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The Epidemiology of Non-Hodgkin's Lymphoma: Why the Increased Incidence?

The incidence of non-Hodgkin's lymphoma continues to increase in the United States. Improvements in diagnostic techniques, changes in disease classifications, and the increase in AIDS-related lymphomas account for only a small percentage of the increase, leaving most of the increased incidence unexplained. Viruses clearly play a major role in the pathogenesis of some subtypes of non-Hodgkin's lymphoma, especially Epstein-Barr virus and HTLV-1, and improvements in molecular diagnostic techniques may identify additional viruses that have a role in the pathogenesis of lymphomas. Immunodeficiencies, whether acquired, congenital, or iatrogenic, clearly predispose to the development of non-Hodgkin's lymphoma. Numerous environmental exposures have also been linked to an increased risk of non-Hodgkin's lymphoma and may account for a portion of the continuing increased incidence of the disease.

Lymphomas were the fifth most common cancer in the United States in both men and women in 1992 with approximately 30,000 new cases.[1] Although lymphomas represent the fifth leading cause of death in men and the seventh leading cause of death in women, the average age at diagnosis is only 42. Combination chemotherapy can cure approximately one third to one half of affected patients, depending on specific prognostic factors. However, the remaining patients will ultimately die of their disease, leading to a significant number of life-years lost.

The incidence of non-Hodgkin's lymphoma continues to increase. Incidence data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) demonstrate a 4% per year increase in men and a 3% per year increase in women since the 1970s.[2] While the initial impulse is to attribute the increased rates of non-Hodgkin's lymphoma solely to the AIDS epidemic, this is not the case, as will be explained below. Thus, we are left with what epidemiologists and cancer researchers have termed an "epidemic of non-Hodgkin's lymphoma." The dramatic rise of non-Hodgkin's lymphoma incidence rates led the NIH to sponsor a symposium in October, 1991, to evaluate whether this increase was real or due to improvements in diagnosis and classification, and increased cases of AIDS. Clearly, the increase is real. This review will summarize our current knowledge about the possible etiology of non-Hodgkin's lymphoma (NHL).

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Role of Improved Technology

With the development of newer diagnostic studies, approximately 20% of cases of undifferentiated carcinoma can now be recognized as non-Hodgkin's lymphoma. However, this accounts for a very small percentage of all new cases of the disease.[3] The advent of newer methods of identifying cells, ie. immunophenotyping, has allowed pathologists to reclassify variant forms of T-cell lymphomas and Ki-1 lymphomas as non-Hodgkin's lymphoma. Thirty years ago, these diseases would have been classified as Hodgkin's disease. In addition, the availability of T-cell receptor and immunoglobulin gene rearrangement studies has resulted in an ability to recognize monoclonal processes and diagnose as NHL diseases that were previously considered to be "premalignant" by older pathologic techniques.

Experts in this field postulate that these changes in diagnosis may account for 10% to 15% of the current cases of non-Hodgkin's lymphoma.[4] However, improved diagnostic capabilities do not account for the continued yearly rise in non-Hodgkin's lymphoma since the time these techniques became available.

Role of AIDS

If AIDS-related lymphomas were to explain the rising rates of non-Hodgkin's lymphoma, one would expect the majority of the increase to be seen in younger men and mostly in areas with large numbers of high-risk populations. However, SEER studies demonstrate that this is not the case and confirm that the increasing incidence of non-Hodgkin's lymphoma has affected both sexes, all ages, and multiple geographic areas in the United States.[5] If San Francisco, where the largest numbers of AIDS-related non-Hodgkin's lymphoma occur, is excluded from these data, we still see an increased incidence of 2.6% per year in males and 2.0% per year in females. The large increase in the rural midwest is particularly notable, as this is not a population heavily affected by AIDS.

In fact, when the variation of non-Hodgkin's lymphoma incidence trends is divided and analyzed by the Working Formulation, increases are seen in all categories (low-grade, intermediate-grade, and high-grade non-Hodgkin's lymphoma).[5] The largest *proportional* increase is seen in the high-grade lymphomas (100% to 300% increase), which includes most AIDS-related lymphomas. Although the percent increase in high-grade lymphomas has been the greatest, this still accounts for only 20% of new non-Hodgkin's lymphoma cases. The majority of new cases (50%) are intermediate-grade lymphomas, followed by low-grade lymphomas (30%).

The American Cancer Society has collected data on the trends in cancer death rates by site and gender over two time periods: 1956 to 1958 and 1986 to 1988.[1] The number of cases of non-Hodgkin's lymphoma per 100,000 persons increased from 4.6 to 7.2 in males and from 3.0 to 4.8 in females over the two periods. This has led to a threefold increase in the number of deaths in both sexes. In addition, the increased incidence seen in males spans all ages in the adult population. If we assume that the incidence rates of non-Hodgkin's lymphoma in women and elderly men are unaffected by HIV infection, we find that, although AIDS contributes to a small percentage of new cases, it cannot account for the majority of the increase.

Occupational and Environmental Links

A number of occupations have been associated with higher risks for developing non-Hodgkin's lymphoma. Some of these occupations are relatively rare, so that even if associations exist, they are unlikely to account for a significant number of the increased cases of non-Hodgkin's lymphoma. These occupations include clerical workers, metal workers, workers with exposure to vinyl chloride and rubber products, as well as a few other occupations.[6,7] However, a few occupational exposures deserve closer attention, such as those associated with pesticide use (farmers) and the use of hair dyes.

• **Pesticides**—Farming has been associated with a statistically increased risk of non-Hodgkin's lymphoma in at least eight studies.[8] The range of estimated risks is small (0.6 to 2.6). However, epidemiologic studies that group patients into large categories can miss certain exposure risks if a significant proportion of the group does not have the particular exposure in question. Recent studies that have focused on specific exposures among farmers and gardeners have identified a two- to eightfold increase in non-Hodgkin's lymphoma incidence associated with the frequent use of phenoxyacetic acid herbicides.[8] Studies linking non-Hodgkin's lymphoma with phenoxy herbicides have been conducted in Sweden and Canada, as well as in the Midwest (Nebraska and Kansas). Other pesticides possibly linked to non-Hodgkin's lymphoma include triazine herbicides, organophosphate insecticides, fungicides, and fumigants. Dermal absorption is believed to be the predominant route of exposure for most of these compounds.[9]

Phenoxy herbicides include a number of related compounds commonly used in agriculture as broadleaf herbicides. In the agricultural industry, they are widely used on crops such as wh[eat], corn, oats, rye, barley, and sugar c[ane]. It is estimated that 40 to 65 mi[llion] pounds of these compounds are app[lied] to crops yearly in the United Stat[es]. Zahm and Blair[8] have summarized th[e] major studies that have looked at [the] association between non-Hodgki[n's] lymphoma and phenoxy herbicides. [The] Kansas study demonstrates that fa[rm]ers who use these compounds hav[e a] twofold excess of non-Hodgkin's ly[m]phoma. The risk increased to seven[fold] among farmers with more than 21 d[ays] of exposure per year. Similar re[sults] were obtained from a study perfor[med] in Nebraska. A study done in New Z[ea]land did not show a convincing [link] between phenoxy herbicide expo[sure] and non-Hodgkin's lymphoma, but [the] compound used had a different che[mi]cal structure than that used in the [Kan]sas and Nebraska studies.

