

Non-Hodgkin's Lymphoma

Becomes More Common, More Treatable

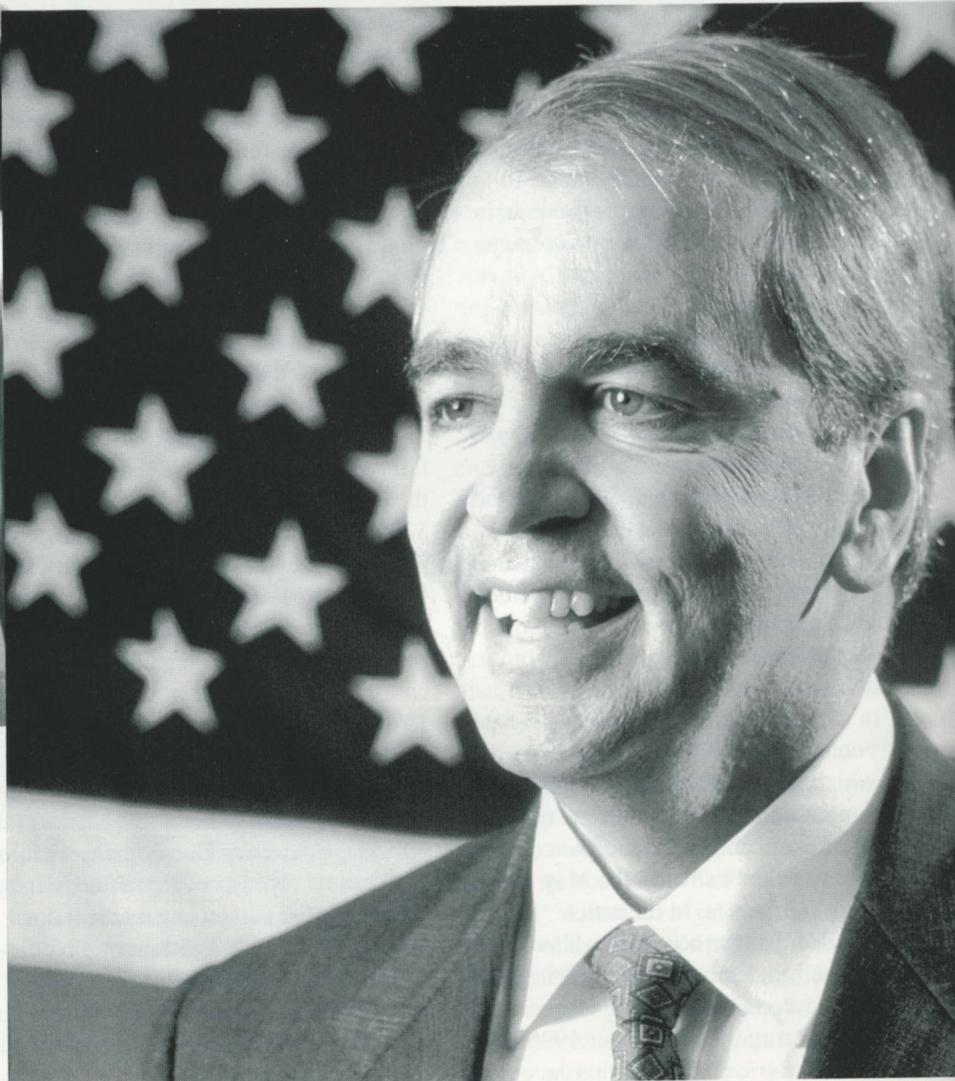
by Margie Patlak

Non-Hodgkin's lymphoma is now the sixth most common cancer in the United States.



The late Jacqueline Kennedy Onassis

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Senator Paul Tsongas

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Mary Relles of Philadelphia never heard of non-Hodgkins lymphoma until her father was diagnosed with it in 1990. Since then, three of her friends—and Relles herself, 49—have developed this relatively unknown yet deadly cancer of the immune system.

