I know which treatment I receive?
- What is likely to happen in my case with, or without, this new treatment?
- What are my other choices and their pros and cons?
- How could the study affect my daily life?
- What side effects can I expect from the study? Can the side effects be controlled?
- Will I have to stay in the hospital? If so, how often and for how long?
- Will the study cost me anything? Will any of the treatment be free?
- If I am harmed as a result of the research, what treatment would I be entitled to?
- What type of long-term follow-up care is part of the study?
- Has the treatment been used to treat other types of cancers?

How Can I Find Out More About Clinical Trials That Might Be Right for Me?

The American Cancer Society offers a clinical trials matching service for patients, their family, and friends. You can reach this service at 1-800-303-5691 or on our Web site at http://clinicaltrials.cancer.org.

Based on the information you give about your cancer type, stage, and previous treatments, this service can put together a list of clinical trials that match your medical needs. The service will also ask where you live and whether you are willing to travel so that it can look for a treatment center that you can get to.

You can also get a list of current clinical trials by calling the National Cancer Institute's Cancer Information Service toll free at 1-800-4-CANCER (1-800-422-6237) or by visiting the NCI clinical trials Web site at www.cancer.gov/clinicaltrials.

For even more information on clinical trials, the American Cancer Society has a document called *Clinical Trials: What You Need to Know.* You can read this on the Web site, www.cancer.org, or have it sent to you by calling 1-800-ACS-2345.

Complementary and Alternative Therapies

When you have cancer you are likely to hear about ways to treat your cancer or relieve symptoms that are different from mainstream (standard) medical treatment. These methods can include vitamins, herbs, and special diets, or methods such as acupuncture or massage—among many others. You may have a lot of questions about these treatments. Here are some you may have thought of already:

- How do I know if a non-standard treatment is safe?
- How do I know if it works?
- Should I try one or more of these treatments?
- What does my doctor know/think about these methods? Should I tell the doctor that I'm thinking about trying them?
- Will these treatments cause a problem with my standard medical treatment?
- What is the difference between "complementary" and "alternative" methods?
- Where can I find out more about these treatments?

The Terms Can Be Confusing

Not everyone uses these terms the same way, so it can be confusing. The American Cancer Society uses *complementary* to refer to medicines or methods that are used *along with* your regular medical care. *Alternative* medicine is a treatment used *instead of* standard medical treatment.

Complementary Methods

Complementary methods, for the most part, are not presented as cures for cancer. Most often they are used to help you feel better. Some methods that can be used in a complementary way are meditation to reduce stress, acupuncture to relieve pain or aromatherapy or peppermint tea to relive nausea. There are many others. Some of these methods are known to help, while others have not been tested. Some have been proven not be helpful. A few have even been found harmful. However, some of these methods may add to your comfort and well-being.

There are many complementary methods that you can safely use right along with your medical treatment to help relieve symptoms or side effects, to ease pain, and to help you

enjoy life more. For example, some people find methods such as aromatherapy, massage therapy, meditation, or yoga to be useful.

Alternative Methods

Alternative methods are those that are used instead of standard medical care. These treatments have not been proven safe and effective in clinical trials. Some of these methods may even be dangerous and some have life-threatening side effects. The main danger with trying any of these is that you may lose the chance to benefit from standard treatment. Delays or interruptions in your standard medical treatment may give the cancer more time to grow. Most of these methods are not covered by insurance.

Deciding What to Do

It is easy to see why people with cancer may consider alternative methods. You want to do all you can to fight the cancer. Sometimes mainstream treatments such as chemotherapy can be hard to take, or they may no longer be working.

Sometimes people suggest that their method can cure your cancer without having serious side effects, and it's normal to want to believe them. But the truth is that most non-standard methods of treatment have not been tested and proven to be effective for treating cancer. As you consider your options, here are 3 important steps you can take:

- Talk to your doctor or nurse about any method you are thinking about using.
- Check the list of "red flags" below.
- Contact the American Cancer Society at 1-800-ACS-2345 to learn more about complementary and alternative methods in general and to learn more about the specific methods you are thinking about.

Red Flags

You can use the questions below to spot treatments or methods to avoid. A "yes" answer to any one of these questions should raise a "red flag."

- Does the treatment promise a cure for all or most cancers?
- Are you told not to use standard medical treatment?
- Is the treatment or drug a "secret" that only certain people can give?
- Does the treatment require you to travel to another country?
- Do the promoters attack the medical or scientific community?

The Decision Is Yours

Decisions about how to treat or manage your cancer are always yours to make. If you are thinking about using a complementary or alternative method, be sure to learn about the method and talk to your doctor about it. With reliable information and input from your health care team, you may be able to safely use the methods that can help you while avoiding those that could be harmful.

Treatment of Specific Lymphomas

Treatment usually depends both on the type of lymphoma and on the extent of the disease in the body. Other factors may be important as well.

B-Cell Lymphomas

Diffuse large B-cell lymphoma : The main treatment for diffuse large B-cell lymphoma (DLBCL) is chemotherapy, usually with a regimen of 4 drugs known as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Recent studies have found that patients respond well to adding the monoclonal antibody rituximab (Rituxan) to CHOP. It is too early to tell whether the cure rate will be higher, but early results are very encouraging. Most cancer specialists in the United States are using this combination (known as R-CHOP) for about 6 months to treat patients with diffuse large B-cell lymphoma. Many consider this the standard treatment.

