Emerging Links between Chronic Disease and Environmental Exposure

Non-Hodgkin's Lymphoma
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AS OUR KNOWLEDGE about the etiology of disease progresses, the evidence for environmental contributions to disease grows. There is a need to evaluate the findings from this research to assess possible emerging trends in chronic diseases. Physicians for Social Responsibility (PSR) has partnered with environmental health researchers to assess the emerging links between chronic diseases and environmental exposures and to generate a set of policy and research recommendations. PSR’s goals are to elucidate and raise awareness of health care providers, researchers, and policy makers about increased evidence suggesting linkages between environmental factors and chronic diseases. PSR has chosen Parkinson’s disease, non-Hodgkin’s lymphoma, and diabetes as the three focus areas.

The next few pages review the diseases that were considered when conceptualizing this project. The comprehensive report that follows delves much more deeply into the three specific chronic conditions and their connections to the environment.

In evaluating the candidate diseases, PSR used three sets of criteria:

1. Public health importance: disease incidence and prevalence, years of productive life lost, and associated costs;
2. Scientific evidence supporting a link between the disease and environmental exposures;
3. Public concern and interest: the likelihood that the disease is of significant concern to the public and to health care providers treating the public.

In developing the initial process to examine emerging environmental links to chronic conditions, PSR identified several possible candidate conditions for evaluation: attention deficit hyperactivity disorder (ADHD); amyotrophic lateral sclerosis (ALS); Alzheimer’s disease; autism, i.e., the spectrum of pervasive developmental disorders; diabetes; non-Hodgkin’s lymphoma (NHL); and Parkinson’s disease (PD). Though PSR could only select three chronic illnesses on which to focus, PSR wanted to consider many different illnesses before making a selection. These three reports review the existing research and provide a framework and a context for the future work. PSR
encourages this research because it will clearly assist in building a foundation for understanding the total impact of the environment on our nation’s health.

This report is intended to further discussion among health care providers about the emerging links between chronic disease and environmental exposure. PSR understands that these connections are not always automatically drawn by clinicians, and this report does not intend to produce diagnostic expertise on the diseases, but instead offers an assessment of the scientific evidence about possible associated and causative factors related to chronic disease. Diseases such as asthma, cancer, diabetes, and Parkinson's disease all have delineable associations with environmental problems such as air pollution, drinking water contamination, and exposure to toxic chemicals. It is important to emphasize this connection and encourage the health care community to begin to recognize that these relationships do exist.

During the last two decades, chronic disease has replaced infectious disease as the major focus of public health concern, even with the appearance of AIDS. Seventy percent of all deaths annually are attributable to chronic illness. The top four and seven out of the top ten leading causes of death in the U.S. are chronic diseases (1). These illnesses account for more than $750 billion of the $1 trillion spent annually on health care. If anything, the economic impact of chronic diseases will increase in this century as this pattern becomes predominant worldwide. According to the World Health Organization, chronic diseases will become the top cause of death in most countries in the next few decades.

Among chronic diseases, cancer has received much attention. The “War on Cancer,” initiated in the 1970s, resulted in the creation of national tracking efforts like cancer registries and large expenditures of research dollars. Much of the research, however, has focused on treatment and the search for cures, while very little is known about the etiologies of many cancers. Other chronic diseases, such as chronic degenerative diseases of the central nervous system, have received even less attention. Such diseases, most notably Alzheimer's disease and Parkinson's disease (PD), place very heavy burdens on society. Most people have a family member or friend who has been affected by one of these diseases. However, we do not have the kinds of tracking systems in place to monitor these conditions that we have for cancer. The discovery of causes and cures is even more elusive. As society ages, these diseases are expected to exact a greater burden on families and the medical care system and human suffering overall.

Whether it is cancer or autism that is affecting our families and showing up in our examination rooms, the growing rates of chronic disease compel us to search for clues and answers to determine the true causes of these increasingly prevalent illnesses. Evidence from disease cluster investigations has shown that exposure to certain chemicals increases the risk for certain cancers. However, a comprehensive analysis of existing research and better tracking mechanisms are key to truly differentiating real science from coincidence.

These three brief overviews introduce the three diseases PSR has chosen for in-depth analyses. Though a significant review of the existing research was done on all seven of the possible conditions prior to selection, these conditions met the three-project criteria most directly. This in no way minimizes the potential links of the environment to the other conditions, and certainly PSR would encourage additional research to assess links on the four remaining conditions as well as other critical chronic illnesses.

**PARKINSON'S DISEASE**

More than 60,000 people each year are diagnosed with PD in the U.S., and more than a million Americans are living with the disease at any one time (2). PD is a progressive brain disorder that affects patients for many years. The disease usually strikes people over age 60, but in some cases can develop much earlier. Idiopathic PD, the most common form, is defined by the absence of an identified, specific cause, as opposed to forms of
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Parkinsonism that are due to a specific environmental exposure, like manganese poisoning (3) or other defined nosologic entities. PD affects both men and women and is the second most common neurodegenerative disorder of the elderly, after Alzheimer's disease. The disease is associated with progressive and irreversible damage to the dopaminergic projections from the substantia nigra to the dorsal striatum, and with the formation of Lewy bodies, the pathological hallmark of idiopathic PD.

Parkinson's disease involves the death of brain cells that produce dopamine, a necessary chemical messenger that serves to control movements mediated by the extrapyramidal system. Loss of dopamine and the secondary effects on other neural systems lead to the cardinal symptoms of PD, tremor, rigidity, bradykinesia (slow movements) and a loss of postural reflexes. As the disease progresses, other problems may emerge, including personality changes, bradyphrenia (slowing of thought processes), sleep disturbances, sexual dysfunction, Alzheimer's-like dementia, paranoia, psychosis, and even hallucinations and severe depression.

Although some patients have an inherited form of PD (particularly those with an onset prior to age 50) a large twin study showed that hereditary factors are of little importance among patients who contract the disease in later life (4). Among identical twins with one affected member of the pair, the probability of the second twin contracting the disorder was no higher than in the general population. An editorial that accompanied this landmark article urged a return to the focus on environmental chemicals, especially pesticides, as a cause (5).

The causes of PD have been a subject of debate for decades. In the 1980s, the medical community began thinking of Parkinson's disease as a neurological disorder that might be caused by chemical exposures because a group of young people developed Parkinson's-like symptoms after taking an illegal designer drug contaminated with a chemical byproduct called MPTP. Subsequently, similar symptoms were induced in monkeys by administering MPTP. This type of parkinsonism is very similar to idiopathic PD. This led to the realization that a single adverse exposure could start a complex chain of events leading to regionally specific neurodegeneration (3). Oxidative stress, induced by a variety of factors, including pesticides, might contribute to the development of parkinsonism. The structure of MPTP is similar to that of paraquat, a widely used herbicide. This finding led to investigations of PD and pesticide exposure. Pesticide exposure has been identified as a risk factor for the development of PD in numerous epidemiological and case control studies (6,7).

NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphomas form a group of related cancers. A lymphoma is a cancer of the white cells that is localized in lymph nodes or location other than the bone marrow. NHL is the fifth most common cancer and the sixth most common cause of cancer death, accounting for about 16 new cases per 100,000 people each year (8). Rates of NHL have risen sharply in the U.S. over the last 20 years, especially among older people and those who have AIDS.

A recent twin study on cancer and heredity indicates that a genetic contribution to NHL, if present, is small, although the authors could not provide a quantitative estimate because of a small sampling size (9).

Non-Hodgkin's lymphoma seems to be caused by factors that are involved with genetic damage to cells and/or factors that are associated with immunosuppression. People with inherited immunodeficiency syndromes (which are very rare) have elevated rates of NHL, as do people who receive immunosuppressive drugs for transplants or have immunosuppression for some other...
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reason. NHL tumors have a high rate of genetic alterations; these are thought to be due to various environmental and infectious exposures. People with inherited defects in DNA repair (for example, ataxia telangiectasia syndrome) have high rates of NHL.

For many years it has been recognized that Epstein-Barr virus plays an important role in NHL incidence. However, in the U.S., Epstein-Barr virus seems to play a relatively minor role compared to in African cases.

More recently, infection with HIV/AIDS has been recognized as a risk factor for NHL and may be responsible for about 60% of the rise in incidence over the last 20 years (10). A rare type of rapidly progressive NHL is related to infection caused by HTLV-I (human T-cell lymphotropic virus type I), a retrovirus similar to HIV.

Numerous agricultural and industrial chemicals have been associated with NHL. Farmers have higher rates of NHL than non-farmers, and exposure to herbicides (including Agent Orange) and to certain insecticides (including organophosphates) seem to be important risk factors (11–14). There is also good evidence for involvement of PCBs and dioxins (15–16).

NHL is an example of where we still have much to do in the “war on cancer.” While cancers related to smoking are falling, NHL rates have risen and now seem to have reached a plateau.

DIABETES MELLITUS TYPE II

Diabetes is a disease in which the body does not produce or use insulin properly. The cause of diabetes is unknown, although both genetic and environmental factors, such as obesity and lack of exercise appear to play roles. There are two major types of diabetes: Type I is a disease in which the body does not produce enough insulin, most often occurring in children and young adults. People with Type I diabetes must take daily insulin injections to stay alive. Type I diabetes accounts for 5 to 10% of all diabetes cases. Type II is a metabolic disorder resulting from the body's inability to make enough or properly use insulin. Type II diabetes is nearing epidemic proportions, due to an increased number of older Americans and a greater prevalence of obesity and sedentary lifestyles.

Diabetes mellitus is one of the most serious threats to American health. Recent studies indicate that the prevalence of diabetes is increasing among the general population in the U.S. and worldwide. More than 135 million people are affected by diabetes worldwide including more than 8.5 million Americans. In many developed countries, 10 to 20% of people over 45 are affected by non-insulin dependent diabetes mellitus. About 15% of people over age 70 have type II diabetes.

The World Health Organization has concluded that diabetes is becoming a global epidemic and predicts that the disease will be one of the world’s major contributors to morbidity by 2025 (17). Blacks and Hispanics have a twofold to threefold increased risk of developing type II diabetes; poverty is also an important risk factor. Diabetes increases the risk of blindness, loss of limbs, heart disease, stroke, kidney failure, and depression (18) and generally reduces life expectancy. The costs of diabetes arise from the treatment of the disease, its complications, lost workdays, and disability. Of the three diseases under consideration, diabetes clearly has the greatest public health impact.