The use of phenoxy herbicides is [not] limited to the agricultural industry. [They] are currently the most commonly [used] pesticides in the United States. [It is] estimated that 70 million pounds of [pes]ticides are applied to lawns each [year], and the use of pesticides for lawn [care] continues to increase by 5% to 8% [an]nually.[11] The Environmental Protect[ion] Agency (EPA) estimated that in 19[89] one third of single family household[s] either self-applied a lawn herbicide [or] had it applied by a commercial lawn [and] care service. If this linkage can be [de]finitively established, this may accou[nt] for a substantial portion of cases [of] non-Hodgkin's lymphoma.

• **Hair Dye**—A second occupational and environmental exposure possibly linked to non-Hodgkin's lymphoma that deserves further comment is the exposure to hair dyes. Hair dyes contain chemicals that are clearly carcinogenic and mutagenic in animals.[12] Three case-control studies have examined the possible association between non-Hodgkin's lymphoma and hair dye exposure. The first study, which excluded women, found an overall relative risk of developing non-Hodgkin's lymphoma of 2.0 in the men surveyed, with an increased risk associated with increased frequency and duration of use.[12] But with only 3% of the controls reporting hair dye use, the population attributable risk was only 3%.

Data from a study by Zahm et [al]

Special acknowledgment to Robert Krigel, MD (Chief, Hematology/Oncology and Cancer Program Medical Director, Lankenau Hospital) and Robert Young, MD (President, Fox Chase Cancer Center) for their editorial assistance.

included both men and women.[13] In contrast to the above study, the relative risk estimate in men who used hair-coloring products was not elevated (RR 0.8). However, results in women indicated the use of any dye is associated with a relative risk of developing NHL of 1.5, with a slightly higher association among women who use permanent dyes (RR 1.7). In addition, women who used darker-colored products appeared to have a higher risk. The authors suggested that hair dye use could account for as much as 20% of all cases of NHL in women.

The largest cohort study to date was performed by the American Cancer Society (ACS) and reported in February, 1994.[14] This prospective study examined the relationship between permanent hair dye use and death rates from selected cancers in over 570,000 women. In this study there was no increased risk of NHL among all users of permanent hair dyes, but in the small group of women who used black hair dyes for greater than 20 years, there was a significant increased risk of fatal NHL (RR 4.3). The authors conclude that women who have prolonged exposure to dark-colored hair dyes have a higher risk of fatal NHL, but these women represent for only a small fraction of all hair dye users.

This last study in particular is supportive of the conclusion that hair dye use alone cannot account for a significant proportion of the increased incidence of NHL. In the American Cancer Society study, if the use of dark hair dyes was causal, this would only account for an attributable risk in exposed women of 3%, much lower than the attributable risk estimated in the Zahm study. In addition, based on these studies, hair dye use would not account for the increase seen in men.

Other Possible Occupational/Environmental Exposures—Benzene-containing solvent exposure has also been associated with non-Hodgkin's lymphoma in several studies.[15,16] A variety of other environmental exposures have been examined, including exposure to radiation and electromagnetic fields, alcohol, tobacco abuse, and nutritional factors. No clear and consistent correlation with an increased risk of developing non-Hodgkin's lymphoma has been found. A study linking non-Hodgkin's lymphoma mortality with levels of trihalomethanes in drinking water has not yet been confirmed.[17]

Role of Viral Diseases

In cats, chickens, cows, and immunodeficient mice, viruses have been shown to cause hematopoietic malignancies. Feline leukemia virus causes leukemia in cats, and inoculation against this virus can prevent the development of this leukemia. A similar situation is true for a virus that causes lymphomas in chickens. Viruses have been implicated in a number of nonhematologic malignancies in humans. Some cases of primary hepatocellular carcinoma are linked to persistent hepatitis B virus infection, cancers of the cervix are linked to specific subtypes of human papillomavirus, and Epstein-Barr virus is thought to cause some cases of undifferentiated nasopharyngeal carcinoma. Thus far, two viruses are thought to have a causal role in certain cases of non-Hodgkin's lymphoma in humans: human T cell leukemia virus type 1 (HTLV-1) and Epstein-Barr virus. The exact mechanisms by which these viruses are involved in the pathogenesis of the resulting lymphomas remain unclear.

- **HTLV-1**—Some of the strongest evidence for a possible viral etiology of non-Hodgkin's lymphoma in humans is the occurrence of adult T-cell leukemia/lymphoma in patients infected with HTLV-1. This agent is a retrovirus that is endemic in southwestern Japan, the Caribbean, and the southeastern United States. The virus was isolated in 1978 from tumor cells of patients with mature T-cell malignancies.[18] Not all patients infected with HTLV-1 develop adult T-cell leukemia/lymphoma. The cumulative lifetime risk for development of adult T-cell leukemia/lymphoma in infected individuals is estimated to be approximately 5%.[19] Thus, there are likely to be additional host factors that allow for malignant transformation of lymphocytes in infected individuals.

The exact mechanism by which HTLV-1 transforms T cells into a clinically evident malignancy remains unknown. A specific oncogene, DNA translocation, or common integration site has not been identified. Yosida et al have proposed[20] a possible model for lymphomagenesis In this model, HTLV-1 infects CD4-positive lymphocytes, primarily T-helper cells, and integrates randomly into the host genomic DNA. A long latency period ensues, during which the infected individual is asymptomatic and the virus continues to replicate and infect additional target cells. There is polyclonal expansion of infected T cells due to a mitogenic effect of viral gene products. In normal individuals, the lymphoproliferation would be counterbalanced by immunologic defense mechanisms, either destruction or inhibition of growth of the infected cells. Since most of these malignancies are monoclonal, this model proposes a chance integration so that viral proteins are not expressed and recognized, allowing for the monoclonal expansion of a population of virally transformed cells. An additional event then leads to overt malignancy.