Non-Hodgkins lymphoma (NHL) has become more common in the last few decades and is now the sixth most common cancer in the United States, according to the National Cancer Institute (NCI). Striking such luminaries as Jacqueline Kennedy Onassis, Senator Paul Tsongas, and the Shah Mohammed Reza Pahlevi of Iran, NHL has increased 75 percent over the last 20 years, making it the most rapidly rising cancer after lung cancer and melanoma, according to NCI. Although recent studies have provided some intriguing clues, the cause of what some experts call the “NHL epidemic” is not known. (See accompanying article.) Fortunately, advances in treatment seem to be keeping pace; the five-year survival rate for NHL rose from 31 percent to 51 percent over the past 30 years, according to NCI.

Cancers of the Immune System

NHL is a collection of more than a dozen different cancers of the lymphatic system, which generates the body's immune defenses. This system includes a network of channels akin to blood vessels through which lymphocytes—important white blood cells of the immune system—patrol the body for invading microbes. Along these lymphatic routes in the neck, armpits, abdomen, and groin are clusters of bean-shaped lymph nodes that house platoons of the infection-fighting lymphocytes. These cells also cluster in areas that serve as gateways to the body, including the mucous membranes lining the respiratory and digestive tracts, and the skin. Lymphocytes travel in the bloodstream, as well. The lymphatic system also includes such organs as the spleen, thymus and tonsils.

Because NHL can develop wherever in the body lymphocytes can be found, the cancer can crop up nearly anywhere. Symptoms can vary widely, depending on the cancer site. The most common symptom is a noticeable, usually painless swelling of a lymph node. NHL in the digestive tract can cause nausea, vomiting, or abdominal pain; in the chest, shortness of breath or cough may develop. If the brain is involved, patients may have headaches, vision changes, or seizures. If the bone marrow is affected, lymphoma cells may crowd out red blood cell precursors, causing anemia. Reddened patches on the skin can occur when lymphoma cells there prompt localized inflammation.

Because NHL can foster a hyperactive immune response, it often causes symptoms that develop when the body is fighting an infection, such as fevers, night sweats, tiredness, and weight loss. Another NHL symptom is widespread itching, apparently triggered by immune cells' release of histamines, the same compounds that cause itchiness in allergic reactions.

NHLs can affect people of all ages, although the incidence of NHL increases with age. About half of all cases are in people aged 60 and older.

The treatments for NHL include drugs and radiation therapy regulated by the Food and Drug Administration.

Diverse Group of Cancers

To diagnose NHL, doctors remove a small sample of the tissue thought to be cancerous. This procedure, known as a biopsy, is usually done with a local anesthetic. A pathologist examines the tissue under a microscope to look for cancer cells. The appearance of these cells and the proteins on their surfaces helps the pathologist determine the type of NHL the cancer is. The various types have distinctive appearances, carry different prognoses (predicted outcomes), and have different treatments. Whereas one

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type may be extremely deadly, another may be highly curable.

NHLs are classed as low-, intermediate- and high-grade. This classification scheme accurately predicts the survival of untreated patients, but is not as reliable in predicting outcome after treatment. Low-grade lymphomas are slow-growing tumors, and some patients can survive for more than a decade without treatment. Although chemotherapy often can shrink low-grade lymphomas, the cancer usually recurs within five years. Recurrent tumors can also be treated with chemotherapy or radiation, but over time, low-grade NHLs tend to become more aggressive and less responsive to therapy. Consequently, these types of lymphomas are not cured with currently available treatment.

In contrast, intermediate-grade and high-grade lymphomas are fast-growing tumors that, without treatment, generally are fatal within a year or two of diagnosis. Chemotherapy may cure many types of these lymphomas.

Doctors determine the stage of the cancer according to the number and location of tumors. This information, which also affects prognosis, is obtained from a physical exam, blood tests, and x-rays, CAT-scans, or ultrasound scans of various organs and tissues. Biopsies of the bone marrow and lymph nodes often are necessary. Regardless of NHL type, patients have a better prognosis with appropriate therapy if they have:

- the cancer in only one lymph node area or in only one area or organ outside the lymph nodes
- no tumors more than 10 centimeters in diameter
- no systemic symptoms, such as fevers or night sweats.

Younger patients also usually fare better than older ones.

A number of studies have pinpointed the genetic flaws that characterize different types or subtypes of NHL. Experts predict that this information will soon foster a new classification scheme that more accurately predicts outcome.

