What Are the Non-Hodgkin's Lymphomas?

There is no single definitive description of the non-Hodgkin's lymphomas because the term NHL encompasses a collection of diseases. How they relate to other lymphomas and leukemias—and if they really are different entities—is still under debate. There are certain general medical descriptions of NHL that can be made, as well as comparisons to other lymphomas and other cancers.

What is the lymphatic system?

The lymphatic system is an infection-fighting circulatory system of body fluids and lymphocytes traveling in delicate vessels called ducts that collect fluid squeezed from veins during normal metabolism and bring it back to the veins near the heart. The lymphatic system relies on gravity and muscle compression to propel lymphatic fluid. This fluid resembles blood serum—that is, blood fluid containing only lymphocytes—and is returned to the bloodstream at various points in the body so that waste products can be removed by the kidneys.

The lymphatic system also includes various infection-fighting or lymphocyte-producing organs, such as the spleen, tonsils, appendix, thymus, and intestinal Peyer's patch.

A lymph node is a kidney-bean-shaped swelling along a lymphatic duct, responsible for filtering lymphatic fluid of foreign substances. The body has hundreds of lymph nodes. Healthy nodes vary in size from very tiny to almond-size, depending on their position and function near or within various organs.

What is lymphoma?

Lymphomas and leukemias are cancers of white blood cells at various stages of maturation. White blood cells are part of the immune system. They travel through the blood and the lymphatic system and are supposed to protect us from illness and, ironically, from cancer.

As with other cancers, the wayward cells that characterize lymphoma and leukemia do not die as normal cells do, nor do they honor the cycles of orderly cell division as normal cells do: many have no resting phase, instead dividing continuously. What's worse, they divide before they are fully mature, which makes them unable to fight infection as normal white blood cells do. This means that our bodies accumulate nonfunctional white blood cells that, by dividing rapidly or not undergoing normal cell death (apoptosis), crowd out other functioning white blood cells and other nearby normal cells within affected organs. For instance, red blood cells and platelets may be crowded out of the nurturing bone marrow matrix if the white blood cells of lymphoma have affected the bone marrow. The path of lymphatic fluid and its infection-fighting mechanisms may be compromised if lymphoma arises within a lymph node. Lymphomas lodged within the thyroid can cause the secretion of thyroid hormones to go amiss.

Both lymphomas and leukemias can circulate in the bloodstream or lodge in lymph nodes or other organs. Some researchers feel that, because of this and other similarities, such as the existence of viruses that can cause both lymphoma and leukemia, separating lymphomas from leukemias is an outmoded idea. They believe that lymphoma and leukemia are different manifestations of the same malignant cell, and this is partly reflected in the new Revised European American Lymphoma (REAL) classification system of hematologic cancers.

Many lymphomas arise within a lymph node, perhaps suggesting an error in cell division or maturation during the calling forth of white blood cells from the lymph node following an infection or other stimulation of the immune system. Others arise within the bone marrow, within other immune system organs such as the spleen or thymus, or within areas of the intestine called Peyer's patches that are rich in lymphocytes. Despite their predilection for lymph nodes and other lymphocyte-rich sites, lymphomas can arise essentially anywhere. Some rare NHLs arise within the bone itself, as opposed to the bone marrow.

What is NHL?

The name "non-Hodgkin's lymphoma" might lead you to believe it's a single lymphoma type that just isn't quite one of the Hodgkin's lymphomas, about which more is said below. NHL is actually a collection of many

What Are the Non-Hodgkin's Lymphomas?

varied lymphomas. There are many more types of NHL than there are types of Hodgkin's lymphomas.

Industrialized nations experience a higher incidence of NHL than do developing countries, and the highest incidence rate in the world is seen in the United States and Canada, with forty to fifty thousand new cases per year in the US. Some estimates range as high as 80,000 cases a year.