Epidemiologic studies indicate that individuals infected perinatally with HTLV-1 are most likely to develop adult T-cell leukemia/lymphoma.[21] However, HTLV-1 has a unique geographic distribution and a relatively low level of transmission, and causes a specific subtype of non-Hodgkin's lymphoma that is still very rare. Therefore, HTLV-1 is unlikely to account for the current increase in non-Hodgkin's lymphoma.

- **Epstein-Barr Virus**—The role of Epstein-Barr virus in the pathogenesis of lymphomas is not as well defined, although there is a vast body of literature linking the virus to both Hodgkin's disease and non-Hodgkin's lymphoma. There are at least two subtypes of Epstein-Barr virus, referred to as type 1 (or A) and type 2 (or B). The subtypes differ in the configuration of their EBNA genes, their ability to transform cells in vitro, and their geographic distribution. Preliminary data suggest specific subtypes of Epstein-Barr virus are associated with the different types of lymphoproliferations seen in immunosuppressed and normal patients.

Unlike HTLV-1 infection, Epstein-Barr virus is a highly prevalent infection in the adult population, with the vast majority of adults having evidence of previous infection by age 40. Epstein-Barr virus is not a retrovirus, but a herpesvirus that establishes latency in B cells and nasopharyngeal epithelium. Nearly all cases of the endemic Burkitt's lymphomas can be shown to contain Epstein-Barr virus viral genomic

DNA, but the frequency is much lower (15% to 20%) in sporadic Burkitt's.

Epstein-Barr virus was discovered and identified as a human tumor virus in lymphoblastoid cell lines cultured from children with African/endemic Burkitt's lymphoma.[22] As in HTLV-1 induced adult T-cell leukemia/lymphoma, Burkitt's lymphoma arises several years after primary infection with Epstein-Barr virus, consistent with the models for viral pathogenesis of malignancies. The clustering of cases around the equatorial belt of East Africa remains unexplained. It has been postulated that chronic hyperstimulation of the immune system by diseases such as malaria may lead to a subtle dysfunction of the immune system that plays a role in the pathogenesis of this disease. The native population of this region has been shown to have impaired T-cell viral cytotoxicity in response to infection with Epstein-Barr virus.

Burkitt's lymphomas contain characteristic chromosomal translocations that transpose the *c-myc* oncogene on chromosome 8 with immunoglobulin genes on chromosomes 2, 14, and 22. This translocation leads to activation and expression of *c-myc*, which has been shown in vitro to cause malignant transformation of B lymphocytes. The transformation appears specific for the tumor cells, as these chromosomal translocations are not detected in normal lymph nodes or peripheral blood of patients with Burkitt's lymphoma. Several scenarios have been postulated to explain how Epstein-Barr virus infection and the observed chromosomal translocations interact to result in malignant transformation into a clinically recognized Burkitt's lymphoma. All of these theories incorporate viral infection, spontaneous or virally induced mutations, environmental factors, and host factors/immune dysfunction.

Recent data have implicated Epstein-Barr virus in the pathogenesis of a variety of non-Burkitt's lymphomas. Clonality assays performed on lymphomas that arise in the setting of HIV infection indicate that most of these lymphomas are monoclonal, as opposed to the predominance of polyclonal and oligoclonal lymphoproliferative disorders that occur in the setting of transplantation recipients taking immunosuppressive drugs. Epstein-Barr virus has clearly been implicated in the vast majority of transplant-related lymphoproliferative disorders, but studies of viral expression indicate that many of these lymphoproliferative disorders are composed of a heterogeneous population of infected cells.[23]

Although all AIDS-associated primary central nervous system (CNS) lymphomas appear to be related to Epstein-Barr virus,[24] the association between Epstein-Barr virus and systemic lymphomas in the AIDS population is less well defined. Studies demonstrate monoclonal expression of Epstein-Barr virus genes in 38% to 66% of cases of systemic disease in AIDS patients.[25] When Epstein-Barr virus is detected in AIDS-related lymphomas, analysis of viral gene expression demonstrates a monoclonal origin of the infected tumor cells, but these cases are not limited to a specific subtype of non-Hodgkin's lymphoma; the virus is found in approximately one half of diffuse large cell, small noncleaved, immunoblastic AIDS lymphomas.

Since Epstein-Barr virus is known to establish latency in B cells, we might assume that the virus causes only B-cell non-Hodgkin's lymphomas. This has not turned out to be the case. T-cell non-Hodgkin's lymphomas have also been associated with Epstein-Barr virus, especially peripheral T-cell lymphomas, angioimmunoblastic lymphadenopathy, angiocentric lymphomas, and T-cell non-Hodgkin's lymphoma of the midline granuloma type.[26-30] A recent study by Kanavaros et al[31] has demonstrated Epstein-Barr virus incorporation and gene expression in all of six tested cases of nonoriental nasal T-cell lymphoma. In all cases, Epstein-Barr virus latent membrane protein expression was found. Several in vitro studies have demonstrated that latent membrane protein appears to play a crucial role in malignant transformation.[32-34] In addition, latent membrane protein expression has been found in Epstein-Barr virus-associated cases of nasopharyngeal carcinoma and in other human malignancies linked to Epstein-Barr virus, suggesting that the virus is not merely a passenger but plays a role in the malignant transformation.[35,36]

Epstein-Barr virus has also been implicated in the development of Hodgkin's disease. The risk of developing Hodgkin's disease has long been noted to be increased in persons with infectious mononucleosis. In the past, the association was difficult to establish because of reliance on serology. With the advent of specific probes for viral DNA, Epstein-Barr virus DNA has been detected in 15% to 25% of adult Hodgkin's disease tumor specimens from Europe, Japan, and North America.[37,38] The histology most frequently associated with Epstein-Barr virus is the mixed cellularity subtype. Epstein-Barr virus analysis by polymerase chain reaction has detected Epstein-Barr virus DNA in a larger percentage of patients with Hodgkin's disease, and in situ hybridization has identified Epstein-Barr virus DNA in Reed-Sternberg cells. Additional studies have now been able to detect Epstein-Barr virus gene expression in Reed-Sternberg cells, again suggesting that viral gene products play a role in transformation.[39-41]

Role of the Immune System

From our current knowledge of immunology, it would seem intuitive that alterations in immune surveillance play a role in the pathogenesis of non-Hodgkin's lymphoma. The immune system is a highly self-regulated network of lymphoid and myeloid cells that communicate with each other via the release of soluble factors, as well as through surface antigen recognition. An extensive review of immunology is beyond the scope of this article, but a few basic observations serve to point out some unique features of lymphoid malignancies.