Tracking the Cause of a Cancer Increase

Medical researchers have been trying to find a reason or reasons for the rising incidence of non-Hodgkin's lymphoma, which has been increasing in this country since the 1950s. Suspects include: pesticides, hair dyes, AIDS, immune-suppressing therapies, and improved diagnosis.

Studies on a possible relationship between pesticides and NHL were prompted by two observations. First, the central part of the United States, which is predominantly an agricultural area, has been a hot spot for NHL since 1950. Second, NHL incidence also has been increasing more rapidly in rural areas than urban areas. These findings suggest certain pesticide exposures might cause NHL in some people. The National Cancer Institute's Sheila Zahm, Sc.D., and others found a two- to eightfold increase in NHL incidence among farmers who frequently used phenoxy herbicides such as 2,4-D, which are widely used on crops such as wheat, corn, oats, rye, barley, and sugarcane. These herbicides are also commonly used to rid lawns of weeds. More research needs to be done, however, to assess the possible link between NHL and pesticides.

Researchers are also examining the potential for hair dyes to cause NHL. The largest study on this, conducted by the American Cancer Society and reported in 1994, found women who used black hair dye for 20 years or more were more than four times as likely to develop NHL than women who didn't use hair dye. This finding confirms those of other studies.

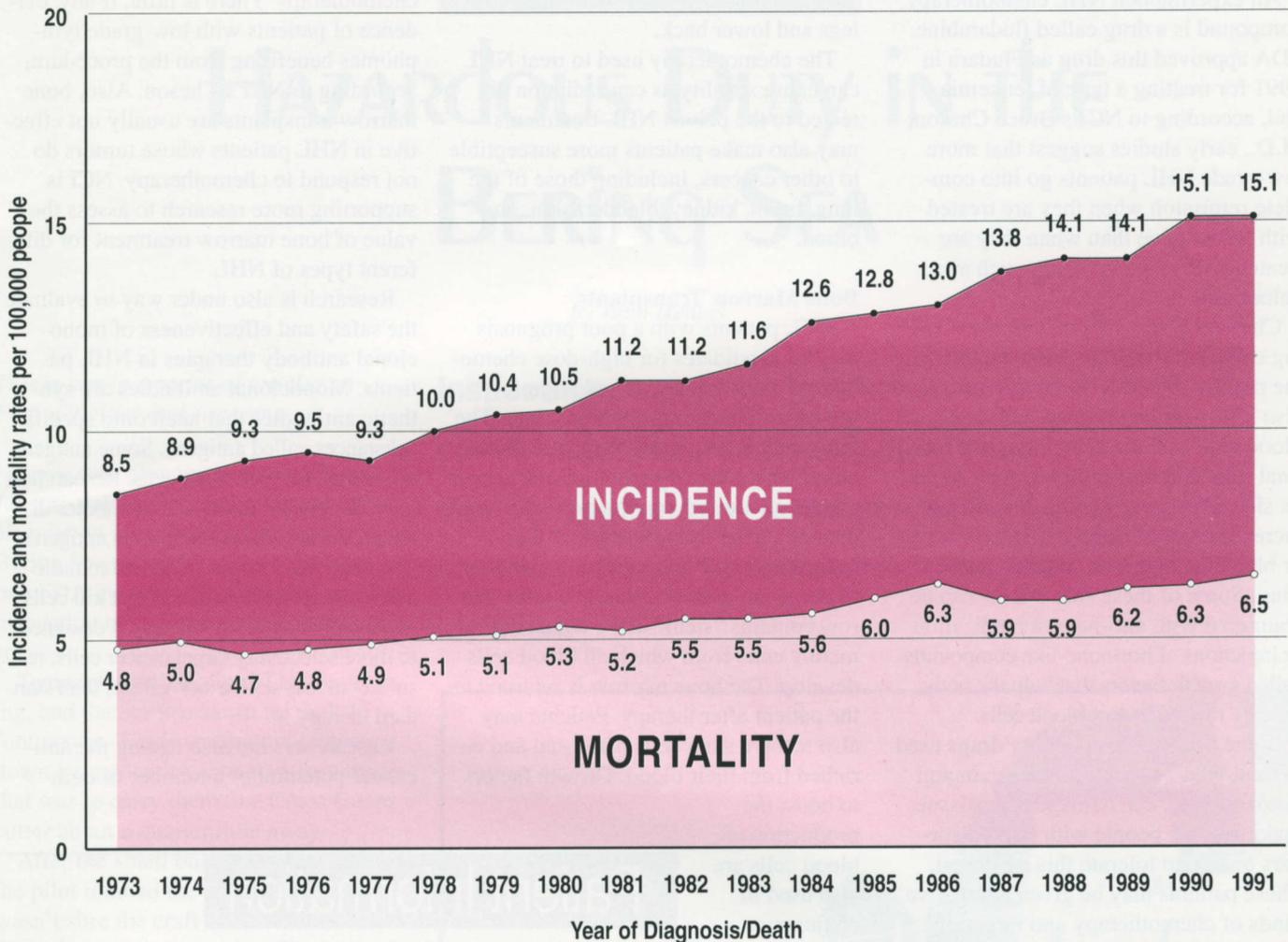
But because only a small fraction of women who dye their hair use black hair dye, this alone cannot contribute significantly to the increase in NHL in recent years.