Types of non-Hodgkin's lymphomas

There is a confusing array of NHLs. If you attempt to compare yourself to others who appear to have the same diagnosis, bear in mind that their diagnosis may have been made using criteria that are different, perhaps in subtle ways, from those used by your own diagnosticians. This means that treatment decisions from one person to the next may differ as well.

Most NHLs arise within a lymph node, but a significant and increasing number arise in areas other than nodes, such as the jaw or brain, especially among children and those with AIDS. The range from low-grade, indolent disease to aggressive, high-grade disease does not fall into discrete categories but is instead a continuum. Mixed grades, as determined by the appearance of the tumor cells or other criteria, sometimes are found in the same patient at the same time—in the same node, in different nodes, or in both nodes and marrow. When mixed grades are present in the same patient, this may represent the progression of disease.

Why are so many of these cancers, some quite different from the others, clustered under one name? Until recently, science was not able to make fine distinctions among these subtypes. Advances in molecular genetics have shown, though, that NHL is actually many diseases.

With these improved diagnostic techniques and advances in microbiology and genetics, it is becoming increasingly common for subtypes of NHL to emerge from a background of confusing similarities. The mucosa-related lymphoid tissue (MALT) lymphomas, viral T-cell leukemia/lymphoma, cutaneous T-cell lymphoma, as well as primary central nervous system lymphoma so frequently seen among AIDS survivors, are examples of the diversity of NHLs. Some of the NHLs more closely resemble leukemias than they do the Hodgkin's lymphomas. As more becomes known, some lymphomas that were categorized as NHLs may be reclassified with other cancers.

It is beyond the scope of this fact sheet to describe each cellular and behavioral difference among the many types of NHL. A superb source of detailed information on these differences is the 1997 edition of *The Non-Hodgkin's Lymphomas*, edited by Ian Magrath.

How is NHL different from Hodgkin's?

While NHL is characterized by many different cell types and may arise in many different locations, sometimes simultaneously and via unknown paths, Hodgkin's lymphoma (HL) consists of just four subtypes and in many cases is a more orderly cancer. It is more likely to occur entirely within nodes and to spread into adjacent, contiguous nodes, probably spreading through lymphatic ducts.

NHL is more frequently diagnosed in older people, whereas, in the US, HL most often arises during the second and third decades of life.

One subtype of NHL, anaplastic large-cell lymphoma (ALCL), resembles one subtype of Hodgkin's lymphoma, lymphocyte-depleted Hodgkin's lymphoma (LDHL). Care must be taken when diagnosing these subtypes, as their treatments differ.

Although many of the same drugs are used for both NHL and HL, treatments that are successful for NHL are less so for HL and vice versa.

Epstein-Barr virus (EBV) seldom is found in B-cell NHL tumors unless they arise in an immune-suppressed person or in cases of Burkitt's lymphoma in Africa, whereas about 40 percent of HL tumor samples test positive for Epstein-Barr virus.

The appearance of NHL cells under the microscope is different from most types of HL, and the non-Hodgkin's cell-surface antigens, which are markers on the outside of the cell membrane, are different from those for most, but not all, HLs.

What Are the Non-Hodgkin's Lymphomas?

How is NHL different from some leukemias?

Some NHLs resemble certain leukemias known as lymphoid leukemias. Nonetheless, there are differences as well. Most NHLs arise within a lymph node or solid organ and do not release large numbers of easily detectable cancerous cells into the bloodstream, whereas most leukemias arise in the bone marrow and circulate readily in the bloodstream.

In spite of these differences, the lymphoblastic and small lymphocytic NHLs are very similar to acute lymphoblastic leukemia (ALL) and to chronic lymphocytic leukemia (CLL). At times, diagnostic efforts are unable to differentiate these illnesses, and the patient is described as having NHL/ALL or NHL/CLL. Indeed, the new REAL classification system of lymphomas includes some leukemias such as CLL, lymphoblastic leukemia, and plasma-cell multiple myeloma (MM) as neoplasms related to NHL.

How is NHL different from other cancers?