• **Immunology and Lymphomas**—The humoral arm of the immune system is represented by B cells whose chief function is to clear the body of foreign microorganisms, proteins, and carbohydrates through interactions with T cells or other antigen-presenting cells. This interaction allows the production of specific factors that promote the proliferation and differentiation of B cells. Most stimulated B cells will terminally differentiate into antibody-producing plasma cells and subsequently go through programmed cell death.

T cells represent the arm of the immune system known as cellular-mediated immunity. These cells undergo a complicated developmental pathway and subsequent differentiation into T-cell subsets that have cytotoxic and/or immunoregulatory functions. Advances in molecular immunology have al-

lowed the identification of specific subsets of T cells by the presence of specific antigens or combinations of antigens on the cell surface, ie, cluster of differentiation (CD) antigens. In the past, CD4-positive cells were called T-helper cells. We now know there are at least two subsets of CD4-positive cells, a helper-inducer or T_h subset (CD4/CD29) and a suppressor-inducer subset (CD4/CD45). Likewise, CD8-positive cells used to be called suppressor cells, but several subsets of CD8 cells have been identified such as the suppressor or T_s subset (CD8/CD11B+) and the cytotoxic or T_c subset (CD8/CD11B-).

Normal T_c cells recognize and destroy virally infected or transformed cells. T_h cells interact with and stimulate B cells. T suppressor-inducer cells stimulate T_s cells, which negatively regulate this network. One can easily see that there are multiple possible mechanisms by which alterations in this complex system could allow involved cells to expand in a monoclonal fashion, whether the cell involved was virally transformed or not.

Natural killer (NK) cells represent another arm of the immune system; they constitute 10% to 15% of circulating mononuclear cells and are recognized as large granular lymphocytes. Unlike T cells, NK cells can lyse target cells without previous sensitization or involvement of the major histocompatibility antigens. They appear to have two functions, either direct killing or killing of antibody-coated cells via the F_c receptors. They play a major role in killing viral-infected cells, and in animal models, NK cells proliferate and have cytolytic responses to viral infections prior to any detectable T-cell response.[42] Biron et al[43] have published a case report of a patient with NK-cell deficiency who developed multiple, uncontrolled viral infections and a lymphoproliferative disorder. Thus, NK cells may play a key role in killing viral-transformed cells in humans, and persons with NK-cell deficiencies may be destined to develop uncontrollable lymphoproliferations.

• **Role of Immune Deficiencies**—We can easily postulate how a variety of immune deficiencies, either congenital or acquired, could contribute to the pathogenesis of non-Hodgkin's lymphoma. What evidence do we have to support a role of immune dysfunction in lymphomagenesis? Even before the appearance of AIDS, it had long been recognized that immunosuppressed persons are at greater risk for developing non-Hodgkin's lymphoma. In patients with congenital immunodeficiency states, non-Hodgkin's lymphoma accounts for approximately 50% of all tumors.[44] This fact in itself does not clearly point to the role of a dysfunctional immune system in the pathogenesis of non-Hodgkin's lymphoma. However, with the development and increased use of immunosuppressive agents to treat autoimmune diseases and to prevent rejection in organ and bone marrow transplant recipients, a rise in non-Hodgkin's lymphoma in this iatrogenically immunosuppressed population is now being noted.

The relative risk of developing non-Hodgkin's lymphoma in immunocompromised persons is highest (RR greater than 15) in recipients of multiple transplants, those who have received cadaver transplants, patients with congenital immunodeficiencies (Wiskott-Aldrich syndrome and ataxia-telangiectasia), and those with long-term acquired and iatrogenic immunodeficiencies such as AIDS and transplant recipients.[45] Patients with rheumatoid arthritis taking azathioprine (Imuran) or cyclophosphamide (Cytoxan, Neosar) have a 10-fold increase in non-Hodgkin's lymphoma over the normal population.[46,47]

The Cincinnati Transplant Tumor Registry (CTTR) has kept data on 6,123 cancers that arose in 5,753 organ transplant recipients up to January, 1992.[48] This registry includes data on kidney, heart, liver, bone marrow, and several other organ transplants. The most common malignancies reported were skin and lip cancers; however, non-Hodgkin's lymphoma accounted for the second highest number of malignancies in the entire population. Recipients of cardiac transplants are taking higher doses of immunosuppressive drugs, and in these patients, non-Hodgkin's lymphomas were the most common secondary malignancy. Overall, only 2.5% of the lymphomas that occurred in this population were Hodgkin's disease. The vast majority of lymphomas in these transplant recipients were intermediate- to high-grade non-Hodgkin's lymphomas, with a propensity for extranodal and CNS disease. Also of note in the transplant population is the tendency for involvement of the allograft. In the CTTR data, the allograft was involved in 20% of the cases of non-Hodgkin's lymphoma.

There are a large number of data suggesting that Epstein-Barr virus plays a crucial role in virtually all cases of transplant-related lymphoproliferation.[49] The spectrum of Epstein-Barr virus-induced lymphoproliferation ranges from a predominance of polyclonal disease to true monoclonal, aggressive non-Hodgkin's lymphoma. Analysis of immunoglobulin gene rearrangements and immunohistochemical assessment of light chain production has demonstrated that many transplant-related lymphoproliferative disorders are initially polyclonal, ie, uncontrolled proliferation of multiple clones of lymphocytes. The lymphomas found to be monoclonal are thought to arise from polyclonal lymphoproliferations, consistent with the previously discussed proposed models of virally induced non-Hodgkin's lymphoma involving Epstein-Barr virus or HTLV-1.

Furthermore, successful therapy of Hodgkin's disease for the past several years has led to a number of survivors who have been followed for several years. These patients can develop therapy-induced secondary leukemias, but this risk diminishes at the end of the first decade post-treatment. The risk of developing non-Hodgkin's lymphoma is 1.6% at 15 years. The exact etiology of non-Hodgkin's lymphoma after successful treatment of Hodgkin's disease is unknown, but is thought to be due to the altered immune function of Hodgkin's disease patients. Patients with Hodgkin's disease have evidence of immune suppression at diagnosis, which persists long after completion of treatment. Whether Epstein-Barr virus plays a role in the etiology of these lymphomas remains to be definitively demonstrated.