If the lymphoma is localized to 1 or 2 lymph node groups on the same side of the abdomen (that is, if it is stage I or II), radiation therapy to the lymph node areas may be added to treatment with R-CHOP. If patients with stage I or II lymphoma , are to be given radiation, then the treatment time with R-CHOP may be shortened. Sometimes if the lymphoma mass is large, radiation may be added after a full course of treatment (about 6 months) with R-CHOP.

For stage III or IV lymphoma, most doctors will give R-CHOP as first-line treatment. Another approach is to give CHOP, but to shorten the interval between chemotherapy treatments from 3 weeks to 2 weeks. This means drugs will need to be used to boost the white blood cell count -- either G-CSF (Neupogen or Neulasta) or GM-CSF (Leukine). This is still experimental -- it isn't known if this is better than CHOP plus rituximab.

Some studies have suggested that for patients under 60 years old with a high International Prognostic Index score, high-dose chemotherapy followed by an autologous stem cell transplant seems to be better than chemotherapy alone. But these were done before rituximab was part of the standard treatment approach, so it's not clear if this treatment is better than CHOP and rituximab. As of yet, it is not clear if transplants are better than standard treatment as the initial treatment for some lymphomas.

If the lymphoma recurs (comes back) after treatment or is refractory (doesn't respond well to primary treatment), doctors will suggest another chemotherapy regimen. Several different regimens are being used, and they may or may not include rituximab. If the lymphoma shrinks with this treatment, a stem cell transplant is often suggested if possible, because otherwise the lymphoma is likely to grow back. Stem cell transplants are not effective unless the lymphoma responds to chemotherapy.

New techniques for studying the gene composition of DLBCLs have shown there may be 2 types. One responds well to usual treatment and the other doesn't. Clinical trials are now in progress to find out how best to treat the type that doesn't respond well.

This lymphoma can be cured in about 40% to 50% of patients. Survival after treatment depends on the stage of the disease and the International Prognostic Index. Patients with lower disease stages have better survival ratess, as do patients with lower IPI scores.

Follicular lymphoma: None of the standard treatments have been shown to cure this type of lymphoma , although it is often slow growing. For some cases, it is not clear if treating the lymphoma right away is helpful. Because of this, some doctors recommend no treatment until the lymphoma has begun to cause symptoms or abnormalities in the organs. In these patients, treatment is often needed after an average of about 3 to 4 years.

In rare cases where the lymphoma is localized to 1 lymph node group or to 2 adjacent groups on the same side of the abdomen (stage I or early stage II), it can often be treated with radiation therapy to the lymph node areas. If radiation can't be used, chemotherapy may be an option if the patient has symptoms or the lymph nodes are getting larger. Otherwise, many doctors will watch these patients closely but not start treatment.

If the lymphoma is not localized or involves a large mass ("bulky" stage II, or stage III or IV), just watching with no treatment may be an option if there are no symptoms and the lymphoma is not growing quickly. Radiotherapy can also be given to any large areas of lymphoma to reduce symptoms even if it is not stage I or II. This is reasonable if the lymphoma isn't very large and isn't causing symptoms, harming vital organs, or growing fast. Although some patients aren't comfortable with this approach, it's important to remember that because follicular lymphoma generally isn't curable, the point of therapy is to control the disease for as long as possible while causing the fewest side effects.

When follicular lymphoma does need treatment, there are several options. Many doctors will first try rituximab (Rituxan) because it causes few side effects. It may used alone or combined with chemotherapy, using either a single drug (such as fludarabine or chlorambucil) or a combination of drugs, such as the CHOP or CVP (cyclophosphamide, vincristine, and prednisone) regimens. Chemotherapy alone (either one or several drugs) may also be used.

The newer radioactive monoclonal antibodies, ibritumomab tiuxetan (Zevalin) and tositumomab (Bexxar) are also possible treatment options, although in newly-diagnosed patients their use is largely limited to clinical trials at this time.

If follicular lymphoma doesn't respond to initial treatment or if it comes back later, other treatment approaches such as chemotherapy, monoclonal antibodies, or some combination of these can be tried. If the lymphoma responds to this treatment, a stem cell transplant can be considered. This may help some patients, but it is best done in a clinical trial. A non-myeloablative (mini) transplant may be another option.

In some cases, follicular lymphoma can change (transform) to or return as a diffuse large B-cell lymphoma. When this happens, the treatment is the same as for this more aggressive disease.

Chronic lymphocytic leukemia/small lymphocytic lymphoma: Like follicular lymphoma, these types of lymphoma are not thought to be curable at this time, although they are slow growing. The treatment of chronic lymphocytic leukemia (CLL) is described in the separate American Cancer Society document, *Leukemia -- Chronic Lymphocytic*.

Treatment for both CLL and small lymphocytic lymphoma (SLL) is generally similar to that for follicular lymphoma. For early stage disease that isn't causing any symptoms or growing quickly, observation without immediate treatment may be an option. When treatment is needed, chemotherapy, with or without rituximab, is the usual first-line treatment.

A monoclonal antibody known as alemtuzumab (Campath) is sometimes used for patients whose SLL has specific genetic changes. It may also be used as a second-line treatment if the disease doesn't respond or comes back after initial treatment.