According to Carol Palackdharry, M.D., of the Medical College of Ohio, changes in diagnostic criteria can account for only about 10 to 15 percent of the current cases of NHL. A similar percentage of cases can be attributed to AIDS, researchers M.H. Gail and colleagues estimated in a 1991 issue of the *Journal of the National Cancer Institute*. The immune suppression AIDS induces makes people more susceptible to NHL. The increased use of immune-suppressing therapies to prevent rejection of organ transplants, and to treat rheumatoid arthritis, cancer, and other disorders might also account for a small percentage of NHL cases, according to Palackdharry.

Further research is needed to fully explain the rising incidence of NHL. As Dan Longo, M.D., formerly at NCI and now at the National Institute on Aging, sums up in the August 1994 issue of the journal *Oncology*, "... it appears that lymphoma incidence is a building tidal wave. What remains unclear is whether we can rapidly learn enough about the various causes to implement successful prevention strategies that will enable us to diminish the damage done by the coming wave." ■

—M.P.

Non-Hodgkin's Lymphoma Incidence and Mortality Rates



(Source: National Institutes of Health, National Cancer Institute)

■ Incidence Rate
■ Mortality Rate

Treatment Varies

Doctors tailor treatment of NHL to the type of tumor, the stage of the disease, and the patient's age and general health. Most patients receive chemotherapy, radiation therapy, or both.

Because low-grade lymphomas usually grow slowly and cause few symptoms but eventually become resistant to treatment, doctors may postpone treatment until the cancer shows signs of spreading, or causes systemic symptoms (such as fevers or weight loss), or until the tumors become excessively bulky or threaten vital organs such as the kidneys or lungs. NCI researchers and others

have shown that delaying treatment does not adversely affect long-term survival and may actually improve patients' quality of life, as the treatments themselves can be debilitating. A substantial proportion of patients with low-grade NHL have spontaneous remissions, although these disease-free periods rarely last for long.

Chemotherapy for NHL usually involves several different drugs given at the same time. Some drugs, such as chlorambucil (marketed as Leukeran), are given by mouth; others, such as cyclophosphamide (marketed as Cytosan), are injected into a vein or muscle. To

treat disease that has spread to the brain, chemotherapy may be delivered to the fluid that surrounds the brain through a needle in the spine. Chemotherapy is usually given in cycles: a treatment period followed by a rest period, then another treatment period, and so on.

A frequently used chemotherapy regimen for NHL combines cyclophosphamide, doxorubicin hydrochloride (marketed as Adriamycin), vincristine (marketed as Oncovin), and the anti-inflammatory drug prednisone. Although used for about 20 years, recent studies suggest this regimen is as effective and has less serious side effects than some of

the newer drug combinations, according to Alan Aisenberg, M.D., of Massachusetts General Hospital.

An experimental NHL chemotherapy compound is a drug called fludarabine. FDA approved this drug as Fludara in 1991 for treating a type of leukemia, and, according to NCI's Bruce Cheson, M.D., early studies suggest that more low-grade NHL patients go into complete remission when they are treated with fludarabine than when they are treated with standard drugs such as chlorambucil.