Is There a Common Denominator?

How can the available information be integrated? Even though Epstein-Barr virus is now being identified in many lymphomas, it is unlikely that Epstein-Barr virus infection is solely

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responsible for the increase in non-Hodgkin's lymphoma, since the prevalence of infection has not changed for generations. Why is it that most people who become infected with Epstein-Barr virus or other transforming viruses such as HTLV-1 do *not* develop lymphomas? The answer may lie with subtle alterations of the immune system, changes that we have yet to identify or define.

A review by the Working Group on the Epidemiology of Hematolymphopoietic Malignancies in Italy has assembled data implicating pesticide-induced immunosuppression as a risk factor for the higher incidence of non-Hodgkin's lymphoma seen in workers exposed to pesticides.[50] Perhaps some of the environmental and occupational factors associated with non-Hodgkin's lymphoma increase the risk of developing non-Hodgkin's lymphoma by causing some type of immunosuppression in the exposed individual. This could lead to an inability to recognize and to kill or suppress virally transformed cells. Once an infected individual becomes immunosuppressed, Epstein-Barr virus-transformed cells could escape the normal host cytotoxic response, leading to an uncontrolled proliferation of the transformed clone and a clinically recognized malignancy. In support of this hypothesis are studies showing that when peripheral blood cells from healthy individuals with persistent Epstein-Barr virus infection are inoculated into SCID mice, transplantable human B-cell lymphomas develop that subsequently kill the mice.[51]

In conclusion, the incidence of non-Hodgkin's lymphoma continues to increase in the United States. Changes in diagnostic techniques, changes in classification of Hodgkin's disease and malignant versus nonmalignant lymphoproliferative disorders, and the increase in AIDS-related lymphomas account for only a small percentage of the increase and leave most of the increased incidence unexplained. Viruses clearly play a major role in the pathogenesis of some subtypes of non-Hodgkin's lymphoma, especially Epstein-Barr virus and HTLV-1. With further advances in molecular diagnostic techniques, additional viruses may be identified that play roles in the pathogenesis of lymphomas. Acquired, congenital, and iatrogenic immunodeficiencies clearly predispose affected individuals to the subsequent development of virally associated non-Hodgkin's lymphoma, as well as non-Hodgkin's lymphoma for which no known viral association yet exists. Numerous environmental exposures have been linked to an increased risk of developing non-Hodgkin's lymphoma, including phenoxy herbicides and exposure to hair dyes. The exact association between environmental and infectious factors has yet to be determined, but chemically induced immunosuppression may be the mechanism by which latent viruses subsequently cause clinically recognizable non-Hodgkin's lymphoma.

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Among the multitude of animals which scamper, fly, burrow, and swim around us, man is the only one who is not locked into his environment. His imagination, his reason, his emotional subtlety and toughness, make it possible for him not to accept the environment but to change it. And that series of inventions by which man from age to age has remade his environment is a different kind of evolution—not biological, but cultural evolution. I call that brilliant sequence of cultural peaks The Ascent of Man.

—Jacob Bronowski in The Ascent of Man

Man's ability to influence his environment is remarkable; the ingenuity that man has demonstrated to overcome environmental obstacles cannot be lauded too highly. However, there is also a dangerous aspect to man's intervention into complicated ecosystems. Most often, the price of man's remaking of the environment is paid by other species of plants and animals. But sometimes it is man himself who gets slapped by the same intervention that was supposed to beneficially alter the environment. And so it seems to be for the increasing incidence of lymphomas. The emerging epidemic of lymphocytic lymphomas appears to be due in large part to chronic exposure to man-made chemicals designed to control the environment.

Lymphoma has increased in incidence at a rate of about 3% to 4% per year since the early 1970's, faster than all other cancers except lung cancer in women and melanoma. Lymphomagenesis is usually considered to be a multistep process. There are many factors that have contributed in varying degrees to the increased incidence of lymphomas and many of these have been discussed by Dr. Palackdharry. In the past, some new cases would have been misdiagnosed as Hodgkin's disease or undifferentiated carcinoma.

The prevalence of immunosuppressed individuals has also increased. A small increase in lymphoma can be related to cases diagnosed in patients with primary (genetic) immunodeficiency diseases; better methods of caring for many of these patients has led to improved survival and longer periods at risk for developing lymphoma. The use of iatrogenic immunosuppression has risen sharply over the past 20 years and has brought with it increases in Epstein-Barr virus (EBV)-related lymphoproliferative diseases. The most important recent cause of immunosuppression is HIV infection. Lymphomas are increasing in frequency in AIDS patients, who are surviving longer as a result of antiviral therapy and improvements in the management of opportunistic infections.

Lymphomas occurring in the setting of primary and acquired immunodefi-

ciency are extremely important in that they affect a substantial number of patients and reflect significant features about host-tumor interactions in viral (particularly EBV) lymphomagenesis. However, lymphomas occurring in the setting of immunodeficiency are generally high-grade lymphomas and usually occur in younger patients. Lymphoma in AIDS patients usually occurs in men. The lymphoma epidemic has been shown to include follicular and large-cell lymphomas and to affect both men and women of all age groups (except young children). Thus, the lymphomas that occur in patients with AIDS and other immunodeficiencies cannot account for the overall increase in lymphomas; indeed, they represent only a fraction of the increase.

Autoimmunity also appears to be a factor in lymphomagenesis. Patients with Sjogren's syndrome and rheumatoid arthritis are at increased risk of lymphoma, apparently independent of the therapy, which may induce immune deficiencies. Intestinal T cell lymphoma may develop in the setting of gluten-induced enteropathy. It appears that either too much or too little immune reactivity is bad for you.

Age as a Factor

Another factor that may contribute to the increase in lymphoma is the increase in number of people surviving into old age. People age 65 and over are the fastest growing segment of the American population. It is possible that the aging immune system is somehow more susceptible to factors involved in lymphomagenesis, either related to a poorly defined immune defect that interferes with surveillance or related to genomic instability that makes lymphomagenesis faster or easier. It is recognized that about two thirds of the expressed genes are located near the chromosomal telomeres and that telomeres are lost or broken down with age. It is certainly possible that normal immune stimuli may elicit an abnormal response in the setting of age-related genetic changes. However, aside from the fact that the incidence of lymphoma is highest in older people, there is little specific information that would help convert these idle speculations into an explanation for the emerging lymphoma epidemic.