Mantle cell lymphoma: Although not a fast-growing lymphoma, this disease is often fatal within several years and requires intensive treatment. Because there is no curative or generally accepted treatment for this lymphoma, patients should consider entering a clinical trial.

Early stage cases (stages I or II), which are extremely rare, can sometimes be treated with radiation therapy. Otherwise, chemotherapy plus rituximab is the usual treatment. Rituximab added to chemotherapy leads to a higher response rate, but isn't curative. Common chemotherapy regimens include combinations of drugs and have names such as hyper-CVAD, CHOP, and EPOCH. No specific regimen has proved better than others, although there are reports that higher doses of chemotherapy are more effective. For this reason, clinical trials are studying the use of high-dose chemotherapy and stem cell transplant for those who have a good response to initial chemotherapy.

Another treatment approach now under study is the use of the monoclonal antibody ibritumomab tiuxetan (Zevalin) given in high doses, followed by stem cell transplant.

For mantle cell lymphomas that don't respond or come back after initial treatment, chemotherapy with drugs such as fludarabine, cladribine, or pentostatin may be used, sometimes along with other chemotherapy drugs or with rituximab. Newer drugs such as bortezomib (Velcade) and thalidomide (Thalomid) have also helped patients who did not respond to other drugs. The exact role of these drugs in treating mantle cell lymphoma is still being worked out in clinical trials.

Extranodal marginal zone B-cell lymphomas -- mucosa-associated lymphoid tissue lymphomas: The most common of these, gastric (stomach) lymphoma, is thought to occur as a result of a chronic infection with the bacterium, *H. pylori*. Because of this, treatment for gastric lymphomas is different from the other lymphomas in this group.

Treatment of early stage gastric mucosa-associated lymphoid tissue **(**MALT) lymphomas (stages I and II) often consists of antibiotics directed against *H. pylori,* along with proton pump inhibitors , drugs that block acid secretion by the stomach. Usually the drugs are given for 10 to 14 days. This may be repeated after a couple of weeks. Examination of the stomach lining using gastroscopy (where a flexible tube with a viewing lens is passed down the throat) is then repeated at certain intervals to see if the *H. pylori* is gone and if the lymphoma has decreased in size. About 2 out of 3 of these lymphomas respond completely to antibiotic treatment, but it can sometimes take several months to be effective. In cases where symptoms need to be relieved before the antibiotics take effect or where antibiotics don't shrink the lymphoma, radiation therapy to the area is often the preferred treatment. The monoclonal antibody rituximab may be another option.

For more advanced (stage III or IV) gastric MALT lymphomas (which are rare), treatment is often similar to that for follicular lymphoma (see above). Lymphomas that are not progressing may be observed without treatment right away. If the lymphoma is large, is causing symptoms, or is growing, radiation therapy to the stomach or chemotherapy may be used. The drugs used are the same as those used for follicular lymphoma, and may include single agents such as chlorambucil or fludarabine or combinations such as CVP (cyclophosphamide, vincristine, and prednisone). Rituximab is also effective in many patients.

For MALT lymphomas that arise in sites other than the stomach (non-gastric lymphomas), treatment depends on the site of the lymphoma and how extensive it is. Early stage lymphomas can often be treated with local radiation. In certain sites (such as the lungs, breast, or skin), surgical removal may be an option. For more advanced disease (stage III or IV), treatment is generally the same as for follicular lymphoma.

Nodal marginal zone B-cell lymphoma: This rare type of lymphoma is generally slow growing. It is usually treated like follicular lymphoma (see above) with either observation or low-intensity chemotherapy. It can also change into a fast-growing large cell lymphoma, which would require more aggressive chemotherapy such as CHOP.

Splenic marginal zone B-cell lymphoma: This is also a slow-growing lymphoma. If it is an early stage, it is sometimes observed without treating it right away. Because this lymphoma invades and enlarges the spleen (an organ in the left upper part of the abdomen), doctors may decide to surgically remove it, especially if the patient has symptoms. This alone can sometimes lead to a long-term remission of the disease. Radiation therapy to the spleen is occasionally an alternative to surgery. Patients who have chronic hepatitis C virus infection may also benefit from anti-viral drug treatment. The monoclonal antibody rituximab may be another option.

If the disease is more advanced or progresses, it is usually treated in the same way as a follicular lymphoma , which might include chemotherapy or other options.

In some cases this lymphoma can transform into an aggressive large-cell lymphoma, which requires more intensive chemotherapy.

Primary mediastinal B-cell lymphoma: This lymphoma is treated like a localized diffuse large B-cell lymphoma . The main treatment is radiation to the chest mass along with about 6 courses of CHOP chemotherapy, to which rituximab may be added. Radiation may also be given to the area when the patient goes into remission.

Burkitt lymphoma: This is a very fast-growing lymphoma that usually must be treated in the hospital with intensive chemotherapy. Most regimens for this disease include high doses of several drugs, including cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), cytarabine (Cytosar), and methotrexate, along with standard doses of vincristine (Oncovin). Many regimens also include a steroid drug such as prednisone or dexamethasone. Rituximab may also be added. Because this lymphoma tends to invade the spinal fluid, chemotherapy with methotrexate is given into the spinal fluid.

An important part of the initial treatment of this disease is making sure these patients, who are at risk for tumor lysis syndrome (described in the *Chemotherapy* section) get plenty of fluids and drugs like allopurinol.