There is strong evidence for both inherited and environmental risk factors for diabetes. Type II diabetes has been associated with certain genetic sequences in the NIDDM1 region of chromosome 2. Recently, Horikawa and colleagues (19) have proposed that the gene in this region might be CAPN10, a gene that encodes calpain. The authors estimate that the removal of the risk factor resulting from the combination of two genetic variants would reduce the prevalence of diabetes by 14% in Mexican-Americans and 4% in Europeans.
Environmental risk factors include lifestyle factors, like diet and exercise habits, are even more important than environmental exposures. Obesity is a risk factor for type II diabetes; 80 to 90% of the people with this disease are obese. The incidence of non-insulin dependent diabetes mellitus has also been found to increase, up to a point, with the number of cigarettes smoked per day. Rates of diabetes have risen with those of obesity and poor physical fitness.

However, a component of diabetes seems to be related to environmental exposures, most notably arsenic and dioxins. Specifically, diabetes has been linked to exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Low-level dioxin exposure has been shown to affect glucose metabolism and thyroid function in some (but not all) occupationally exposed populations (20–23). The most compelling evidence is from a study of Vietnam veterans who were involved in handling Agent Orange, an herbicide that contained dioxin as a contaminant (24). A total of 989 of these so-called “Ranch Handers” were compared with 1,276 veterans who served elsewhere in Southeast Asia during the same period. The study found higher rates of diabetes among the Ranch Hand group, with a dose-response relationship between blood dioxin level and severity of diabetes.

Arsenic is also of interest, in the U.S. and worldwide, because of continual high exposures in communities due to natural and industrial sources of arsenic pollution of water. The strongest evidence for a linkage between arsenic and diabetes comes from several epidemiological studies in Taiwan that identify higher prevalence levels of diabetes in arseniasis-endemic areas relative to non-endemic areas (25–27).

Diabetes is an important and growing health problem that brings with it a number of interesting environmental dimensions. Certainly the problems of obesity and lack of physical exercise could be related to the environment in which individuals live as well as the natural environment; communities today are not designed to facilitate walking and other forms of physical exercise.

**EDUCATION, RESEARCH AND POLICY RECOMMENDATIONS**

As a nation, we can begin to address an emerging link between chronic disease and the environment in a number of ways. It is time to bring together the mounting information from health and scientific researchers, clinicians, and public health officials and call for additional research, public education, and as appropriate, policy changes to reduce exposures. There are a number of policy steps that should be taken to address this critical issue.

First, we need a public health infrastructure to track chronic diseases in the U.S., including the three addressed in these papers, and to monitor the environmental exposures that may be related to these diseases. Such a system will allow us to determine whether linkages exist and the strength of those linkages. Public health policies and programs that effectively link exposure monitoring, biomonitoring of chemicals in the human body, and chronic disease will greatly enhance our ability to understand and reduce these emerging links in the future.

A Nationwide Health Tracking Network, the beginnings of which have been established through the Centers for Disease Control and Prevention (CDC), should contain three primary components and should be organized to facilitate a search for interactions (28):

**HAZARDS TRACKING**: measuring the amount, concentration, and geographic distribution of known and potential toxic chemicals in the environment (such as the Toxics Release Inventory).

**EXPOSURE TRACKING**: assessing and measuring human exposure to environmental chemicals, including levels of exposure among population subgroups (such as CDC biomonitoring capacity).

**HEALTH OUTCOME TRACKING**: monitoring disease events and trends in health risk behaviors within populations over time through tracking systems such as vital statistics, health surveys, and disease registries.
As of January 2003, representatives from 17 states, three large cities, and three schools of public health began to develop the infrastructure and pilot projects to launch the first phase of this network. The national tracking system will collect data that will help further illustrate the link between chronic conditions and environmental exposures, thereby supporting the calls by public health and environmental advocates for health-protective policies.

Second, we need to educate physicians, nurses, and other health care providers about the possible connections between the environment and disease. Health care providers are on the front lines of protecting the nation’s health and can identify and prevent environmental exposures in their patients that may lead to disease later in life. Health care providers are one of the most trusted sources of information for their communities and their patients.

Third, we need to invest in further research of these and other emerging links between chronic disease and the environment. Adequate funding of centers of excellence, academic researchers, and community-based prevention intervention research is required to ask the next set of questions. As an example, the proposed National Children’s Study will track exposures to children over a 30-year period to determine when and how exposures at different developmental stages impact growth, development, and morbidity.

Finally, environmental policy solutions exist that can begin to reduce human exposures to a number of the toxicants—such as agricultural pesticides, dioxin, arsenic, and PCBs—implicated in the evaluation of the three chronic conditions we have targeted. These policies include

- Ratification of the **Stockholm Convention on Persistent Organic Pollutants (POPs)** by the U.S. and ratification by 49 other countries for entry into force by the end of 2003;

- Full implementation of the **Stockholm Convention in the U.S.**, including
  - An expedited phase-out of PCBs still in use;
  - Additional funding for international development, particularly focused on alternatives to DDT in malaria control; and
  - Provisions for domestic action on future POPs, such as the brominated flame-retardants known as PBDEs that might be added to the treaty in the future.

- Release of EPAs **Dioxin Reassessment** and development of an EPA regulatory scheme focusing on pollution prevention measures aimed to achieve significant reductions in dioxin releases and human exposures.

- Additional regulatory action on **pesticides**, including further restrictions and phase-outs of organophosphate insecticides, federal legislation restricting pesticide use in schools, a permanent ban on the use of human subjects in tests of pesticide toxicity, and full implementation of the Food Quality Protection Act.

- Protection of hard-earned “right-to-know” provisions such as the Toxics Release Inventory and passage of further protections and the expansion of public information guarantees for people with chemical hazards in their communities.

These reports are not meant to provide health care providers with all of the answers, but to start clarifying the links between environmental exposures and causes of chronic illness so that preventive measures can be taken, more comprehensive diagnoses made, and more effective treatments explored. Certainly more research needs to be done to understand these links and to develop evidence that will effectively impact important policy action.
REFERENCES


WHAT IS NON-HODGKIN’S LYMPHOMA?

LYMPHOMA is a group of cancers arising in lymphoid tissue. These cancers are classified into two large groups, Hodgkin’s disease and non-Hodgkin’s lymphoma (NHL). The single major difference between the two is the presence of large, usually multinucleate cells called Reed-Sternberg cells in tumor biopsy sample from Hodgkin’s disease patients (1). Most likely, NHL is not a single disorder but rather a mixture of different disease entities of potentially varying etiology.

Diagnosis

Over two thirds of NHL patients first notice a painless swelling of the lymph nodes (2). Other symptoms are nonspecific and include unexplained fever, night sweats, constant fatigue, unexplained weight loss, itchy skin, and/or reddened patches on the skin (3). The presence of a mass of lymph tissue can be confirmed by imaging techniques such as X-ray, CT, MRI, or lymphomagram (4). Pathological examination of biopsy sample using specific markers for lymphocytes establishes the presence of cellular patterns consistent with the definitive diagnosis of NHL (5). If the biopsy sample shows characteristic feature of Hodgkin’s disease, most notably the presence of Reed-Sternberg cells, diagnosis of Hodgkin’s disease is made.

Classification

Cells associated with lymph system, (B and T lymphocytes and others) originate from hematopoietic stem cells and undergo complex differentiation processes to become cells of a specific phenotype, which express a specific set of receptors on the cell membrane and have a distinct morphology under the microscope. In this process, they move through several stages of differentiation (6,7). It is currently understood that the tumor cells in NHL are a malignant form of a precursor (immature lymphocyte) arrested at a stage of such normal differentiation processes. There are many subtypes of NHL, which appear to relate to different classes and stages of development of lymphocytes.

The heterogeneity of NHL presents a special challenge for classification. More than 25 classification systems for NHL have been proposed since 1925 (8). The World Health Organization (WHO) recently adopted a new scheme for the classification of hematologic malignancies (9), which is pending publication (WHO in press). In brief, the new WHO classification defines distinct subtypes according to a combination of morphology, immunophenotype, genetic features, and clinical
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syndromes” (9). It is expected that the new WHO scheme will replace the two classification schemes that are currently in use (8): the Formulation for Clinical Use and the Revised European-American Lymphoma (REAL).

Worth noting about these classification schemes is that the goal of the WHO classification is “to define disease entities that can be recognized by pathologists, and that have clinical relevance” (9). This goal is based on an underlying hope that treatment be optimized for each subtype of NHL, which has a different clinical course and varying levels of responsiveness to various cancer treatments such as chemotherapy and radiotherapy. This emphasis on the clinical relevance has implications for prevention of the disease, since NHL entities of a common etiology may be classified as different subtypes according to such a scheme.

Weisenburger (1992) argues for grouping all NHL subtypes together for epidemiologic study (10). This will ensure that disease of common etiology, along with other “misclassified” diseases that do not involve the particular etiology, will be included without loss of information. A drawback of this approach is that a small increase in risk associated with certain etiologically relevant NHL subtypes can be diluted. For this reason, subtype-specific analysis needs to be conducted where possible. This approach — treating all NHL subtypes tentatively as a single entity, with some additional discussion on NHL subtypes when appropriate — will be taken in this review. Since chronic B-cell leukemias and multiple myeloma are closely related biologically to NHL (11), findings on these neoplasms will be mentioned where they appear to be relevant. These are usually considered separately from NHL, though, in part because changes in their incidence appear to occur independently from that of NHL (12). In the future, with the development of new technologies to assess patterns of altered expression of DNA and proteins in cells (genomics and proteomics), it is likely that new classifications will arise that will provide opportunities for etiologic studies of associations with environmental exposures.

DESCRIPTIVE EPIDEMIOLOGY

Current status

In 2001 there were an estimated 56,200 newly diagnosed cases of NHL. It was the fifth most common cancer in the U.S., following prostate, breast, lung, and colon cancers (13). The age-adjusted incidence rate for 1994 through 1998 was 16.1 per 100,000 per year based on the Surveillance, Epidemiology, and End Results (SEER) program (14). The SEER is a U.S. population-based cancer registry, which is maintained under contract to National Cancer Institute and covers 14% of the U.S. population (1). The estimated deaths from NHL in 2001 were 26,300. In 1997, the deaths from NHL accounted for about 1% of the total deaths in the USA (1). Since mortality can be influenced by survival of patients, which can change due to treatment improvement, and our main interest lies in primary prevention (i.e., reduction of incidence), we will focus mainly on incidence data for the rest of the report.