The foremost difference between NHL and other cancers is that, as a cancer of the white blood cells, NHL is a cancer of the body system that is supposed to protect us from cancer. While upon first thought this may seem a cruel betrayal, it may also account for the great success seen in treating some lymphomas. The ongoing research done for curing NHL and other lymphomas—efforts involving therapeutic vaccines derived from tumor samples and antibody therapy, for example—tend to become bellwether strategies for improving progress against other cancers.

For many cancers, detection while the cancer still has not spread outside the original organ greatly improves one's chances of survival. While it is generally true that NHL caught early may be more successfully treated than that caught late, it is not unusual nor is it a hopeless prognostic sign for NHL to arise in multiple locations at the same time. Metastases, even to bone marrow, are not always of the same dire significance that they may be for some other cancers, because frequently these NHLs continue to respond to treatment and to cease spreading. Likewise, aggressive NHLs can at times be more successfully treated than low-grade or indolent tumors.

NHL is more likely to arise in certain organs and not in others, specifically but not always the organs of the immune system such as the lymph nodes, spleen, tonsils, and thymus. It is rare, however, to find a primary NHL in certain organs such as the pancreas or muscle. Perhaps owing to the hormonal connections between the central nervous system and white blood cells, lymphomas can arise first in the brain or central nervous system, not necessarily as a result of spread from elsewhere.

Grading and staging NHL

It is most important that your disease be correctly identified, graded, and staged so that the best treatment can be planned. All biopsies of tumor tissue should be reviewed by an experienced hematopathologist to be certain that subtype and grade are correctly identified.

Brief definitions of stage and grade are:

Staging describes how far the disease has spread from its original site. Staging for many, but not all, cancers consists of stages I through IV.

Grading describes how aggressive the tumor is. A tumor can be graded as low (or indolent), intermediate, or highly aggressive by several measures. Many researchers combine intermediate- and high-grade disease in discussions of treatment. All NHL tumors are graded on their appearance under the microscope, known as histologic grade; some are graded on behaviors that leave traces of tumor activity in the bloodstream or other body tissues. There are important deviations in what these characteristics mean to success of treatment. It is not always true, for instance, that a stage IV, high-grade patient has fewer hopes for cure than a stage IV, low-grade patient.

For years, the Rappaport and Ann Arbor systems used for Hodgkin's lymphoma, and the Working Group and Kiel systems, were adapted to describe NHL in a way that attempted to reflect tumor characteristics, and thus to some degree prognosis, but none was entirely satis-

What Are the Non-Hodgkin's Lymphomas?

factory. Most recently, the Revised European American Lymphoma (REAL) classification system was proposed by an international cooperative group of researchers to more correctly identify lymphomas based on immunologic characteristics.

The lack of fully acceptable staging and grading systems for NHL has resulted in many universities and cancer treatment centers devising their own systems. Each system attempts to correlate cellular or disease characteristics to treatment outcome. An excellent discussion of these staging controversies can be found in Magrath's *The Non-Hodgkin's Lymphomas*. One consequence of this variety of descriptive systems is that you may become confused when talking to other survivors who state that they have the same subtype, grade, and stage as you do but who are receiving different treatment with perhaps different results.

Some cases of NHL have characteristics of two or more known entities. In these cases, identity or staging decisions can be difficult to make. The following sections describe efforts to grade and stage NHLs for choosing the best treatment.

Recurrent disease

Often you'll find in the medical literature that patients who have relapsed are no longer discussed by stage, but are instead described as having recurrent disease. In some cases, recurrent disease may be the equivalent of stage I, such as is seen in the relapse of certain patients with limited low-grade disease. For intermediate- and high-grade disease, though, recurrent disease often is considered to be the equivalent of stage III or IV.

This fact sheet was adapted from *Non-Hodgkin's Lymphomas: Making Sense of Diagnosis, Treatment, and Options*, by Lorraine Johnston, For more information, call **(800) 998-9938** or see *www.patientcenters.com*.