More than half of all patients with Burkitt lymphoma can be cured with modern treatments.

Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia): The main treatment for this lymphoma is usually chemotherapy or rituximab. For more detailed information see the separate American Cancer Society document, *Waldenstrom Macroglobulinemia*.

Hairy cell leukemia: This is also a slow-growing lymphoma that tends to invade the spleen and lymph nodes as well as the blood. Patients without symptoms often don't need to be treated right away, but they do need to have careful follow-up exams. These are done every few months to check for disease progression and the appearance of symptoms. Some patients with hairy cell leukemia (HCL) live for many years without having any symptoms or receiving any treatment.

Treatment may be advised for HCL patients with low blood cell counts, recurrent infections, or an enlarged spleen or lymph nodes. One of the purine analog drugs -- either cladribine (2-CdA) or pentostatin -- is most often used to treat HCL. Up to 80% to 90% of patients respond to these drugs, and the responses last more than 5 years in most patients. Even if HCL recurs, many patients will respond to a second treatment with these drugs.

Giving rituximab after these drugs may get rid of any remaining disease in people who haven't fully responded. Because this is a fairly rare disease, too few people have been treated with rituximab to know if it will make a difference in the long term.

In rare cases, HCL may not respond to chemotherapy. Rituximab or interferon-alfa, a type of biologic therapy, may be helpful. If a patient is uncomfortable because of an enlarged spleen, removing the spleen by surgery (splenectomy) can often help relieve pain or other symptoms.

T-Cell Lymphomas

Precursor T-lymphoblastic lymphoma/leukemia: This disease can occur in both children and adults. Treatment of the leukemic form of this disease is discussed in more detail in the American Cancer Society documents, *Leukemia--Acute Lymphocytic* and *Childhood Leukemia*.

It is called a lymphoma if there are tumor masses and the number of lymphoma cells in the bone marrow is less than 25%. This is a fast-growing disease and is treated with intensive chemotherapy.

Many drugs are used. These can include cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin), L-asparaginase, methotrexate, prednisone, and, sometimes, cytarabine (Cytosar). Because of the risk of spread to the brain and spinal cord, chemotherapy with methotrexate is also given into the spinal fluid. Some doctors suggest maintenance chemotherapy for up to 2 years after the initial treatment to reduce the risk of recurrence. High-dose chemotherapy followed by a stem cell transplant may be another option.

An important part of the initial treatment of this disease is making sure patients get plenty of fluids and drugs like allopurinol, as they are at risk for tumor lysis syndrome (described in the Chemotherapy section).

Although this lymphoma is fast-growing, if it hasn't spread to the bone marrow when it is first diagnosed, the chance of cure with chemotherapy is quite good. Once it has spread to the bone marrow, only about 40% to 50% of patients can be cured.

Cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome): Treatment of these lymphomas is discussed in the separate American Cancer Society document, *Lymphoma of the Skin*.

Angioimmunoblastic T-cell lymphoma: This fast-growing lymphoma is often first treated with steroids (such as prednisone or dexamethasone) alone. This treatment can reduce fever and weight loss, but the effect is often temporary, and usually some form of chemotherapy is needed. Chemotherapy rarely results in long-term remissions, so autologous stem cell transplant is often suggested if possible.

Extranodal natural killer/T-cell lymphoma, nasal type: Because this lymphoma is often confined to the nasal passages, it can usually be treated with radiation therapy. Chemotherapy is often added, using a regimen such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). If the lymphoma has spread, the chemotherapy regimen may be more intense. Multiple drugs are used at high doses, and a stem cell transplant may be done if possible.

Enteropathy type T-cell lymphoma: This lymphoma develops from hypersensitivity to gluten, and is almost always in the intestines. If the symptoms of this hypersensitivity are recognized early, then a gluten-free diet may help prevent the lymphoma from developing. There is no accepted standard treatment, although a clinical trial of chemotherapy may be suggested.

Anaplastic large cell lymphoma: This fast-growing lymphoma mainly affects lymph nodes and is treated with CHOP or similar chemotherapy regimens. In some cases, doctors may recommend radiation therapy as well. Response rates to treatment are generally high, and long-term survival is common, especially if the lymphoma cells stain positive for the ALK protein. If the cells lack the ALK protein or if the lymphoma returns after initial treatment, an autologous stem cell transplant may be an option.

Peripheral T-cell lymphoma, unspecified: These lymphomas are generally treated the same way as diffuse large B-cell lymphomas. Chemotherapy with CHOP or other drug combinations is used. For early stage disease, radiation therapy may be added. Stem cell transplants may be recommended as part of the treatment when possible. Immunotherapy drugs such as alemtuzumab (Campath) may be tried if other treatments are no longer working. The outlook is usually not as good as in diffuse B-cell lymphoma, so taking part in a clinical trial of newer treatments is often a good option.

Special Types of Lymphoma

Some types of lymphoma are treated differently enough to deserve separate mention.

Primary central nervous system lymphoma: This lymphoma begins in the brain or spinal cord. The symptoms are like those of other brain tumors, which can include headache and sometimes loss of functions such as using a limb, speech, etc. Seizures can also occur. This type of lymphoma often develops in older people or those with immune system problems caused by AIDS or drugs given to prevent rejection of transplanted organs.