Chemotherapy kills off rapidly dividing cells. Although its prime targets are the rapidly reproducing cancer cells, it also kills healthy dividing cells such as blood cells and the cells lining the intestinal tract and hair follicles. As a result, its side effects can include anemia, an increased risk of infection, mouth sores or bleeding, hair loss, nausea, and vomiting. Some of these side effects can be countered with anti-nausea medication or injections of hormone-like compounds called growth factors that help the body quickly restore its lost blood cells.

Some of the chemotherapy drugs used to treat NHL, such as doxorubicin and mitoxantrone, can damage heart tissue, making some people with heart disorders unable to tolerate this treatment. These patients may be given alternative kinds of chemotherapy and radiation therapy. Radiation therapy alone may be the treatment of choice for some patients, especially those who have only a single, small tumor. Some types of NHL respond best to chemotherapy followed by radiation therapy.

Radiation therapy uses high-energy x-rays to damage cancer cells and stop their growth. Radiation therapy is directed to the areas of the body known to harbor cancer cells. As an extra precaution, radiation may be directed to a broader area, such as to all the lymph nodes in the region of a known cancerous site. The treatment is generally given on an outpatient basis.

Radiation therapy can cause fatigue and red or dry skin in the treated area. Radiation directed to the chest and neck can cause patients to have a dry, sore throat and some trouble swallowing. Patients may also have shortness of breath or a dry cough. Radiation therapy

to the abdomen may cause nausea, vomiting or diarrhea. Some patients who receive radiation to the spine may also have tingling or numbness in their arms, legs and lower back.

The chemotherapy used to treat NHL can cause sterility as can radiation directed to the pelvis. NHL treatments may also make patients more susceptible to other cancers, including those of the lung, brain, kidney, bladder, skin, and blood.

Bone Marrow Transplants

NHL patients with a poor prognosis may be candidates for high-dose chemotherapy with or without radiation followed by a bone marrow transplant. The transplant is necessary to restore the blood cells killed by the intensive cancer therapy. Before therapy, a portion of the patient's bone marrow is usually extracted and may be treated in an attempt to purge any cancer cells. The bone marrow contains "stem" cells, which are immature cells from which all blood cells develop. The bone marrow is returned to the patient after therapy. Patients may also receive stem cells harvested and enriched from their blood. Growth factors to boost the production of blood cells are also used in conjunction with bone marrow transplants.

Intensive radiation or chemotherapy followed by a bone marrow transplant has a number of potential serious side effects, including life-threatening infections, bleeding, damage to the liver, kidneys, lungs or heart, and subsequent leukemia. Although FDA has approved the chemotherapy drugs and growth factors most commonly used in conjunction with bone marrow transplants for cancer therapy, it does not regulate the procedure itself, just as it does not regulate other surgery and medical procedures considered "practice of medicine."

Studies provide strong evidence that bone marrow transplants improve the

long-term survival of patients with intermediate- or high-grade lymphomas that have relapsed but are still sensitive to chemotherapy. There is little, if any, evidence of patients with low-grade lymphomas benefiting from the procedure, according to NCI's Cheson. Also, bone marrow transplants are usually not effective in NHL patients whose tumors do not respond to chemotherapy. NCI is supporting more research to assess the value of bone marrow treatment for different types of NHL.

Research is also under way to evaluate the safety and effectiveness of monoclonal antibody therapies in NHL patients. Monoclonal antibodies are synthetic antibodies that latch onto specific substances called antigens. Some antigens are unique to lymphoma cells. Researchers have designed monoclonal antibodies directed towards these lymphoma antigens. The antibodies may be attached to radioactive compounds or toxins that kill cells. Monoclonal antibody therapy is designed to more selectively target cancer cells, resulting in less severe side effects than standard therapy.

Researchers are also testing the anti-cancer potential of a number of com-

Patient Information

Patients who wish to participate in research evaluating experimental NHL treatments should contact the National Cancer Institute at (1-800) 4-CANCER. ■

pounds produced by immune cells. These compounds, which include interleukin 2 and alpha-interferon, are usually given in addition to standard chemotherapy or radiation therapies.

"We're at an exciting time in lymphoma research," said Cheson. "There are a lot of promising new drugs on the horizon." And people are eyeing that horizon more intently as NHL becomes more common. ■

Margie Patlak is a writer in Elkins Park, Pa.