The evidence is quite strong that environmental factors are involved in the increased incidence of lymphoma. Riggs and Chen[1] have performed longitudinal Gompertzian analysis on the epidemiologic data on lymphoma incidence and mortality. The details of the analysis are beyond the scope of this commentary; however, the data are consistent with the notion that environmental factors are dominant over genetic and competitive influences.

A variety of occupational and environmental exposures have been linked to lymphoma. Scherr and colleagues[2] found an increased risk of lymphoma among persons employed in the agriculture, forestry, and fishing industries (relative risk 3) and the construction and leather industries (relative risk 2.1). In particular, plant farmers and gardeners, painters and plasterers, carpenters, brick and stone masons, plumbers, and roofers were at increased risk. Those employed in construction had an increased risk of follicular lymphoma; those in the agriculture industry were at increased risk of diffuse large-cell lymphoma.

An interesting effort is being made to correlate exposures with genetic alterations that frequently occur in lymphomas. The majority of chromosome translocations in lymphoma involve receptor genes, which normally rearrange to form antigen receptors, instead rearranging aberrantly to a gene that can affect the control of cell growth, such as c-*myc*. The recombinase responsible for normal gene rearrangements sometimes makes errors resulting in the formation of hybrid receptors comprised of abnormal combinations of gene segments. This is called interlocus recombination. Usually these are repaired. However, in patients with ataxia-telangiectasia, who are at risk of developing lymphoma, the ability to repair these abnormal recombinations is impaired. Lipkowitz and colleagues examined agricultural workers thought to be at risk for lymphoma on the basis of pesticide exposure (including insecticides, herbicides, fumigants, and fungicides) and found that their peripheral blood lymphocytes showed a markedly increased incidence of interlocus recombinations.[3] The frequency of the abnormalities was related to the degree of exposure. Since agricultural work is often seasonal, they examined in
uals with high exposure at times
pesticide use was lower. The freq
of abnormal recombinations was
lower with time since the last exp
to pesticides. Whether such a test c
be used to identify people at parti
ly high risk is not clear. Howeve
spective studies are likely to be
informative.

Another study by Garry and
leagues examined peripheral bloo
phocytes for gene rearrangement
pesticide workers who were exp
phosphine.[4] The exposed group
significant excess of chromo
breaks in four bands: 1p13, 2
14q32, and 21q12. These sites a
commonly involved in most seri
lymphomas; so it remains un
whether the abnormalities have p
tive significance.

The role of hair dye in lymp
genesis has recently been sugge
be lower than in the original rep
ed by Dr. Palackdharry. Thun a
leagues found no increased risk
hematopoietic malignancy among
who had ever used permanent hai
In this study of over 500,000 w
there was an increased risk of fatal
phoma only in women who had
black hair dye for 20 years or mo

Chronic antigenic exposure has
implicated in the development o
phoma; however, with the excepti
the very rare intestinal T-cell lym
ma and more recently, gastric MA
lymphoma,[5] particular antigenic st
li have not been clearly defined. It
appears that gastric MALT lympho
is related to infection with *Helicobac
er pylori* in that a small number of p
tients have completely cleared th
lymphoma with therapy directed against
the infection. *Helicobacter pylori* in-
fection is quite common. However, gas-
tric MALT lymphoma is not. If it w
shown that this infection may also lead
to gastric large-cell lymphoma, it could
account for a higher fraction of the not-
ed increased incidence of lymphoma.

The Reasons Remain Unexplained

Even accounting for all of these po
tential sources for increased lymphom
incidence, Hartge and Devesa have e
timated that about 80% of the increa
remains unexplained.[7] It seems un
ly that a single environmental expo

will be found to account for an increase this dramatic. I doubt that there is some hit-and-run virus that infects and transforms a lymphocyte and then disappears without a trace. Thus, we are left without a complete answer to the question of what is causing the increase in lymphomas. A diverse set of environmental factors seem to act on a genetically unstable target cell to lead to lymphomagenesis.

Lymphocytes are the only terminally differentiated cells in the body that retain the capacity to proliferate and their life span can be decades long. They link their proliferative machinery to a variety of stimulatory and costimulatory cell surface receptors including their antigen receptors. Their proliferation is normally tightly controlled both within the cell (by factors related to the biology of growth control) and by soluble factors or cytokines that modify immune responses. Furthermore, some fraction of the proliferating cell population must overcome the aging process to survive in order to respond again to subsequent antigenic stimulation. However, the mechanisms that normally control lymphocyte proliferation and regulate cellular aging are presumably vulnerable to genetic, chemical, and [illegible]ological (eg, viruses) alterations. We are only beginning to understand the complexity of cell growth regulation in lymphocytes and we know nothing about lymphocyte aging. The more we learn, the more wise seem the comments of Lewis Thomas, who expressed the view that, given the second law of thermodynamics (the natural tendency toward randomness), something as complex as a human being could survive and function at all.

It seems to be a reasonable guess that lymphomas are diverse diseases that represent some final common pathological response to a wide range of environmental stimuli. From the epidemiologic data, it appears that lymphoma incidence is a building tidal wave. What remains unclear is whether we can rapidly learn enough about the various causes to implement successful prevention strategies that will enable us to diminish the damage done by the [illegible] wave.

—Dan L. Longo, MD

References appear on page 77

SALAGEN® Tablets (pilocarpine hydrochloride)

MGI PHARMA

Brief Summary
Consult Package Insert for Full Prescribing Information

INDICATIONS/USAGE: For the treatment of symptoms of xerostomia from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck.

CONTRAINDICATIONS: Contraindicated in patients with uncontrolled asthma, known hypersensitivity to pilocarpine and when miosis is undesirable, e.g. in acute iritis and narrow-angle glaucoma.

WARNINGS:

Cardiovascular Disease: Patients with significant cardiovascular disease may be unable to compensate for transient changes in hemodynamics or rhythm induced by pilocarpine. Pulmonary edema has been reported as a complication of pilocarpine toxicity from high ocular doses given for acute angle-closure glaucoma. Pilocarpine should be administered with caution in and under close medical supervision of patients with cardiovascular disease.

Ocular: Careful examination of the fundus should be carried out prior to initiating therapy with pilocarpine. An association of ocular pilocarpine use and retinal detachment in patients with preexisting retinal disease has been reported. The systemic blood level associated with this finding is unknown.