Most patients are treated with chemotherapy and/or radiation. One problem with treating this disease is that most chemotherapy drugs commonly used to treat lymphoma don't reach the brain when given intravenously. For those in reasonably good health, high intravenous doses of the drug methotrexate have been shown to be the most effective treatment. This is given along with the drug leucovorin and intravenous fluids, which help limit serious side effects. Other chemotherapy drugs, such as cytarabine, may be added. For those who aren't able to tolerate this treatment, other, less intensive chemotherapy regimens may be tried.

Radiation to the brain is often used (either alone or with chemotherapy), but some doctors are trying to avoid it, especially in older patients, because it often causes mental changes. Studies looking at this are now under way.

Historically, the outlook for patients with primary CNS lymphoma has not been as good as for other lymphomas, but this is at least partly related to the fact that they tend to be older or have other serious health problems.

HIV-associated lymphoma: As mentioned previously, people with HIV infections are at increased risk for developing lymphoma. Although people with HIV often have aggressive forms of lymphoma such as diffuse large B-cell lymphoma or Burkitt lymphoma, their outlook has improved considerably in recent years. The use of highly active antiretroviral therapy (HAART) against the HIV has allowed patients getting it to better tolerate chemotherapy.

The major problem in the past was that patients with HIV infection tended to have low blood cell counts to begin with, which made treatment with full courses of chemotherapy difficult. But this problem has been relieved somewhat by the use of HAART and by the use of growth factors that stimulate the patient's bone marrow to produce white blood cells and red blood cells. Still, doctors give chemotherapy cautiously, and monitor blood counts closely.

Most experts believe that the prognosis (outlook) for a person with HIV-associated lymphoma relates more to the HIV infection than to the lymphoma. Because modern anti-HIV therapy is controlling the immune deficiency in patients with AIDS, the outlook for those patients who develop lymphoma has improved considerably. The treatment is tailored to the specific type of lymphoma.

More Treatment Information

For more details on treatment options -- including some that may not be addressed in this document -- the National Comprehensive Cancer Network (NCCN) and the National Cancer Institute (NCI) are good sources of information.

The NCCN, made up of experts from many of the nation's leading cancer centers, develops cancer treatment guidelines for doctors to use when treating patients. Those are available on the NCCN Web site (www.nccn.org).

The American Cancer Society collaborates with the NCCN to produce a version of some of these treatment guidelines, written specifically for patients and their families. These less-technical versions are available on both the NCCN Web site (www.nccn.org) and the ACS Web site (www.cancer.org). A print version can also be requested from the ACS at 1-800-ACS-2345.

The NCI provides treatment guidelines via its telephone information center (1-800-4-CANCER) and its Web site (www.cancer.gov). Detailed guidelines intended for use by cancer care professionals are also available on www.cancer.gov.

What Should You Ask Your Doctor About Non-Hodgkin Lymphoma?

It is important to have frank, open discussions with your cancer care team. They want to answer all of your questions, no matter how minor they might seem. For instance, consider asking these questions:

- What kind of non-Hodgkin lymphoma do I have?
- Has my biopsy been reviewed by a pathologist who is an expert on lymphoma?
- Have cell surface markers been used to confirm my diagnosis of lymphoma?
- What is the stage (extent) of the lymphoma, and what does that mean in my case?
- What is my International Prognostic Index (IPI) score, and does it affect my options?
- What treatment options do I have? Do we need to treat the lymphoma right away?
- What do you recommend, and why?
- What risks or side effects are there to the treatments you suggest?
- What is my outlook for survival?
- What are the chances of recurrence with these treatment plans?
- What should I do to be ready for treatment?
- Should I get a second opinion? Can you suggest someone?

Along with these sample questions, be sure to write down some of your own. For instance, you might want more information about recovery times so that you can plan your work schedule. Or you may want to ask about clinical trials for which you may qualify.

What Happens After Treatment for Non-Hodgkin Lymphoma?

Completing treatment can be both stressful and exciting. You will be relieved to finish treatment, yet it is hard not to worry about cancer coming back. (When cancer returns, it is called recurrence.) This is a very common concern among those who have had cancer.

It may take a while before your confidence in your own recovery begins to feel real and your fears are somewhat relieved. Even with no recurrences, people who have had cancer learn to live with uncertainty.

Follow-up Care

Lymphomas are a diverse group of diseases that require different treatments and can have very different prognoses (outlooks). Your care after treatment will depend to a large extent on what type of lymphoma you have, what type of treatment you received, and how effective it was.

Follow-up Tests

Your doctor will probably want to see you regularly to discuss any symptoms you may have and to do physical exams, usually every few months for the first year and gradually less often after that. Your physical exam will include careful attention to size and firmness of lymph nodes.

You may need to have frequent blood tests to check that you have recovered from treatment and to look for possible signs of problems such as disease recurrence. Blood counts can also sometimes become abnormal because of a disease called *myelodysplasia*, which is a defect of the bone marrow that can lead to leukemia. Some chemotherapy drugs can cause this disease. For more on this, see the American Cancer Society document, *Myelodysplastic Syndromes*. It is also possible for a person to develop leukemia a few years after being treated for lymphoma. These blood disorders may occur in as many as 10% of lymphoma patients who were treated with either standard chemotherapy or high-dose chemotherapy followed by stem cell transplant.