Secular trends and geographic variations in the U.S. and worldwide

The age-adjusted incidence of NHL is rising worldwide in all places where secular trend data of good quality are available (15–18). The countries in which the increase is noted include Canada, the U.K., New Zealand, Finland, Sweden, Norway, India, Japan, the U.S. (12), France, the Netherlands, Spain (16), China (19), and Singapore (20).

In the U.S., age-adjusted incidence rate rose by 3.5% annually for the period from 1973 through 1991 then almost leveled off for the period from 1991 through 1998 (14). From 1985 to 1992, the yearly rate of increase was 4.2% overall in the data gathered in seven European countries and ranged from 2.7 to 8.0% by country (16).

International comparison of incidence is difficult since valid incidence data based on well-maintained cancer registries are available only from limited parts of the world. Nonetheless, some comparison
is possible with limited data. Newton et al. (1997) provide 1980s annual incidence data from 14 countries (21). In this survey, the highest annual incidence was 10 in 100,000 for whites in the U.S., the lowest being 2 per 100,000 for Thailand.

Among the seven European countries from which data were collected from 1985 to 1992, Finland and Denmark had the highest incidence of 18.0 and 16.8 (16). (Note that these numbers cannot be absolutely compared because of the use of different age-standardizing populations and possible difference in medical practices, reporting, and time periods.) Nonetheless, similar to the U.S., the rate of increase in incidence rates for these two countries appears to level off toward the end of the period.

Changes in NHL diagnostic practice over time cannot account for rising incidence rates (22). Prior to 1970, some cases we would now classify as NHL would have been classified as Hodgkin’s disease, however, this change in diagnostic practice would have resulted in a decrease, not an increase, in reported rates in the 1980s and 1990s. While there are two new variants of NHL that were not classed as NHL prior to the late 1980s, these comprise less than 3% of all NHL cases, therefore, contributing only a small proportion of the observed rise in incidence. What can account for the rising incidence? This will be discussed in later sections on etiology.

Demographic factors

The risk of NHL increases with age (12, 18, 23). NHL incidence is about 100 times greater for the elderly—75 years and older—than for children under 15 years of age (17). This age dependence is observed for most NHL subtypes with the exception of lymphoblastic and small noncleaved NHLs, which most frequently occur in childhood. Therefore, in looking at variations of NHL rates by time and space, age-adjustment of incidence rates or looking at age-group specific rates is appropriate, since the average age has increased over time, and there is a great regional and national difference in age compositions. Data from the U.S. can be used to compare incidence rates for different race groups. (International comparisons


Based on Surveillance, Epidemiology and End Results (SEER) Data
of incidence across regions inhabited by various race groups are less helpful, since there are many other factors that differ across such regions.) Annual age-adjusted incidence rates for white males and females were 17.1 and 11.5 per 100,000 person-years, respectively, and for white and black females, 12.6 and 7.4 per 100,000 for the period from 1978 through 1995 (17). Clearly, whites and males have a higher risk for NHL. Secular trend for incidence shows different patterns for each major race-sex group (14). Rates for blacks have steadily increased at an average annual percentage change of 4.1% for males and 3.0% for females for 1973 to 1998. Whites give different pictures. Rates for white males increased at an average annual percentage change of 2.4% for 1973 through 1979, at an even more rapid 5.0% for 1979 to 1988, and at a lower rate of 1.7% for 1988 to 1995. Their rates decreased at a rate of –3.3% for 1995 to 1998. Rates for white females rose 3.0% annually for 1973 to 1988, followed by a slower annual increase of 1.3% for 1988 to 1998.

Secular trend also differs by age group. Overall, across the time period from 1947 through 1990, incidence rose by more than half for both males and females 25 to 44 years old; it doubled for ages 45 to 64; and it tripled for ages 65 and older (15). The incidence of childhood NHL has not increased over time (24,25). So while the proportion of elderly among the population in the U.S. is increasing, the risk of NHL among the elderly is also increasing over this time period.

Subtypes
It is important to know if the observed increase is for all NHL subtypes or limited to specific NHL subtypes. If the increase is limited to specific subtypes, prevention efforts ought to target those subtypes. Because of the rarity of some subtypes, the changes over time in classification, and limited reproducibility of the classification scheme to date, there are few comprehensive evaluations.

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One such evaluation was done recently by Groves et al. (2000) using SEER data (17). Investigators found that for the most of the 12 subtypes classed according to Working Formulation, increasing age-adjusted incidence was seen for the period between 1975 and 1995. For the NHL subtypes covering approximately three quarters of total NHL cases, incidence rose between 1978 and 1995 irrespective of race and sex. There are three subtypes with a trend dissimilar to the remaining majority; these comprise 23% of all NHL cases. The subtype follicular small lymphoma had a constant incidence rate over time. The incidence rate for diffuse small lymphoma seems to have decreased over this period. The incidence rate for diffuse mixed lymphoma increased for the first 9-year period and then decreased for the second 9-year period among whites; among blacks, overall the rate shows a small increase for the entire 18-year period (17).

If some subtypes or groups of subtypes have common causal factors, one might expect to see higher incidence rates of such subtypes in the same population groups. An analysis based on such rationale was done using data from 14 countries (21). There was statistically significant correlation between incidences of nodal and extranodal lymphoma across countries. When extranodal lymphoma was further divided into primary gastric, primary small intestinal, and primary skin lymphomas, the incidence rates for each of these were correlated with the rates for nodal lymphoma. This observation lends some support for the hypothesis that there are common exposures that cause increased risk for these subtypes of NHL.

BURDEN OF DISEASE
Morbidity and mortality
The 5-year relative survival rates (i.e., proportion of NHL patients surviving 5 years after diagnosis
adjusted for expected mortality) were 53.1% for the period of 1992 to 1997, meaning only about a half of the patients were alive 5 years or longer after diagnosis (14). This is a small but significant improvement from 47.2% for 1974 to 1976, but the improvement is limited to women, whose 5-year survival rate increased from 47.3% for 1974 to 1976 to 57.8%. Blacks overall have a worse prognosis than whites (5-year survivals are 38.9% for black males and 51.4% for black females for 1992 to 1997). No improvement in prognosis was seen for blacks across the two periods. Generally, patients age 75 or older at diagnosis have worse prognoses.

Treatment costs

Treatment for NHL is chosen considering the stage of the disease, the type of cells involved, patient characteristics, and efficacy of available treatment options (26). It can include chemotherapy, radiotherapy, and other new modalities, such as DNA vaccine against cancer antigen. In spite of the progress made in the treatment, the majority of NHL patients cannot be cured. Information on medical costs specifically associated with NHL is scarce. This scarcity seems striking, as such estimates are necessary in assessing potential benefit of primary prevention strategies targeted at specific cancer (27).

Burden on society

As mentioned earlier, new NHL cases for the year 2001 were estimated to be 56,200 and deaths estimated to be 26,300. Person-years of life lost (PYLL) due to NHL for 1998 was 358,000 years, ranking the fifth among cancer-related PYLL (14,28). This is about one sixth of PYLL due to lung cancer, one half of that due to either breast or colorectal cancer, and one eighth of that due to unintentional injuries. It is 4% of the total PYLL due to all cancers. Premature deaths cost society in future output, which could otherwise have been produced by the deceased if he or she survived productive years of their life, lost due to cancer. Such costs are termed mortality costs. The mortality cost for NHL was estimated to be a total of $3,938,000,000 for the year 1990 in the U.S. (27).

There are two approaches for measuring the cost of cancer. One approach estimates a macroeconomic aggregate of burden to society called prevalent cost. The aforementioned mortality costs are estimated using this kind of macroeconomic approach. Another approach, a microeconomic one, estimates incidence cost to individual cancer patients by tracking expenditures. Taking the microeconomic approach and using data collected for the period of 1987 to 1991, long-term cost attributable to NHL from diagnosis until death or 15 years is estimated to be $48,000 per case (29). Barnett et al. (30) estimated costs attributed to NHL to an employer due to medical care, as well as work loss, to be $136,083 per active employee case. For retirees, spouses, and dependants, who presumably would not incur work loss-related cost to the employer, the cost was estimated to be $45,963, showing close agreement with the results from Fireman et al. (29). It should be noted that the disease results in additional costs beyond those for health care and work loss measured in these studies. A major source of these additional costs is labor expended to care for the patient by family members, which on average amounted to $18,000 per year for various cancers combined (31). A diagnosis of cancer also affects the health—mental and physical—of the diseased as well as his or her significant others. Costs due to these are not systematically counted but are significant (27).

ETIOLOGY

In assessing potential causal factors for NHL, the discussion is organized according to three areas of determinants of health (as defined by Blum, 1976): biological, environmental, and social (32). Before we start specific discussion, it seems useful to review a type of epidemiological analysis called an immigrant study, which describes how disease occurrence changes in an ethnically defined group
of people as they migrate to a cultural setting different from where they originated and gradually acquire new habits, such as diet, level of exercise, etc. The one immigrant study for NHL in the literature evaluated SEER incidence data collected in Hawaii, California, and Western Washington for Whites compared with Chinese and Japanese immigrants and later generations. No clear risk gradients were shown, implying that exposures involved with NHL may not be related to cultural differences like diet (that evolve over generations), nor to conditions of development per se (e.g., decreased childhood infections).

Areas of determinants of health

Cancer is considered a complex disease in which multiple low penetrance genes and external factors, most likely both modifying the effect of each other, influence the risk of developing it. Biologically speaking, cancer is a genetic disease in the sense that it is caused by changes in genetic material of cells. Cancer, for the most part, is not an inherited disease, because the genetic changes in cancer are mainly somatic mutations as opposed to germ-line mutations with which one is born. It is possible to have more genetic susceptibility to the development or failure to repair such somatic mutations. These observations of cancer in general are applicable to NHL. In addition, the immune system and genetic repair mechanisms play an important role in carcinogenesis. NHL in particular is related to a number of conditions that are associated with immunodeficiency. Immunosuppressive agents may increase NHL risk by allowing cancerous cells to escape immune surveillance. These kinds of agents can be described as cancer permitters. As will be discussed further, immunosuppression, either congenital or induced, is associated with a markedly increased risk, as high as 100-fold, for developing NHL. Other factors may also play a role. There have been several experimental and epidemiological studies evaluating the relationship between physical activity and the risk of NHL. Physical activity appears to have an effect on the immune system, and thus there is a potential mechanism for an association.