Ocular formulations of pilocarpine have been reported to cause blurring which may result in decreased visual acuity, especially at night and in patients with central lens changes, and to cause impairment of depth perception. Caution should be advised while driving at night or performing hazardous activities in reduced lighting.

Pulmonary Disease: Pilocarpine has been reported to increase airway resistance, bronchial smooth muscle tone and bronchial secretions. Pilocarpine HCl should be administered with caution to and under close medical supervision of patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease.

PRECAUTIONS:

General: Pilocarpine toxicity is characterized by an exaggeration of its parasympathomimetic effects. These may include headache, visual disturbance, lacrimation, sweating, respiratory distress, gastrointestinal spasm, nausea, vomiting, diarrhea, atrioventricular block, tachycardia, bradycardia, hypotension, hypertension, shock, mental confusion, cardiac arrhythmia, and tremors.

The dose-related cardiovascular pharmacologic effects of pilocarpine include hypotension, hypertension, bradycardia, and tachycardia.

Pilocarpine should be administered with caution to patients with known or suspected cholelithiasis or biliary tract disease. Contractions of the gallbladder or biliary smooth muscle could precipitate complications including cholecystitis, cholangitis, and biliary obstruction.

Pilocarpine may increase ureteral smooth muscle tone and could theoretically precipitate renal colic or ureteral reflux, particularly in patients with nephrolithiasis.

Cholinergic agonists may have dose-related CNS effects. This should be considered when treating patients with underlying cognitive or psychiatric disturbance.

Renal Insufficiency: The pharmacokinetics of orally administered pilocarpine in patients with renal and hepatic disease is not known.

Information for Patients: Patients should be informed that pilocarpine may cause visual disturbances, especially at night, that could impair their ability to drive safely.

If a patient sweats excessively while taking pilocarpine HCl and cannot drink enough liquid, the patient should consult a physician. Dehydration may develop.

Drug Interactions: Pilocarpine should be administered with caution to patients taking beta adrenergic antagonists because of the possibility of conduction disturbances. Drugs with parasympathomimetic effects administered concurrently with pilocarpine would be expected to result in additive pharmacologic effects. Pilocarpine might antagonize the anticholinergic effects of drugs used concomitantly. These effects should be considered when anticholinergic properties may be contributing to the therapeutic effect of concomitant medication (e.g. atropine, inhaled ipratropium).

Carcinogenesis, Mutagenesis, Impairment of Fertility: No definitive long term animal studies have evaluated the carcinogenic potential of pilocarpine HCl.

No evidence that pilocarpine HCl has the potential to cause genetic toxicity was obtained in a series of studies. In a published report, male rats who received pilocarpine at a dosage of 39 mg/kg/day (approximately 11 times the maximum recommended dose for a 60 kg human based upon body surface area estimates) exhibited morphologic evidence of reduced spermatogenesis. The possibility that pilocarpine may impair male fertility in humans cannot be excluded. The effects of pilocarpine on male and female fertility in humans have not been systematically studied.

Pregnancy Category C: Pilocarpine HCl was associated with a reduction in the mean fetal body weight and an increase in the incidence of skeletal variations when given to pregnant rats at a dosage of 90 mg/kg/day (approximately 26 times the maximum recommended dose for a 60 kg human based upon body surface area estimates). These effects may have been secondary to maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SALAGEN® Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: The most frequent adverse experiences associated with SALAGEN® Tablets in controlled studies were a consequence of the expected pharmacologic effects of pilocarpine. The incidence of the most common adverse events increases with dose.

Adverse Event	Placebo t.i.d (n=152)	5 mg t.i.d (n=141)	10 mg t.i.d (n=121)
Sweating	9%	29%	68%
Nausea	4	6	15
Rhinitis	7	5	14
Chills	<1	3	14
Flushing	3	8	13
Urinary Frequency	7	9	12
Dizziness	4	5	12
Asthenia	3	6	12

In addition, the following adverse events (1-11% incidence) were reported at doses of 5 and 10 mg in the controlled clinical trials: headache (11%), dyspepsia (7%), lacrimation (6%), diarrhea (6%), edema (5%), abdominal pain (4%), amblyopia (4%), vomiting (4%), pharyngitis (3%), hypertension (3%), conjunctivitis (2%), tachycardia (2%), epistaxis (2%), tremor (2%), dysphagia (2%), voice alteration (2%), rash (1%), taste perversion (1%), sinusitis (1%), abnormal vision (1%), myalgias (1%), and pruritis (1%).

The following events were reported rarely in treated patients (<1%). Causal relation is unknown:

Body odor, hypothermia, mucous membrane abnormality, bradycardia, ECG abnormality, palpitations, syncope, anorexia, increased appetite, esophagitis, gastrointestinal disorder, tongue disorder, leukopenia, lymphadenopathy, anxiety, confusion, depression, abnormal dreams, hyperkinesia, hypesthesia, nervousness, paresthesias, speech disorder, twitching, increased sputum, stridor, yawning, seborrhea, deafness, eye pain, glaucoma, dysuria, metrorrhagia, urinary impairment.

In long-term treatment were two patients with underlying cardiovascular disease of whom one experienced a myocardial infarct and another an episode of syncope. The association with drug is uncertain.

The following adverse experiences have been reported rarely with ocular pilocarpine: malignant glaucoma, macular hole, shock, middle ear disturbance, A-V block, depression, delusion, eyelid twitching, visual hallucination, confusion, agitation, dermatitis, ciliary congestion, and iris cysts.

MANAGEMENT OF OVERDOSE: Pilocarpine fatal overdosage resulting from poisoning has been reported in the scientific literature at doses presumed to be greater than 100 mg in two hospitalized patients. 100 mg of pilocarpine is considered potentially fatal. Overdosage should be treated with atropine titration and supportive measures to maintain respiration and circulation. Epinephrine may also be of value in the presence of severe cardiovascular depression or bronchoconstriction. It is not known if pilocarpine is dialyzable.

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...cle by Dr. Palackdharry re... ...es of how little is currently ...n regarding the epidemiolo... ...Hodgkin's lymphoma (NHL). ... cancer and breast cancer, ... epidemiologic studies of ... in their formative years, ...erous risk factors that ... related to immune func... ... various drugs, chron... ...gic reactions, chem... ...ions and iatrogenic im... ...n.