Imaging tests may be done, based on the type, location, and stage of lymphoma. If internal lymph nodes or other internal organs are or were affected, CT scans and/or PET scans may be used to measure the size of any remaining tumor masses. PET scans are particularly useful if your doctors aren't sure if a mass seen on CT scan is an active lymphoma or scar tissue.

After treatment it is important to keep your health insurance coverage. Even though no one wants to think about the cancer coming back, it is always a possibility. If it happens, the last thing you want to have to worry about is paying for treatment.

Seeing a New Doctor

At some point after your cancer diagnosis and treatment, you may find yourself in the office of a new doctor. Your original doctor may have moved or retired, or you may have moved or changed doctors for some reason. It is important that you be able to give your new doctor the exact details of your diagnosis and treatment. Make sure you have the following information handy:

- a copy of your pathology report from any biopsies or surgeries
- if you had surgery, a copy of your operative report
- if you were hospitalized, a copy of the discharge summary that every doctor must prepare when patients are sent home from the hospital
- finally, since some drugs can have long-term side effects, a list of your drugs, their doses, and when you took them

Lifestyle Changes to Consider During and After Treatment

Having cancer and dealing with treatment can be time-consuming and emotionally draining, but it can also be a time to look at your life in new ways. Maybe you are thinking about how to improve your health over the long term. Some people even begin this process during cancer treatment.

Make Healthier Choices

Think about your life before you learned you had cancer. Were there things you did that might have made you less healthy? Maybe you drank too much alcohol, or ate more than you needed, or smoked, or didn't exercise very often. Emotionally, maybe you kept your feelings bottled up, or maybe you let stressful situations go on too long.

Now is not the time to feel guilty or to blame yourself. However, you can start making changes today that can have positive effects for the rest of your life. Not only will you feel better but you will also be healthier. What better time than now to take advantage of the motivation you have as a result of going through a life-changing experience like having cancer?

You can start by working on those things that you feel most concerned about. Get help with those that are harder for you. For instance, if you are thinking about quitting smoking and need help, call the American Cancer Society's Quitline® tobacco cessation program at 1-800-ACS-2345.

Diet and Nutrition

Eating right can be a challenge for anyone, but it can get even tougher during and after cancer treatment. For instance, treatment often may change your sense of taste. Nausea can be a problem. You may lose your appetite for a while and lose weight when you don't want

to. On the other hand, some people gain weight even without eating more. This can be frustrating, too.

If you are losing weight or have taste problems during treatment, do the best you can with eating and remember that these problems usually improve over time. You may want to ask your cancer team for a referral to a dietitian, an expert in nutrition who can give you ideas on how to fight some of the side effects of your treatment. You may also find it helps to eat small portions every 2 to 3 hours until you feel better and can go back to a more normal schedule.

One of the best things you can do after treatment is to put healthy eating habits into place. You will be surprised at the long-term benefits of some simple changes, like increasing the variety of healthy foods you eat. Try to eat 5 or more servings of vegetables and fruits each day. Choose whole grain foods instead of white flour and sugars. Try to limit meats that are high in fat. Cut back on processed meats like hot dogs, bologna, and bacon. Get rid of them altogether if you can. If you drink alcohol, limit yourself to 1 or 2 drinks a day at the most. And don't forget to get some type of regular exercise. The combination of a good diet and regular exercise will help you maintain a healthy weight and keep you feeling more energetic.

Rest, Fatigue, Work, and Exercise

Fatigue is a very common symptom in people being treated for cancer. This is often not an ordinary type of tiredness but a "bone-weary" exhaustion that doesn't get better with rest. For some, this fatigue lasts a long time after treatment, and can discourage them from physical activity.

However, exercise can actually help you reduce fatigue. Studies have shown that patients who follow an exercise program tailored to their personal needs feel physically and emotionally improved and can cope better.

If you are ill and need to be on bed rest during treatment, it is normal to expect your fitness, endurance, and muscle strength to decline some. Physical therapy can help you maintain strength and range of motion in your muscles, which can help fight fatigue and the sense of depression that sometimes comes with feeling so tired.

Any program of physical activity should fit your own situation. An older person who has never exercised will not be able to take on the same amount of exercise as a 20-year-old who plays tennis 3 times a week. If you haven't exercised in a few years but can still get around, you may want to think about taking short walks.

Talk with your health care team before starting, and get their opinion about your exercise plans. Then, try to get an exercise buddy so that you’re not doing it alone. Having family or friends involved when starting a new exercise program can give you that extra boost of support to keep you going when the push just isn’t there.

If you are very tired, though, you will need to balance activity with rest. It is okay to rest when you need to. It is really hard for some people to allow themselves to do that when they are used to working all day or taking care of a household. (For more information about fatigue, please see the publication, *Cancer Related Fatigue and Anemia Treatment Guidelines for Patients*.)

Exercise can improve your physical and emotional health.

- It improves your cardiovascular (heart and circulation) fitness.
- It strengthens your muscles.
- It reduces fatigue.
- It lowers anxiety and depression.
- It makes you feel generally happier.
- It helps you feel better about yourself.

And long term, we know that exercise plays a role in preventing some cancers. The American Cancer Society, in its guidelines on physical activity for cancer prevention, recommends that adults take part in at least 1 physical activity for 30 minutes or more on 5 days or more of the week. Children and teens are encouraged to try for at least 60 minutes a day of energetic physical activity on at least 5 days a week.

How About Your Emotional Health?