In general, malignant cells are characterized by the capacity to grow uncontrollably. In the case of NHL, a number of recurring genetic alterations have been observed in many subtypes of both B-cell and T-cell NHLs. Clonal expansion of malignant cells occurs because of malfunction in control of cell growth and/or death. Normally, gene expression is under tight regulation. Translocations of chromosomes can result in deregulation of genes, as a part of the gene leaves the normal location and is placed in a wrong position in the chromosomes. Other forms of alterations, for example, point mutations and gene amplifications and deletions, can render cells malignant and are known to be causal in development of cancers in general. Although such genetic changes have been found in NHL, translocations are by far the most frequent type of genetic alteration and are observed in up to 90% of NHL cases. This results from a feature of immune cells. As a part of maturation, B cells undergo immunoglobulin (Ig) gene rearrangements in order to produce cells that express the diverse antibodies needed for defense against a multitude of agents. This process involves recombination of DNA or splicing and rejoining of DNA. Mistakes can occur during this process, translocating the Ig gene components to a wrong chromosome. The rate of proliferation is correlated with the rate of errors; factors that induce proliferation may thereby lead to more errors in the causal path for NHL. Similar processes can lead to increased rates of T-cell mutations.

Biological determinants

Biological determinants of health are factors that cannot be manipulated, such as inherited genes, age, and sex. It is important to consider them, since biological and environmental determinants can interact in complex diseases such as cancer. The causal role of inherited genetic conditions in the rising incidence of NHL can be deemed limited because of the length of the period for which the
increase is observed compared to the time that is required for substantial changes in the population’s gene pool. As mentioned earlier, the incidence of NHL increased dramatically over the last few decades or longer. This rise cannot be explained by changes in the rates of inherited genetic traits, since this would require generations, much longer than a few decades, for detectable change to occur. Therefore, external factors have played the major role in the rise of NHL incidence. In this chapter, we summarize research findings on the etiology of NHL in the hope that they provide insights into potential measures to prevent avoidable occurrence of NHL, or at least, strategies for future research that eventually may lead to invention of preventive measures. Nonetheless, studies on the inheritance of NHL provide useful information regarding how NHL arises and, in particular, what is the set of sufficient conditions that cause NHL. Some environmental exposures have effects similar to that of inherited genetic traits, and so knowledge on such traits may turn useful in the search of adverse exposure.

The risk of NHL is elevated to a great degree with a few inherited genetic diseases. A lifetime risk for NHL is increased 12 to 25% for patients with primary immunodeficiency diseases such as ataxia telangectasia, Wiskott-Aldrich syndrome, and common variable immunodeficiency (39). These conditions are rather rare and can account only a very small portion of NHL (40). Common variable immunodeficiency is an immunodeficiency disorder characterized by antibody deficiency in blood that leads to chronic and recurrent infection (41). In common variable immunodeficiency, B cells fail to differentiate into immunoglobulin-producing plasma cells (41). In two studies of these patients, 30-fold and greater than 100-fold increased risk of lymphoma were noted (42). Wiskott-Aldrich syndrome is a rare X-linked recessive disease characterized by immune dysfunction and low level of platelets; it occurs in 1 in 250,000 European individuals (43) and is associated with a greater than 100-fold increased risk for NHL (44). A protein called Wiskott-Aldrich syndrome protein and the gene that encodes it have been identified. All hematopoietic cells express this protein, which is involved in both the cytoskeleton and cytoplasmic signaling system, and mutations of Wiskott-Aldrich syndrome protein gene cause the disease (45).

Research on ataxia telangectasia has led to observations of increased frequency of missense mutations of the gene responsible for ataxia telangectasia among non-ataxia telangectasia patients who are diagnosed with T-cell prolymphocytic leukemia and B-cell chronic lymphocytic leukemia. The etiology of these leukemias may be closely related to corresponding NHL subtypes (46). This has led to the hypothesis that environmental agents that cause this mutation might also cause NHL. People with ataxia telangectasia syndrome, an autosomal recessive disorder, have high frequency of chromosomal breakage (39). They have reduced DNA repair capacity, higher frequency of translocations involving immunoglobulin and T Cell Receptor gene locations, defective B-cell maturation leading to low or absent antibody production, and defective thymus development (47). These effects are due to lack of a functional form of a protein involved in detection of and repair of DNA damage due to, for the majority of cases, a frameshift mutation. The increased rate of NHL might be related to the genetic mutations and/or the consequent immunodeficiency (42).

Studies on twins provide some useful information on contribution of heritable factors to the causation of cancer. This is done by showing that monozygotic (identical) twins, who share 100% of genes, have higher concordance for cancer than dizygotic twins, who on average share 50% of their segregating genes. Probably the largest of such twin studies showed that a negligible portion of variance in cancer occurrence was attributable to heritable factors (48).

Environmental determinants

Uncertainties exist for roles of environmental exposures. These uncertainties largely involve small study populations with relatively low and/or not
well-characterized exposures (and therefore small statistical power to find effects). In evaluating the literature on environmental exposures and NHL, issues of statistical power, the quality of the exposure measurements, efforts to control for confounding, dose-response, temporality, and biological plausibility were considered. Information on these will be presented.

All of these studies are difficult methodologically. Exposures to some individual compounds may tend to occur together in certain people, or in statistical terms may be correlated. For example, DDT exposure can be collinear with dioxin and other organochlorines if diet is the major exposure source and with organophosphate exposures if past use for household/farming is the major exposure. It is difficult to assess exposures retroactively. Some large cohort studies have allowed execution of nested case-control studies involving measurement of exposures prior to development of cancer. However, in most cases, exposure has been assessed by questionnaire and cannot be quantified with any degree of accuracy. Finally, some of these measures, like dioxins, are very costly, inhibiting the ability to look at large numbers of people.

**Farming and farm-related exposures**

Since 1979, there have been studies in the literature linking NHL and employment in agriculture (49). It has long been observed by the National Cancer Institute that the mortality rates for NHL are higher in farming states of the central U.S. (50). In 1998, Khuder, et al. published a meta-analysis of 36 studies; they computed a pooled relative risk estimate of 1.1 for farmers compared to non-farmers (51). Some studies have reported a decreased risk for NHL for farmers. This pattern is similar to findings at other cancer sites, such as the lung, owing to farmers’ relatively healthier lifestyles with lower prevalence of smoking and higher amount of physical exercise.

There are many potential exposures involved with farming including animal and/or plant antigens, pesticides, and zoonotic viruses and other pathogens (52). Potential causal roles of antigenic stimulation have been discussed. Some pesticides are carcinogenic as determined by the International Agency for Research on Cancer (IARC) (53) and many of them are immunosuppressive (36). A range of pesticides including herbicides, fungicides, and insecticides are used in farm operation, and those who mix and apply pesticides are at risk, along with workers who are in close contact with treated fields and foliage. Such workers may have exposure to multiple compounds, including pesticides and other toxicants such as diesel exhaust (54). In addition to the active, pesticidal ingredients, pesticides contain other ingredients, which also may be toxic to humans, as well as impurities such as dioxins that historically were contaminants of phenoxy herbicides.

**PHENOXY HERBICIDES:** Commonly used herbicides under this category include 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic Acid (2,4,5-T). Historically both of these were contaminated by dioxins, most notably 2,4,5-T which was contaminated by the most toxic dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). Because dioxin is both a carcinogen and an immunotoxicant, much attention has been paid to trying to establish whether there is an association between phenoxy herbicides and NHL. Agent Orange, an herbicide containing commercial grade 2,4-D and 2,4,5-T, was used widely as a defoliant during the Vietnam War; in consequence, many Vietnam veterans claimed adverse outcomes as a result of Agent Orange exposure. The association between exposure to phenoxy herbicides and NHL among Vietnam veterans has been examined in several studies. Although earlier results of these investigations did not demonstrate an association (55-58), later studies, especially those on more highly exposed occupational populations, have found associations between NHL and phenoxy herbicide exposure (54,59,60). A large multinational occupational cohort study (61) found increased risk for NHL for workers exposed to 2,3,7,8-TCDD contaminated
phenoxy herbicides compared to the general population (standardized mortality ratio [SMR] of 2.6, 95% confidence interval [CI], 1.3-4.7) (61).

A number of studies have investigated exposure to pesticides and childhood NHL and leukemia. For instance, exposure of a child to “herbicides or pesticides” was associated with a two-fold risk for NHL (62). Two reviews (63,64) found a greater number of studies on childhood leukemia and pesticides, but none of them studied specific roles of herbicides. In a recent study by Infante-Rivard et al. (1999), the use of herbicides in and around the home during pregnancy appeared to increase risk for childhood leukemia, and the risk increased as the frequency of the use increased. 2,4-D was the most widely used chlorophenoxy herbicide used in the study population (65). This study found a greater herbicide-related risk increase among children with mutations in P450 enzymes, which would slow the metabolism of a number of pesticides, including organochlorines, organophosphates, and carbamates. This line of research could be pursued for NHL as well. In this study, the use of herbicides and other pesticides overlapped substantially, and the data presented do not allow the separation of effects of herbicides from those of others. Uncertainties about the exposure assessment make it impossible to conclude from this study whether the causal agent was a single pesticide, a class of pesticides, or some other factor associated with the use of pesticides.

A study by Hayes et al. (1991) investigated whether the risk for malignant lymphoma in dogs, a canine equivalent of human NHL, was associated with the use of 2,4-D in and around owners’ homes (66). The risk appeared to increase by 30% if 2,4-D was used for lawn care and by 100% if the owner applied 2,4-D four or more times yearly. A recent case control study in Sweden reported that another phenoxy herbicide (4-chloro-2-methyl phenoxyacetic acid or MCPA) was associated with NHL (67).

**TRIAZINE HERBICIDES:** The triazine herbicides include atrazine, simazine, cyanazine, and propazine. Sathiakumar and Delzell (1997) reviewed one cohort and three case-control studies on triazine herbicides (68). They concluded that little evidence points to an association between triazine exposure and NHL. Elevated risks observed in some studies are likely to be attributed to confounding in the presence of exposure to other pesticides or random error. The IARC classifies atrazine as “possibly carcinogenic to humans” (group 2B) and simazine as “not classifiable as to its carcinogenicity in humans” (group 3) (69). The cancer linked to the triazine herbicides has been mammary tumors, not lymphoma. Recently the EPA Scientific Advisory Panel concluded that triazine likely causes cancer in laboratory animals via a hormonal mechanism. Such a mechanism is not likely to be related to NHL.