...'s lymphoma presents ...ge to epidemiologists ...ion systems are based ...ological differences ...hocytes which may ...tinct etiologic entities. ... Dr. Palackdharry points ...ella of lymphatic malig... ...become increasingly more ... the last 20 years, and we, ...ists, are somewhat at a ... the "epidemic."

...eles County, we have ...monitoring these changes ...ted in the Los Angeles ...y of Southern Califor... ...illance Program.[1] As ..., Epidemiology and ...) registries, non... ...a has been increas... ...among white males and 3% per year among white females since the early 1970s. As reported in Dr. Palackdharry's review, high-grade lymphomas (as classified by the Working Formulation for Clinical Usage [2]) are increasing at a greater rate than intermediate grade and low grade malignancies; in all subtypes, the largest increases are seen among men and women 65 years of age and older.

What should be noted is that the greatest secular increases in NHL incidence are seen for primary malignancies occurring at sites other than lymph nodes (extranodal non-Hodgkin's lymphoma). Since 1972, the incidence of extranodal non-Hodgkin's lymphoma in Los Angeles County residents has increased 6.9% per year among males and 4.3% per year among females (compared with nodal non-Hodgkin's lymphoma rates, which has increased annually by 2.1% among males and 1.2% among females). In fact, between 1980 and 1990, the proportion of extranodal NHL increased by 12%. In males, 42% of these tumors occurred in the gastrointestinal tract, 13% in the brain, 8% in the oropharynx, and 5% in the testes. The increase in extranodal lymphomas was greatest among men and women over 65 years of age, although increases were seen in all age groups.

Risk Factors: Pesticides

Dr. Palackdharry suggests that pesticide exposure and exposure to hair dyes are the most plausible occupational and environmental risk factors for non-Hodgkin's lymphoma. Case-control studies conducted in Nebraska, Kansas, and New Zealand have demonstrated elevated relative risks of non-Hodgkin's lymphoma ranging from 1.5 to 2.2 among farmers who used a particular class of pesticides (phenoxyacetic acids), with risks increasing with greater exposure.[3] The risk of non-Hodgkin's lymphoma among manufacturers of these pesticides has not been evaluated satisfactorily; however, no excess risk of non-Hodgkin's lymphoma has been observed for applicators of pesticides in six sufficiently large studies designed to assess this issue.[4,5]

Furthermore, no excess risk of death from non-Hodgkin's lymphoma was found among farmers in a large meta-analysis of 23 studies.[6] Although the evidence for increased risk from pesticide exposure among farmers is compelling, the relative risks are modest and not conclusive of a cause and effect relationship. In addition, the lack of an effect among pesticide applicators detracts from this hypothesis. Of concern is the possibility that pesticide exposure may serve as a surrogate for another farm-related exposure, one which is more ubiquitous and could affect other segments of the population, such as oncogenic viruses carried by farm animals or ultraviolet (UV) radiation.

It is difficult to assess the possible public health impact of pesticide exposure in terms of the risk of non-Hodgkin's lymphoma. From the studies of farmers, we estimate that the proportion of NHL attributable to phenoxyacetic acids among populations residing in agricultural areas ranges from 6% to 11%,[3,7] depending on the study.

Hair Dyes

Use of permanent dark hair dyes is another possible risk factor for non-

Hodgkin's lymphoma. Excess risks of NHL have been observed among long-term (> 20 years) users of these products in two case-control studies [8,9] and one cohort study of 500,000 women followed for 7 years;[10] another study has suggested that cosmetologists and hair dressers have elevated risk of non-Hodgkin's lymphoma.[11] Based on their study, Zahm and colleagues [8] estimated that the use of any hair dye product would account for about 20% of the non-Hodgkin's lymphoma occurring in women. Thun and colleagues,[10] however, based their estimate of attributable risk on the use of permanent dark hair dyes; from their study, less than 1% of the non-Hodgkin's lymphoma occurring in women could be attributed to this exposure. Although prolonged exposure to certain hair dye products may be important, in the broad picture, this exposure is not likely to account for the long-term trends in NHL incidence.

Viruses

Dr. Palackdharry describes the role of viruses in the pathogenesis of non-Hodgkin's lymphoma, focusing on Human T-cell Leukemia Virus-1 (HTLV-1) and Epstein-Barr Virus (EBV). The evidence linking HTLV-1 and T-cell lymphomas is strong, but, as Dr. Palackdharry points out, where HTLV-1 prevalence is low, this is unlikely to be an important etiologic factor. EBV, on the other hand, is ubiquitous world-wide; in the United States, the prevalence reaches 75% among college seniors and 93% among military recruits. [12]

Dr. Palackdharry suggests that the translocation of the c-myc proto-oncogene (a gene thought to regulate cellular growth) seen in many cases of non-Hodgkin's lymphoma and Burkitt's lymphoma may be related to EBV infection; if so, the relationship is indirect, as typical translocations are not found in EBV-infected lymphoma cell cultures.[13] Instead, the mechanism is probably related to the unchecked proliferation of EBV-infected B-cells such as that seen in immunocompromised patients. The prevalence of EBV genome in HIV-associated NHL tumors ranges from 38% to 66%, depending on the study [14] and this variation likely reflects differences in histologic types, anatomic sites and patient characteristics. Nevertheless, unlike transplant-associated non-Hodgkin's lymphoma and endemic Burkitt's lymphoma in which 100% of tumors are EBV-related, EBV is apparently not necessary for the development of HIV-associated non-Hodgkin's lymphoma.

One interesting hypothesis not mentioned by Dr. Palackdharry concerns the possible risk of NHL associated with exposure to UV radiation, which may have an immunosuppressive effect.[15] Persons with a previous skin cancer have greater risk of non-Hodgkin's lymphoma than those with no such history. Relative risks associated with such a history range from 1.6 in western Washington state[16] to 2.2 in Los Angeles.[17]

Obviously, more research is needed to understand the epidemiology of non-Hodgkin's lymphoma. An important area of pursuit is the characterization of premalignant changes and their association with environmental and genetic factors. Our population is aging and it is clear that aging causes a decline in B and T cell function, as well as other changes in the immune system.[18] The more aggressive use of diagnostic modalities among older persons and therefore more accurate diagnoses, may account, in part, for the marked increase in extranodal non-Hodgkin's lymphoma. Several epidemiologic studies are currently ongoing which are contrasting HIV-associated and non-HIV-associated non-Hodgkin's lymphoma. Hopefully, in time, these will provide greater insight into this disease entity.

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