Once your treatment ends, you may find yourself overwhelmed by emotions. This happens to a lot of people. You may have been going through so much during treatment that you could only focus on getting through your treatment.

Now you may find that you think about the potential of your own death, or the effect of your cancer on your family, friends, and career. You may also begin to re-evaluate your relationship with your spouse or partner. Unexpected issues may also cause concern -- for instance, as you become healthier and have fewer doctor visits, you will see your health care team less often. That can be a source of anxiety for some.

This is an ideal time to seek out emotional and social support. You need people you can turn to for strength and comfort. Support can come in many forms: family, friends, cancer support groups, church or spiritual groups, online support communities, or individual counselors.

Almost everyone who has been through cancer can benefit from getting some type of support. What's best for you depends on your situation and personality. Some people feel safe in peer-support groups or education groups. Others would rather talk in an informal setting, such as church. Others may feel more at ease talking one-on-one with a trusted friend or counselor. Whatever your source of strength or comfort, make sure you have a place to go with your concerns.

The cancer journey can feel very lonely. It is not necessary or realistic to go it all by yourself. And your friends and family may feel shut out if you decide not include them. Let them in -- and let in anyone else who you feel may help. If you aren't sure who can help, call your

American Cancer Society at 1-800-ACS-2345 and we can put you in touch with an appropriate group or resource.

You can't change the fact that you have had cancer. What you can change is how you live the rest of your life -- making healthy choices and feeling as well as possible, physically and emotionally.

What If the Lymphoma Doesn't Respond or Comes Back After Treatment?

Lymphomas are a diverse group of diseases, and the chance of progression or recurrence after treatment varies between types.

Generally, when lymphomas come back, they tend to do so in the same part of the body they started in. For example, if the lymphoma began in lymph nodes in the abdomen, this is the most likely place it will recur. If the bone marrow was involved, it will most likely return there. In many cases, the lymphoma will respond to new kinds of chemotherapy or other drugs. If a remission can be achieved following the second round of treatment, doctors often recommend high-dose chemotherapy with a stem cell transplant or a low-dose, non-myeloablative transplant.

If more than one round of treatment has failed, the lymphoma is much less likely to respond to additional or new chemotherapy. If the lymphoma does respond, the response may be shorter. Over time, chemotherapy provides less benefit, although immunotherapy and other new approaches to treatment available through clinical trials may be effective.

At this time it's important to weigh the possible limited benefit of a new treatment against the possible downsides, including continued doctor visits and treatment side effects. Everyone has his or her own way of looking at this. Some people may want to focus on remaining comfortable during their limited time left.

This is likely to be the most difficult time in your battle with cancer -- when you have tried everything medically within reason and it's just not working anymore. Although your doctor may offer you new treatment, you need to consider that at some point, continuing treatment is not likely to improve your health or change your prognosis or survival.

If you want to continue treatment to fight your cancer as long as you can, you still need to consider the odds of more treatment having any benefit. In many cases, your doctor can estimate the response rate for the treatment you are considering. Some people are tempted to try more chemotherapy or radiation, for example, even when their doctors say that the odds of benefit are less than 1%. In this situation, you need to think about and understand your reasons for choosing this plan.

No matter what you decide to do, it is important that you be as comfortable as possible. Make sure you are asking for and getting treatment for any symptoms you might have, such as pain. This type of treatment is called *palliative* treatment.

Palliative treatment helps relieve symptoms, but is not expected to cure the disease; its main purpose is to improve your quality of life. Sometimes, the treatments you get to control your symptoms are similar to the treatments used to treat cancer. For example, when lymph nodes become enlarged, they may press on nerves and cause pain. Radiation therapy to these areas may help relieve the pain. Appropriate pain medicines should be given. In this situation it is all right to use more potent medicines such as opioids if non-opioid painkillers do not ease the pain.

Other symptoms such as fatigue and low resistance to infections can be caused by low blood counts. Sometimes blood transfusion or treatment with drugs that stimulate blood production is needed. Nausea and loss of appetite can be treated with drugs and high-calorie food supplements. If the lymphoma has spread to the lung, patients may get short of breath. Oxygen may be used to help treat this symptom.

At some point, you may benefit from hospice care. Most of the time, this can be given at home. Your cancer may be causing symptoms or problems that need attention, and hospice focuses on your comfort. You should know that receiving hospice care doesn't mean you can't have treatment for the problems caused by your cancer or other health conditions. It just means that the focus of your care is on living life as fully as possible and feeling as well as you can at this difficult stage of your cancer.

Remember also that maintaining hope is important. Your hope for a cure may not be as bright, but there is still hope for good times with family and friends -- times that are filled with happiness and meaning. In a way, pausing at this time in your cancer treatment is an opportunity to refocus on the most important things in your life. This is the time to do some things you've always wanted to do and to stop doing the things you no longer want to do.

What's New in Non-Hodgkin Lymphoma Research and Treatment?

Research into the causes, prevention, and treatment of non-Hodgkin lymphoma is being done in many medical centers throughout the world.

Genetics

Scientists are making great progress in understanding how changes in DNA can cause normal lymphocytes to develop into lymphoma cells. This is providing insight into why these cells may grow too rapidly, live too long, and not develop into mature cells that take part in

normal immune reactions. Once this is understood, drugs may be developed that block this process.