**ORGANOCHLORINE INSECTICIDES:** Organochlorine insecticides include chlordane, DDT, and hexachlorocyclohexane, which are possible human carcinogens as determined by IARC (69). Several case-control studies have indicated an association between exposure to organochlorine insecticide exposure and NHL. Positive statistical associations were seen for occupational exposure to the following organochlorine insecticides in the respective locations: DDT in Iowa/Minnesota (70), Washington State (71), and Sweden (72); chlordane in Iowa/Minnesota (70); and lindane in Iowa/Minnesota (70). Of these, only lindane is still in use in the U.S. Baris et al. (73) reanalyzed four National Cancer Institute case-control studies from Midwestern states (Nebraska, Iowa, Minnesota, Kansas) that assessed NHL and DDT exposure. The pooled results showed that when adjusted for the use of other insecticides, DDT-associated risk estimates were weakened or diminished. Three
studies compared DDE, a metabolite of DDT, in biological specimens from controls and patients of NHL (74,75) or its subtype, hairy cell leukemia (76); none of these studies found an association between NHL and DDE. Taken together, earlier reports of increased risk associated with DDT use seem to be all or in part explained by other pesticides, the use of which was highly correlated with use of DDT. Risks associated with lindane, another organochlorine insecticide that was assessed in the four state studies, were reevaluated in a similar way by Blair et al. (77). Adjustment for the use of 2,4-D and diazinon reduced the lindane relative risk from 1.5 to 1.2 and 1.3, respectively. These two studies indicated that the use of phenoxy herbicides and organophosphates are more closely related to increased NHL risk.

Chlordane, phased out in the U.S. in the 1970s and 1980s, is nonetheless used widely throughout the world. In the U.S., low-level chronic exposure from dietary sources occurs continuously because of its long environmental half-life and its continued use internationally. It concentrates in the food chain, resulting in continued exposure from fish and seafood (78). Exposure to chlordane in the general population has been investigated recently, using an exposure assessment scheme in which exposure was measured by analyzing adipose tissue obtained from cases and controls. Concentrations of chlordane and its metabolites were elevated among NHL cases compared to controls (75). It is not clear whether this association is due to the independent effect of chlordane, or is confounded by other organochlorine compounds including polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) that may be correlated with chlordane exposure.

**ORGANOPHOSPHATES:** In the 1980s, as use of organochlorine insecticides was phased down, the use of organophosphate (OP), carbamate, and pyrethroid insecticides increased dramatically. Home use of OPs such as chlorpyrifos also increased in 1980s and 1990s. A number of studies have found associations between occupational exposure to OPs and NHL (70,79-81). In a study of NHL in women, the risk was highest (4.5 fold increased risk) among those who reported having handled OP insecticides (80).

In addition to epidemiological evidence, animal experiments and mechanistic theory point toward the possibility that OP pesticides may have a role in NHL. Although OPs as a class have not been found to be carcinogenic in animal bioassays, there are notable exceptions, including dichlorvos and tetrachlorvinfos, for which National Cancer Institute/National Toxicology Program bioassay data have found evidence of carcinogenicity in rodents (82). It has been hypothesized that one of the mechanisms by which certain OPs may increase the risk of NHL is through immunosuppression (83), although other mechanisms such as initiation and promotion cannot be excluded. For instance, some OP insecticides, including malathion, are converted to a reactive metabolite capable of alkylating DNA (84). Another proposed mechanism is that some OPs may stimulate cell proliferation or inhibit apoptosis through phosphorylation of molecules involved in these processes.

A growing body of experimental evidence also suggests that OP compounds may act as NHL permitters (85). A large number of animal studies have demonstrated that OPs have adverse effects on many aspects of immune function (36). A yet-to-be-proven but plausible hypothesis is that OPs inhibit monocyte esterase, which presumably has a functional role in the immunosurveillance process by which premalignant cells are eliminated (83). This is a rapidly evolving area of research, and a new study supporting the possible association between NHL and exposure to organophosphate pesticides was recently published (166,86).

**CARBAMATES:** Carbamates are a class of insecticides that utilize the same toxic mechanisms involved in OP toxicity (i.e., inhibition of enzyme cholinesterase for nerve conduction). Like OP, carbamates do not accumulate in the body, and assessment of exposure to carbamate in the distant past presents a methodological challenge in epidemiological studies.
Some questionnaire-based, case-control studies identified carbamate exposure as a risk factor for NHL. Nanni et al. (1996) found that the use of carbamates among farm animal breeding workers was associated with a three-fold increase in risk for a combined disease category of low-grade NHL and chronic lymphocytic leukemia (CLL) (87). CLL closely resembles small lymphocytic lymphoma histologically and clinically, and a somewhat vaguely defined difference between them is that CLL has a higher degree of bone marrow involvement—30% for adult cases or 25% or greater for pediatric cases (88). There was some evidence for a positive dose response but due to a limited sample size, the possibility of confounding due to concurrent use of phosphates and stannates could not be excluded. Pahwa et al. (2000) reported 5.2 and 6.5 times greater risk associated with the use of carbamates in Quebec and British Columbia, respectively (89). Apparently, these risk estimates are not adjusted for the use of other pesticides, but in general, the greater the magnitude of the observed association without adjustment is, the less likely can confounding account for such association. Cantor et al. (1992) reported increased risk associated with handling a carbamate insecticide, carbaryl, especially when the handling occurred prior to 1965, or no protective equipment was used during the handling (70).

Epidemiological data give some support for the causal roles of carbamates. Toxicological data also add some evidence. Carbaryl, a carbamate, has been found to inhibit proliferation (90) and enhancement (91) of human large granular lymphocytes, which exert most of the natural killer (NK) activity in human peripheral blood. NK cells can kill tumor cells as well as cells infected with virus or bacteria. Some carbamates and organophosphate may inhibit NK-cell proliferation through their inhibitory effects on cell surface serine-hydrolase involved in interleukin 2 signaling pathway for T-cell proliferation (92).

Neutrophils taken from workers exposed to carbamates and organophosphates were found to have decreased ability to kill a species of Candida bacteria (93). Another study on Nebraska farmers for the most part did not find association between pesticide exposure and immunologic indexes, but farmers with high pesticide usage had lower serum complement activity compared to low-usage farmers (94). The absence of a clearer association might reflect the use of a rather crude metric to estimate exposure (acre treated with pesticides) and suboptimal timing for blood collection (i.e., mid-May, during which farmers began applying pesticides rather than later in the growing season, when pesticide application occurs more regularly). It has been found in experimental (90) and epidemiological (93) studies that the immunotoxic effects of carbamates and organophosphate can occur with relatively low exposure, which does not cause neurological symptoms typical of poisoning due to these insecticides.

NITRATE IN DRINKING WATER: Nitrate is a common contaminant of drinking water in rural areas with higher use of agricultural fertilizers (95). Ingestion of drinking water contaminated with nitrate can increase endogenous formation of carcinogenic N-nitroso compounds. In Nebraska, higher nitrate concentrations in drinking water were reported to be associated with increased risk of NHL in an ecological study (10) and a case-control study (96). A case-control study of white men in Minnesota (97) and an ecological analysis in Yorkshire, U.K. (98) did not reveal any nitrate-related risk of NHL. The concentrations of nitrate observed in the Minnesota case-control study was lower than 4 mg/L nitrate-nitrogen; the nitrate concentration above which elevated NHL risk was noted in the Nebraska case-control study and this difference in exposure level may explain the difference in their results. The highest exposure category used in the Yorkshire ecological study (i.e., >3.5 mg/L nitrate-nitrogen reported as >14.85 mg/L nitrate), was comparable to that used in the Nebraska case-control study. The Yorkshire study suffers from potential uncontrolled confounding, a feature particularly problematic in ecological studies. Also, presence of co-contaminants that...
might act synergistically with nitrate, such as atrazine, as was indicated by an \textit{in vitro} genotoxicity study by Meisner et al. (1993) (99), may explain the difference between Nebraska and Yorkshire study.

\textbf{Industrial chemicals}

\textbf{PCBs AND PBBs:} PCBs and PBBs are industrial compounds that were used extensively until their production and certain uses were banned in the 1970s and 1980s in many Western countries, including the U.S. Other uses continue in the U.S. today and the last production, in Russia, is now being phased out. Like other organochlorines, PCBs have persisted in fat of animals such as humans, sea mammals, fish, and domestic animals. The association of PCBs and NHL was assessed in the three aforementioned case-control studies on DDE (74-76). Exposure to PCBs was associated with increased risk for NHL in all of these three studies and positive dose-response relationships were demonstrated. In addition, one of the studies indicated that there might be an interaction between exposure to PCBs and Epstein-Barr virus infection (74). PCB exposure was associated with an increased risk of NHL irrespective of Epstein-Barr virus exposure. Epstein-Barr virus-related risk elevation was seen only among those with higher PCB exposure. However, other studies on NHL and PCB have produced mixed results (reviewed by Rothman et al, 1997) (74). Among Michigan residents accidentally exposed to PBBs in 1973, an increasing dose-risk relationship was seen for lymphoma. Those with highest PBB dose levels, which was more than 10 times that for the lowest dose group, were at 33 times greater risk for lymphoma (100).

\textbf{DIOXINS:} Dioxins are generated as a byproduct of waste and other combustion processes, manufacture of certain chemicals, chlorine bleaching of paper pulp, and other industrial processes. As mentioned earlier, some phenoxy herbicides contained dioxins as a contaminant and studies on workers exposed to those herbicides reported increased NHL risk due to exposure to dioxins (61). 2,3,7,8-TCDD is the most toxic dioxin, and the toxicity of other dioxins is measured in terms of TCDD equivalents or TEQ (au: what is this abbreviation?), with 2,3,7,8-TCDD being assigned a TEQ of one. Both IARC and the National Toxicology Program have concluded that TCDD is a known human carcinogen, based on a combination of human epidemiological evidence, mechanistic studies, and animal toxicity testing data (61). As a class, many of the PCB and PBB compounds are dioxin-like in their action, thus studies on these may be relevant to dioxin risk. Likewise, in the past, phenoxy herbicides marketed in the U.S. had dioxin contaminants and, thus, studies relevant to these herbicides may shed light on dioxin risks as well. The literature on dioxin per se and NHL is mixed. Dioxin and cancer have been studied in two types of settings: general populations with accidental exposures and worker populations with exposures in manufacturing.

In the only study to evaluate general population exposures and NHL, residents of Seveso, Italy, who received accidental dioxin exposure, were found to have three times higher risk for NHL 15 years after the accident (101). In an occupational study, Hardell et al. (75) found increased risk NHL for the higher total concentration of various PCBs, but concentrations of various dioxins and related compounds (polychlorinated dibenzofurans and co-planar PCBs structurally similar to highly toxic dioxins) largely showed no difference across cases and controls. There is strong experimental evidence for immunotoxicity of dioxins (102). Alteration in immune function has been noted in human populations but its significance is unclear (61). Measurement of dioxin exposure levels requires costly laboratory analysis of biological specimens since measurements in environmental media are generally too scarce to be used for retrospectively assessing individual level exposure, and questionnaires are not reliable. As the cost for dioxin analyses decreases with innovation such as immunoassays (103), more studies on association between NHL and dioxin in general population may be conducted.
ORGANIC SOLVENTS: Rego (1998) reviewed a total of 45 epidemiological studies on NHL and solvents published in the period from 1979 to 1997 (104) investigating whether exposure to organic solvents increases the risk for NHL. Studies on solvents often face a challenge similar to the one encountered in those on pesticides—difficulty in separating the effect of exposure to a single solvent from that of multiple solvents to which populations are exposed.

Organic solvents by definition are lipophilic (i.e., have high affinity with oil and fat). Since bone marrow and brain are two of the organs with highest content of fatty lipids and all blood and lymph cells originate from marrow, solvents tend to be preferentially toxic to the lymphopoietic and nervous systems.

There is evidence for increased risk for NHL following exposure to certain solvents. IARC (1995) has declared trichloroethylene and tetrachloroethylene to be probable carcinogens (Group 2A), based on sufficient evidence from animal bioassays and limited evidence from human epidemiological studies (105). The sufficient animal evidence in their evaluation was for liver cancer, not for NHL. For trichloroethylene, IARC concluded that three cohort studies and a case-control study showed a modest increase in risk, and that one animal study showed an increased incidence of lymphoma. Two studies found increases in NHL incidence in areas where trichloroethylene-contaminated ground water was used as a source of drinking water. For tetrachloroethylene, increases in NHL risk were reported in three out of five occupational cohort studies.

It has been theorized that the population increase in NHL may be causally related to benzene exposure, 70% of which is from vehicle exhaust emissions (106). Although exposure in the general population is low, it is widespread (107). There is an ongoing debate on whether exposure to benzene causes NHL. As reviewed by Savitz and Andrews (108) and O’Connor et al. (106), increased risk among people exposed to benzene is reported in a few studies, including a large cohort study in China, which demonstrated an increase in risk dependent on exposure level (109). A meta-analysis, based on results of cohort studies on petroleum workers in Western countries with relatively low levels of benzene exposure, concluded that the workers were not at an elevated risk for NHL as a result of long-term, relatively low level exposure to benzene or benzene-containing products (110). On the other hand, among U.S. workers with substantial exposure to benzene studied in three earlier reports, 13 likely cases of NHL occurred while 10.8 were expected (109). Research on low-level exposure to benzene is hampered by the lack of a sensitive, reliable biomarker for benzene exposure (111).

Exposures to toluene, xylene, or styrene, and occupations involving the use of solvents (e.g., painter) were associated with elevated risk for NHL in some studies (112).

FIRE RETARDANT: Hardell et al. (1998) found higher concentrations of a fire retardant, 2,2’,4,4’-tetrabrominated diphenyl ether, in adipose tissue of NHL patients than in controls (113). A positive dose-response was seen although the finding is based on a small number of subjects (19 NHL cases and 27 controls), and so risk estimates were imprecise. Given great persistence of the compound in humans, further research on this and other similar compounds is needed.

WOOD WORK: Occupations involving contact with wood and wood products have been associated with increased risk for NHL in 10 studies conducted in the U.S., New Zealand, Finland, and Sweden (114). It is not clear whether the risk is due to wood itself, to chemicals applied to wood (e.g., wood preservatives), or other chemicals...
used for wood work. Naturally occurring antifungal compounds are known to be present in wood. Some studies suggested that exposure to wood preservative products, such as chlorophenols, increased risk (115), but others did not. The increased risk has been attributed to the contaminant 2,4,7,8-TCDD and other dioxins, which are present at varying concentrations in chlorophenols depending upon production methods. The variation in concentration may, in part, explain the observed risks across studies.

Radiation

Radiation occurs along a spectrum of frequencies and generally is divided into ionizing radiation and nonionizing radiation. This review will discuss two categories of ionizing radiation exposure, ultraviolet (UV) light and a grouping that includes X-rays and radionuclides and a type of nonionizing radiation exposure (electromagnetic fields).

UV LIGHT: The hypothesis that exposure to UV light increases risk for NHL has attracted some attention in the last few years. It is biologically plausible: exposure to UV light is known to systemically suppress the immune system (116), and as will be noted later, immunosuppression is a notable risk factor for NHL. UV exposure increased lymphoma incidence in mice in a bioassay study (117).

A series of ecological studies showed positive association between incidence of NHL and UV radiation in England, Wales (118), Europe, North America, and Australia (119), causing some speculation that the increase in NHL could be associated with increased exposure to UV light. However, a negative association has also been found for the NHL incidence across 10 areas covered in SEER program of the U.S. (120) and for the NHL mortality across all the states in the U.S. (121). Hartge et al. were cautious in interpreting their negative results as evidence against the UV-NHL hypothesis. “There may, for example, be unsuspected environmental agents that are both correlated with northern latitudes of the U.S. and potent causal agents for non-Hodgkin’s lymphoma and which mask a positive but weaker association with sunlight” (121).

Also, NHL risk is found to increase after diagnosis of skin cancer (122) and skin cancer risk after diagnosis of NHL (123,124). One interpretation for this NHL-skin cancer association is that a common preceding exposure, such as UV exposure, which is a strong risk factor for skin cancer, causes an increase in risk for both skin cancer and NHL. The observation can also be explained by the effects of the immunosuppressive treatment given for the first cancer, or for skin cancer following NHL, the immunosuppression caused by NHL itself (125).

A cohort study was undertaken in Sweden to investigate whether outdoor work increases NHL risk (126); occupational sun exposure was not associated with the risk for NHL, nor for other skin cancers studied. The same pattern was seen among people with higher exposure to pesticides or solvents, which might interact with UV exposure. The study’s failure to demonstrate an occupation-related risk increase for malignant melanoma or squamous cell skin cancer is indicative of the inappropriateness of the job exposure matrix used for classifying occupations regarding sun exposure. NHL risk appears to increase in more southern areas among four areas grouped by latitude.

Results of three case-control studies are available. Risk for hairy cell leukemia, an NHL subtype, appeared to increase in one study (127). No association was seen between NHL and outdoor work (128) nor residential and occupational exposure to sunlight (129). Freedman et al. noted that latitude and other factors associated with sunlight exposure may have varying patterns of association across different countries, thus accounting for the inconsistent findings of ecological studies.

X-RAYS AND RADIONUCLIDES: As reviewed by Boice (130), gamma radiation has been rarely implicated as a cause of lymphomas. The sources of gamma radiation investigated to date include
the atomic bomb among Japanese survivors; radiotherapy for a few types of cancer, menstrual disorders, or scalp ringworm; diagnostic X-rays for tuberculosis; diagnostic or therapeutic use of radionuclides; and occupations involving X-ray exposure. Mostly, these have found no increased risk for NHL associated with radiation, except in a small number of studies, (e.g., a study on thorotrast, a radioactive contrast media that remains in the body and keep emitting particles). This lack of association shows stark contrast with studies on radiation and leukemia, leading to the conclusion that mechanisms of carcinogenicity may be quite different for these cancers.

**ELECTROMAGNETIC FIELDS:** Several studies investigated potential roles of electromagnetic fields in causation of NHL. Two recent studies found positive associations between extremely low frequency (60 Hz) magnetic fields and NHL, with an apparent threshold in one study (131) and without a clear dose response in the other (132). Schroeder and Savitz (1997) briefly summarized results of earlier studies as being suggestive; more recent studies, employing individual exposure assessment, were not confirmatory (132). Apparently protective effects of radio frequency (30, 150, 450, 800 MHz or higher) magnetic fields, however, were found for male workers in a recent study (133).

**Pathogens**

**HIV/AIDS:** People infected with human immunodeficiency virus (HIV) are at high risk for NHL (134). Compared with the general population, they have approximately 150- to 250-fold higher risk. In fact, NHL is so common among the HIV infected that three subtypes of NHL are AIDS-defining: high-grade immunoblastic or diffuse large cell; small noncleaved (Burkitt, Burkitt-like, or non-Burkitt); and primary central nervous system NHL. In other words, NHL of these subtypes, by definition, induces the diagnosis of AIDS (135).

An important fact to note about the role of HIV infection in the rise of NHL incidence is that the rise in NHL had been observed long before the emergence of HIV/AIDS epidemic in the mid-1980s. Therefore, the increase in NHL prior to 1980 is not explained by HIV (12). Moreover, the increase after 1980 is only partly due to HIV. From 1981 to 1988, AIDS-related NHL accounted for 24% of the rise in Florida, Atlanta, and New Jersey and 66% in San Francisco, an epicenter of the AIDS epidemic. In 1988, AIDS-related NHL accounted for 6% of NHL in the first three areas and 28% in San Francisco (136). A similar pattern was seen in the Cote d'Or administrative area of France, where NHL incidence increased 10.9 % annually from 1980 to 1988. Among 380 NHL cases that occurred in this period, only one tested positive for HIV (137).

Studies on HIV/AIDS-related NHL have provided useful information on mechanisms of NHL development in general. For example, Breen et al. (1999) investigated roles of two B-cell stimulatory molecules, soluble CD23 and interleukin 6 in the development of AIDS-associated lymphoma (138). Levels of the former were associated with the risk of lymphoma in general; levels of interleukin 6 were associated only with the risk of Burkitt’s/ small noncleaved cell lymphoma and not large cell, immunoblastic, or central nervous system lymphomas. Findings of this sort may be informative in studying mechanisms for non-HIV-related NHL, since some causal pathways for AIDS and HIV-unrelated NHL are likely to share a common perturbation of immune system components.

**EPSTEIN-BARR VIRUS:** There is strong evidence that Epstein-Barr virus has important causal roles in so-called endemic Burkitt’s lymphoma prevalent in Africa and New Guinea. However, while the vast majority of people worldwide are infected with Epstein-Barr virus by adulthood, only a small portion of them eventually develop NHL. It is believed that early Epstein-Barr virus infection followed by chronic antigenic stimulation from malaria may be responsible for the endemic form of Burkitt’s lymphoma in Africa and New Guinea.