Progress in understanding DNA changes in lymphoma has already provided improved and highly sensitive tests for detecting this disease. Such tests can identify lymphoma cells based on gene changes such as translocations or rearrangements. For example, the polymerase chain reaction (PCR) test can detect one lymphoma cell among a million normal cells. Aside from being used to detect and classify lymphomas, the test is useful in helping determine how completely the lymphoma has been destroyed by treatment and whether a relapse is likely.

One of the more important breakthroughs in recent years has been the development of DNA microarrays. These are tests of gene patterns in a tumor's DNA that may help spot abnormal genes in the tumor. This may lead to new classifications of these diseases. The tests may also be useful in identifying those patients who may need early treatment with high-dose chemotherapy and stem cell transplants. The usefulness and reliability of these tests is now being studied.

Treatment

Much of the research being done on non-Hodgkin lymphoma is focused on looking at new and better ways to treat this disease.

Chemotherapy

Many new chemotherapy drugs are being studied in clinical trials. Others are studying new ways to combine drugs using different doses or different sequences of drugs.

Newer, non-traditional drugs such as bortezomib (Velcade) and thalidomide (Thalomid) have shown some promise in treating certain leukemias. These and similar drugs are now being studied.

Biological Therapy

Lymphoma cells contain certain chemicals on their surface. Monoclonal antibodies that recognize these substances can be targeted to destroy the lymphoma cells while causing little damage to normal body tissues. This treatment strategy has already proven effective. Several such drugs, including rituximab, are already available and are discussed in the section, *How Is Non-Hodgkin Lymphoma Treated?*

Rituximab is often given for a limited amount of time during treatment. Because it has few side effects, new studies are testing its long-term use to see if it helps prevent lymphomas

from coming back. The use of rituximab in this type of "maintenance therapy" is still considered experimental by most doctors.

Because of the success of rituximab and its radioactive counterparts (ibritumomab and tositumomab), new monoclonal antibodies are being developed. Using them in combination with chemotherapy is also being tested in clinical trials.

Bone Marrow and Peripheral Blood Stem Cell Transplants

Researchers continue to improve bone marrow and peripheral blood stem cell transplant methods, including new ways to collect these cells before the transplant.

Autologous (taken from the patient rather than another person) transplants have the risk of reintroducing lymphoma cells back into the patient after treatment. Researchers are testing new and improved ways to remove the last traces of lymphoma from these stem cells before they are returned to the patient. Some of the new monoclonal antibodies developed for treating lymphoma may help remove these remaining cells.

A lot of research is focusing on eliminating graft-versus-host disease in allogeneic (donor) transplants. This work revolves around altering the transplanted T-cells so that they won't react with the recipient's normal cells but still kill the lymphoma cells.

Lymphoma Vaccines

Doctors have known for some time that people's immune systems may help fight their cancer. In rare instances, these people's immune systems have rejected their cancers, and they have been cured. Scientists are now trying to develop ways to encourage this immune reaction by the use of vaccines.

Unlike vaccines against infections like measles or mumps, these vaccines are designed to help treat, not prevent, lymphomas (therapeutic vaccines). With cancer vaccines, the goal is to create an immune reaction in patients who have very early disease or in patients whose disease is in remission. One possible advantage of these types of treatments is that they seem to have very limited side effects. So far, there have been a few successes with this approach, and it is a major area of research in lymphoma treatment. At this time lymphoma vaccines are only available in clinical trials.

MyVax™, *BiovaxID*™, and *FavId*™ are vaccines based on the unique genetic makeup of a patient's B-cell non-Hodgkin lymphoma (NHL). The vaccines use a unique protein (part of an antibody called an idiotype) taken from each patient's own lymphoma cells. This is combined with a substance called an adjuvant that helps stimulate an immune reaction when the combination is injected into the patient. These vaccines are now in late-stage clinical

trials testing their effectiveness against follicular lymphomas. Their use against other types of lymphomas is also being tested.

Additional Resources

More Information from Your American Cancer Society

We have selected some related information that may also be helpful to you. These materials may be ordered from our toll-free number, 1-800-ACS-2345.

After Diagnosis: A Guide for Patients and Families (also available in Spanish)

Home Care for the Person With Cancer: A Guide for Patients and Families (also available in Spanish)

Pain Control: A Guide for People With Cancer and Their Families (also available in Spanish)

American Cancer Society/National Comprehensive Cancer Network (NCCN) Non-Hodgkin's Lymphoma Treatment Guidelines for Patients

The following books are available from the American Cancer Society. Call us at 1-800-ACS-2345 to ask about costs or to place your order.

American Cancer Society's Guide to Pain Control

Cancer in the Family: Helping Children Cope With a Parent's Illness

Caregiving: A Step-By-Step Resource for Caring for the Person With Cancer at Home

National Organizations and Web Sites*

In addition to the American Cancer Society, other sources of patient information and support include:

National Cancer Institute
Telephone: 1-800-4-CANCER
Internet Address: www.cancer.gov

The Leukemia & Lymphoma Society
Telephone: 1-800-955-4572 or 1-914-949-5213
Internet Address: www.lls.org

The Lymphoma Research Foundation
Telephone: 1-800-500-9976
Internet Address: www.lymphoma.org

**Inclusion on this list does not imply endorsement by the American Cancer Society.*

The American Cancer Society is happy to address almost any cancer-related topic. If you have any more questions, please call us at 1-800-ACS-2345 any time, 24 hours a day.

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