Burkitt’s lymphoma occurring outside of Africa
and New Guinea is called sporadic or nonendemic Burkitt’s lymphoma. While tumor cells of endemic Burkitt’s lymphoma are positive for Epstein-Barr virus genome in greater than 90% of the cases, only 30% of Burkitt’s lymphoma in the U.S. were Epstein-Barr virus positive, and 20% of the Burkitt’s lymphoma patients examined had no evidence of Epstein-Barr virus infection.

Present in essentially all Burkitt’s lymphoma is one of three chromosomal translocations, t(8;14), t(2;8), and t(8;22), in all of which the c-myc oncogene is juxtaposed to an immunoglobulin constant region (139). The site of chromosomal breakpoint varies geographically and correlates with Epstein-Barr virus positivity (140). For the vast majority of other types of nonendemic NHL, Epstein-Barr virus is detected only infrequently. However, the level of serum antibody against Epstein-Barr virus has been found to be higher for NHL cases than population controls, indicating there may be a role for Epstein-Barr virus in lymphoma development. Against this theory is the observation that Epstein-Barr virus infection has been ubiquitous for generations, and therefore, by itself cannot explain the rising secular trend in NHL incidence during the last few decades. At the same time, one could speculate that the response to viral infections, especially among older people, might have changed over time (141) due to environmental exposures that alter the immune response to Epstein-Barr virus in a way that might cause the incidence if NHL to rise.

Moreover, based on recent reports on fragments of Epstein-Barr virus genome found in nonendemic Burkitt’s lymphomas and other supportive evidence, some have hypothesized that some sporadic Epstein-Barr virus-negative NHL might originate from Epstein-Barr virus-positive tumors that lose the Epstein-Barr virus genome, thereby becoming undetectable by immune surveillance and acquiring survival advantage (142). Studies on interaction between Epstein-Barr virus and environmental exposure, especially those with immunosuppressive effects, may provide important clues for why NHL incidence has been rising.

**OTHER INFECTIOUS AGENTS:** Human T-cell lymphotropic virus type I (HTLV-I) is an established causal factor for endemic adult T-cell leukemia/lymphoma, endemic in Japan and other areas outside of North America; it is not thought to be a factor for global increase in NHL incidence (141). Recently, *Helicobacter pylori* has been shown to be causally associated with mucosa-associated lymphoid tissue lymphoma of the stomach in case-control and cohort studies (4). Administration of antibiotics resulted in regression of the lymphoma in some cases. Since mucosa-associated lymphoid tissue lymphoma consists small portion of NHL, it is unlikely that *H. pylori* had a major role in the increase incidence of NHL.

Increased risk for NHL was found to be associated with history of other chronic infectious diseases such as herpes zoster, pyelonephritis, tuberculosis, and malaria (143). Infection-related risk increase can be causal (e.g., immunostimulation due to infection leading to polyclonal proliferation of immune cells) or be a result of noncausal association (e.g., antecedent immunosuppression making the host more susceptible to infection as well as increasing risk for NHL) (143).

**Life style factors**

**HAIR DYES:** A systematic review identified five studies on NHL and hair dyes use published between 1966 and 1996 (144). Statistically significant increased risk associated with the use of permanent hair dyes was reported among only males in a case-control study and among only females in another. The elevation in risk observed in these two studies was modest, ranging from 1.5 to 2.0. Another case-control study reported increased risk associated with the use of hair dyes longer than 20 years, black hair coloring, or both, but the results were not statistically significant. Two large cohort studies did not find an increase in risk. The authors stated that the overall data are inconsistent within and across studies. However, some patterns in risk, such as positive dose response or concentration of increased risk associated with longer use among
those with black hair, were seen as well. The author concluded that continued research is warranted, given high prevalence of hair dye use.

**TOBACCO:** The use of tobacco has been associated with increased risk for NHL in many studies (115) while results of others, including a large study with 1177 cases (145), did not support the increased risk associated with tobacco. Zahm et al. (1997) found slight tobacco-related risk increase among women and argued for further research on NHL and tobacco among women (145).

**DIET:** Davis (1992) stated, “There is exceedingly little epidemiological evidence to suggest an etiological link between dietary factors and non-Hodgkin’s lymphoma.” He examined two early studies, one ecological and the other case-control, which indicated increased risk for higher consumption of meat and dairy products and decreased risk for higher consumption of vegetables. The ecological study was based on international comparisons and obviously subjected to potential confounding due to general socioeconomic status, which correlates with meat consumption. Nonetheless, no association was found for NHL and other foods or for meat consumption and other cancers (146). In terms of meat and fat consumption, results from recent studies are mixed. Among women, higher intake of certain meats and fats was associated with higher NHL risk (147,148). Milk consumption was associated with higher risk in one study (148) but not in the other (149). Intake of fruits appeared to reduce risk among women (148,150), but such beneficial effect was seen only among men in another study (149). It is of note that animal fat tends to contain contaminants such as PCBs and dioxins, which as we discussed earlier are suspected to have some roles in the development of NHL or immune dysfunction.

**ALCOHOL:** Results on alcohol intake and NHL risk are mixed. Chiu et al (1999) reported protective effects of alcohol consumption among older women and summarized results of other studies (151). They noted that similar protective effects were found in two population-based case-control studies while three hospital-based case-control studies found no association. The difference can be explained by the assumption that there is a higher prevalence of previous alcohol consumption among hospital patients.

**Other risk factors**

**IMMUNOSUPPRESSION:** Elevated risk for NHL among organ transplant recipients is one of the most well known associations with NHL (42). Speculation on the mechanisms involved in this risk elevation has focused on either immunostimulation or immunosuppression (152). These two are correlated to each other, and it can be difficult to determine the independent contribution of each factor. Among organ transplant recipients, this correlation occurs, since immunosuppressive drugs are used against immunostimulation that is either anticipated or already present. Another way correlation between the two immunological conditions can arise is that most primary immunodeficient patients, who still have some B or T cells that can be activated by an antigen, are incapable of eliminating the antigen because of defects in antibody formation and are prone to chronic immunostimulation (39).

Immunosuppressive therapy without transplant has been found to increase NHL risk (153) (reviewed by Kinlen, 1996). A substantial proportion of the subjects in these studies were rheumatoid arthritis patients, an autoimmune disease. Rheumatoid arthritis patients were 2.2 times more likely to develop NHL compared to general population; in the presence of immunosuppressive therapy, their risk was further elevated to 9.7. Further supporting these observations, patients
who received immunosuppressive therapy for inflammatory bowel disease were found to have 59 times higher risk (95% C.I., 2.0-85.0) of developing NHL (154). No NHL case arose from the inflammatory bowel disease patients without immunosuppressive treatment. (The study found the inflammatory bowel disease patients as a whole, including those with and without the immunosuppressive treatment, had a 31-fold increase in NHL risk.)

A notable feature of the effects of transplant-induced lymphomas is their short latent period. Latent period is defined as “delay between exposure to a disease-causing agent and the appearance of manifestation of the disease” (155). The first evident excess in NHL incidence was observed after only a half-year post transplant, and this latent period is the shortest for any carcinogen known (42). In the study of inflammatory bowel disease patients by Farrel et al. (154), the mean duration of the disease at the time of NHL diagnosis was 3.1 years, and mean duration between initiation of immunosuppressive therapy and diagnosis of NHL was 20 months, which is longer than the latent period for post-transplant NHLs, but still shorter than that for many other cancers believed to be induced by chemical carcinogen. Note that this short observed latent period does not necessarily mean immunosuppression alone can cause NHL within such a short period. From a multifactorial causation perspective, it is conceivable that other causal factors can be involved prior to the time of the transplant, which might have acted as the last trigger for NHL.

OTHER IMMUNOLOGICAL CONDITIONS: History of physician-treated allergies including asthma and food allergy was associated with increased risk for lymphatic or hematopoietic cancer (156,157). History of nonmedicated allergies, though, appeared to reduce risk for NHL in HIV-negative, homosexual men (158).

DIABETES: Findings on diabetes are mixed, but a well-designed cohort study in a population of older women found an elevated risk for NHL among diabetics, which showed monotonous increase with duration of diabetes (159). As discussed in a separate chapter on diabetes, there has been accumulating evidence that dioxin exposure may be causally related to diabetes, especially the non-insulin dependent type. It is tempting to speculate that diabetes and NHL exposure to dioxins share some causative pathways involving exposure to dioxins.

Social determinants
In the U.S. and other developed countries, higher socioeconomic status has been found to confer increased risk for NHL (115). Researchers have speculated that this observation can have a basis on patterns of infection to Epstein-Barr virus or other agents. Presumably, those with higher socioeconomic status have fewer and less severe childhood infections. However, there are numerous differences between higher and lower income groups; good epidemiological data are needed to determine which if any exposures are responsible for these differences.

RECOMMENDATIONS FOR FUTURE RESEARCH
How much of the increase in NHL incidence can be explained by secular changes in prevalence of known or suspected risk factors? Hartge and Devesa (15) showed that after accounting for known causes of NHL rate changes (change in diagnosis practice, HIV, and occupational exposures), 80% of the rise in NHL incidence for the period between 1947 and 1988 has not been explained. Assuming that a single agent caused the observed increase, and if that agent were associated with a two-fold relative risk for NHL, they calculated that the population exposure to that agent would have increased from none to 80% over the same period. Clearly risk factors like genetic traits and immunosuppression could not account for this kind
of change, and environmental causes must be sought.

There are opportunities for better classifying the disease in order to better understand its causation. As mentioned earlier, NHL is probably several diseases. A challenge in identifying risk factors is that it is quite likely that different exposures cause different types of NHL. Grouping NHLs together makes it more difficult to identify such associations. There are new markers, using new biologic techniques, such as protein and DNA arrays (proteomics and genomics) that promise to improve our classification of NHL by providing molecular fingerprints of the different types of NHL. Such markers also can be used to identify those with genetic susceptibilities, in whom the exposures would be expected to confer the greatest risk. These approaches, along with improving our measures of exposure, may offer the best opportunity for enhanced understanding of the etiology of this complex group of diseases.

There are several approaches that could be used to improve measures of exposure. Most epidemiology studies conducted to date have utilized traditional approaches in which exposure is ascertained using a questionnaire or existing records. The exposure assessments in these studies are relatively inexpensive, as it primarily relies on questionnaire, interview, or review of records. However, if exposure occurs such that the recipients of exposure are unaware of it through unknown levels of an agent present in some media (e.g., in seafood as a result of bioaccumulation or in residential environment as a result of pest control applications by a previous resident) this approach will not be able to classify subjects according to their exposure levels. Moreover, exposure assessment by history can lead to serious misclassification errors. However, for many potentially hazardous substances, biologic measures are not likely because of the lack of persistence of the subject in human tissues (i.e., organic solvents). It may be possible to improve nonbiologic exposure assessment by developing GIS mapping to assemble and pool data from a variety of sources, such as questionnaires, environmental monitoring, toxic release reporting, pesticide usage data, and so forth. Exposure assessment is a critical component of future investigations. Biologic measures should be used wherever possible. Some newer studies have built nested case-control designs on cohorts for whom biological specimens from the past are available. (Since cancers have long latency periods, such measures of earlier exposures are more likely to identify causal agents than measures of current exposures. At the time of diagnosis, people may have moved, may be in different occupations, or the cancer itself could affect certain exposure measures.) Typically, these studies measure internal dose or biologically effective dose using biomarkers. Studies to date have investigated organochlorine compounds or other persistent compounds. The compounds or their metabolites have been measured in blood or adipose tissue, better reflecting a lifetime history of exposure. For compounds that have shorter retention times in our body (e.g., phenoxy herbicides or organophosphates), biomarkers that reflect long term past exposure are largely unavailable.

**TRACKING THE DISEASE AND POSTULATED TOXIC EXPOSURES**

**DISEASE TRACKING:** A cancer registry is an indispensable part of any rational cancer control program; it enables continued assessment of cancer occurrence frequency in the population and facilitates identification of causal agents and evaluation of the effects of preventive measures taken (160). In fact, the alarming rise in the NHL incidence could have escaped our attention if no
.registry had been tracking incidence of various cancers. In terms of identification of causal agents, a registry can serve as a valuable source of cases from a defined population for a case-control study (160) and provide population specific standard incidence or mortality for the use in a cohort study conducted within the population covered.

National Cancer Institute’s Cancer Surveillance Research Program represents federal efforts to establish and maintain cancer registries. Its primary component is the SEER Program, a population-based cancer registry that covers 14% of the U.S. population (1). In February 2001, National Cancer Institute announced that the SEER coverage of the U.S. population will increase to 26%. Also, under authorization by the Cancer Registries Amendment Act of 1992, the National Program of Cancer Resources of Centers for Disease Control and Prevention supports cancer registries maintained by the states and territories to achieve more complete, accuracy, and timely data collection. When fully operational, the National Program of Cancer Resources will cover 97% of the U.S. population. Such full coverage will overcome some problems representative of the SEER Program, which under represents rural and less affluent segments of population and areas with relatively limited health care resources (161).

To sum, in terms of coverage of the U.S. population, the infrastructure for tracking of cancer in general seems to be maturing. There are some issues specific to NHL. As noted earlier, NHL is a collection of lymphomas of potentially different etiology. Incidences of some subtypes are increasing more rapidly compared to others, and prevention efforts may need to focus on such subtypes. Subtype-specific information of NHL incidence is therefore important. The ever-changing NHL classification scheme poses a challenge in recording subtype information. As mentioned earlier, Working Formulation, which was used in one of the largest subtype-specific analyses ever done (162), is being replaced by the new WHO classification. Even the new WHO classification will sometime be replaced by an improved version. One way to deal with this issue seems to be recording pathological information. Especially, molecular genetics information may prove very useful, since such information may become the main component of classification. As the use of molecular biomarkers becomes more common and standard practice, along with the use of electronic information retrieval system at hospitals, collecting more detailed information about tumors will become easier. Banking samples of pathological specimens would become valuable sources for information related to subtypes.

Currently, risk factor data are not routinely collected by National Cancer Institute supported cancer registries. Limited amounts of such data are collected in collaboration with other federal health agencies in sample of populations covered by the cancer registries, although there are efforts to increase collection. In the case of NHL, given the associations with pesticides, farming, and certain industrial occupations, information about place of residence and occupation would be useful additions to cancer registries.

EXPOSURE TRACKING: As reviewed in previous sections, our knowledge of what exposures cause NHL is still limited. There is some evidence that exposure to persistent pollutants like PCBs can increase risk for NHL, but a majority of NHL cases have occurred (and will occur, for some time in the future) without known attributable causes. Three broad categories for exposure tracking in the absence of knowledge on causal exposures are conceivable. One is the search of such exposure, the other is preparation for future situations where the knowledge on causative exposures becomes available, and the third is to monitor efforts to control exposures that might be related to NHL and other diseases.

Linkage of specimen banks and cancer registries can allow the conduct of etiological research of a nested case-control design. The causative role of exposure to PCBs and DDE has been investigated through analysis of banked serum samples (74). Studying cross-sectional associations between
putative exposures and an intermediate step in NHL development is a potentially useful research method for screening chemical compounds. Depending upon the intermediate step to study, banking genetic material, such as white cells in blood, may be necessary for this type of analysis.

We can envision another proactive use of exposure-tracking data. The trends in NHL incidence over time could be compared to the trend of exposures recorded through exposure tracking. Basically we would look for an agent, exposure to which matches the required pattern estimated with the use of the incidence data and assumptions. Over time, the uncertainties may be reduced, and the application may become feasible with accumulation of information on exposure trends and on causal roles of various exposures.

Data on exposure status and trends can be used in ecological analysis comparing (secular change in) the level of exposure with (secular change in) NHL incidence. This analysis also requires an assumption of induction time. Although ecological studies tend to be perceived to be capable of generating only weak evidence because of their limited ability to control confounding, they do have some advantages, such as low cost and convenience (163).

In order to assess the contribution of past exposures to suspected causal agents and other agents to the rise in the NHL incidence observed to date, it is necessary to know how prevalence of the exposure presumably increased during the time period for which NHLs were developing before they manifested as a clinical disease. To a great extent, we have lost an opportunity to study past secular trends in certain exposures because of limited availability of historical exposure-tracking data (164) and the difficulty in retrospectively quantifying exposure levels. In some rare cases, biological specimens were collected longitudinally from a relatively large number of people, allowing retrospective exposure assessment with the use of biomarker of exposure; the usefulness of such specimen banks has been limited, since we could know only about exposure trends in the underlying population from which the specimens were collected. In other words, the results of such assessment may not be generalizable to the whole U.S. population.

For NHL, investigating associations between markers of exposure or dose with that for intermediate events in NHL development appears rather promising. Measurements of some intermediate events such as gene trans-rearrangement with biomarkers require specimens rich in DNA from white cells. This would seem to be a very cost-effective approach and one that should be considered for implementation in human biomonitoring efforts in the near future.

**RISK REDUCTION**

The environmental health community strongly supports the phase out of the “dirty dozen” persistent organic pollutants, which include pesticides from classes (organochlorines) that have been suspected to be associated with NHL. In particular, the case for reducing exposures to PCBs and chlorphenoxy herbicides is strengthened by the NHL data.

Generally, there is much room for reduction of pesticide exposures to people in rural areas. First, there is a need to support efforts to generally reduce the use of pesticides and to move toward integrated pest management approaches that emphasize the minimum of pesticide usage and the use of less toxic pesticides. Second, stronger protections of farm workers, who have many fewer protections than industrial workers, who handle the very same pesticide chemicals are crucial. Strong EPA implementation of the Food Quality Protection Act, including assurance that the full health impacts are assessed, would also result in reduction of risks from pesticides.

Emerging evidence that NHL may be related to exposure to polybrominated flame-retardants is disturbing (113). An exponential increase in the concentration of polybrominated diphenyl ethers in breast milk has been documented in the Swedish population over the last 25 years (165); no such
monitoring has occurred in the U.S. This increase is in stark contrast to the decrease seen for dioxin and dioxin-like compounds in breast milk for the same period. Additional work should be done to support increased monitoring of exposures in the population, not only for compounds of known toxicity, but also for newer compounds like polybrominated diphenyl ethers that have not yet been fully assessed. Compounds that are often detected in people, and especially in breast milk, should be fully evaluated for their risks to health and especially the health of children. Since breast milk is the best food for babies, efforts should be made to reduce the levels of such chemicals in the environment and the food supply, to lower levels in breast milk.

In summary, despite research efforts, the vast majority of increase in NHL incidence remains unexplained. The kind of analysis conducted in Hartge and Devesa in 1992 (15) is useful in that we can speculate the magnitude of risk associated with a certain exposure that would be necessary given the secular change of the exposure or vice versa.

CONCLUSIONS

Incidence of NHL has been increasing at high rates, although the incidence seems to be leveling off for white males in the past few years. It is not known if a similar leveling off of risk awaits blacks and white females. The increase was perceived as alarming, and many argued for urgency for action. A large portion of NHL remains incurable; about half of the patients die within five years of diagnosis, and ultimately many others die as well.

Significant effort has been placed on the search for causative exposures, but the majority of the increase in NHL incidence remains unexplained. Some environmental agents such as phenoxy herbicides and PCBs appear to have had some causative roles. Many other industrial chemicals also present evidence of a role in NHL. HIV-related NHLs do not completely explain the observed rise in incidence.

Since we are still in search of causal exposures contributing to the increasing NHL incidence, more etiological research is needed. Approaches that relate exposure to intermediate steps of lymphoma formation and that relate to the intermediate steps to clinical NHL seem promising. New tools are needed for measurement of chronic exposures of nonpersistent compounds. Capacity to bank human biological specimens for determination of exposure, genetic susceptibility, tumor characterization in exposure, and disease tracking systems is a key for their contribution to etiological research and formulation of sound prevention policy based on such research.

Exposure and disease-tracking activities can serve as valuable resources for etiological research in general and especially for these studies involving biomarkers of exposure and effects. Improving our tracking system now is crucial for evaluating success of the prevention policy in the future. The coverage of populations and quality of data collection by cancer registries are being improved and have achieved much progress compared to exposure tracking. Still, tracking of NHL incidence could be further improved by collecting more detailed information on tumor, (e.g., molecular genetics data) and on past exposure of cases, especially residence and occupation. For exposure tracking, longitudinal collection of human biological specimens to be used for exposure assessment will be a critical component. In selecting samples to be collected, the possibility to assess not only exposure but also potential early effects is warranted. In addition to the specimens already under consideration, such as blood, urine, and hair, monitoring for breast milk is strongly recommended.
REFERENCES


