Lymphoreticular Malignancies

Epidemiologic and related aspects

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LYMPHORETICULAR MALIGNANCIES

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From the river flows many streams into the ocean . . .
it is difficult to detect the main current

Preface

No disease can exist by itself but rather each must be viewed as the result of some specific interaction between man and his environment. This fact is appreciated even by people in the most primitive of civilisations and prompts them to ask the basic question: 'Why did I develop this disease'? The astute clinician goes beyond establishing a diagnosis and asks similar questions of himself and his patient. Frequently a singular observation resulting from this type of inquiry provides the working hypothesis for the epidemiologist who again asks the same question, not of the individual but of a definable population at risk. As a science, epidemiology is bound to the laws of logic and statistics, but clearly it must go beyond this point. The epidemiologist faced with a statistically significant observation must also question its biologic relevance. He must evaluate the consistency of his findings with the more established features of the disease under study. He must also be sufficiently imaginative to challenge his results with additional studies, different in their methodologic approach; and, of great importance, he must have the courage to be wrong. But epidemiologic studies alone can never determine the specific aetiology of a disease. Other scientific disciplines with their own inherent limitations are also required. Thus, in cancer research, the laboratory investigator frequently employs animal models, but the applicability of results obtained to humans is always subject to question. This defines another challenge for the cancer epidemiologist in particular: to identify situations in the community that are capable of being studied in the laboratory.

Of the many different malignant diseases, this is an opportune time to study primary lymphoreticular disorders because various medical disciplines have recently contributed new information concerning the pathogenesis and aetiology of these diseases.

This book does not exhaustively review the subject matter of lymphoreticular malignancies, but rather it places major emphasis on recent developments in the epidemiology of this group of disorders. It also takes a broad view of recent contributions made by other scientific

disciplines with the hope that the student of lymphoreticular malignancies might synthesise available information into a workable whole from which future hypotheses might be generated. The first chapter reviews the evidence suggesting that environmental factors might be important in various lymphoproliferative malignancies. Specific hypotheses have been advanced for certain disorders, such as Hodgkin's disease, Burkitt's lyphoma and acute lymphatic leukaemia of childhood, and accordingly individual chapters have been devoted to these subjects. A much broader approach must be taken with the other lymphoreticular disorders since our knowledge is less specific. In this circumstance, consideration has been given to several questions which I consider of central importance to our understanding of the other lymphomas: Is the present classification meaningful and if so what are its limitations? Are there major differences between these disorders and Hodgkin's disease which is grouped with them? Considering available information, is there any central theme which pertains to the other lymphomas? Another section of this book has been devoted to the childhood lymphomas. Although these diseases may be indistinguishable histologically in the young and old, a sufficient number of differences are present both between and within various age groups to warrant considering them separately.

The final chapter deals with factors which might predispose to certain lymphoreticular malignancies. It is hoped that this section will provide a basic framework for future studies. The great diversity in the types of factors identified, both real and potential, poses a clear challenge to the student of lymphomas, one that must not go unanswered.

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Contents

CHAPTER 1

Lymphoreticular malignancies as environmental disorders

Information of considerable importance has been gained from comparisons of the incidence of various malignant diseases, both between and within various populations. Although the role of hereditary factors can never be completely excluded, it is likely that the vast majority of the geographic differences observed for most cancers are environmentally induced. This would also appear to be true of the lymphomas and leukaemias, which are characterised by markedly diverse international patterns. When differences in incidence are polarised to the extent that a disease occurs only or mainly in relatively circumscribed areas, as is true with Burkitt's lymphoma, this allows one to concentrate on the differences between regions of high and low incidence. Do these areas differ mainly with respect to their physical environment (e.g. climate, geology), biologic environment or both? It must be realised, however, that it is difficult to dissect man from his environment; just as the nutritional, hygienic and socio-economic standards set by man can alter his environment so too existing physical and biologic factors can dramatically affect his activities. Despite all its uses, geographic epidemiology has its limitations, largely due to the lack of suitable statistics from certain areas, especially more primitive ones, and under ascertainment of cases which may be a function of the diagnostic facilities available. It is therefore imperative that other methods be employed in evaluating the possibility that a disease is environmentally induced. These include time–space cluster analysis, migration studies and evaluation of peculiar situations such as familial aggregations of a disease. Again each method has its own limitations so that a variety of approaches must be taken to adequately evaluate this question. This chapter examines the evidence that environmental factors might be important in the aetiology of certain lymphoreticular disorders.

HODGKIN'S DISEASE

Marked differences in the frequency of Hodgkin's disease have been observed both on the international level and regionally within certain countries (MacMahon, 1966). Variations have also been noted in overall rates and when such factors as age and sex are considered separately. In the United States (Figure 1.1) overall rates are higher than in Japan

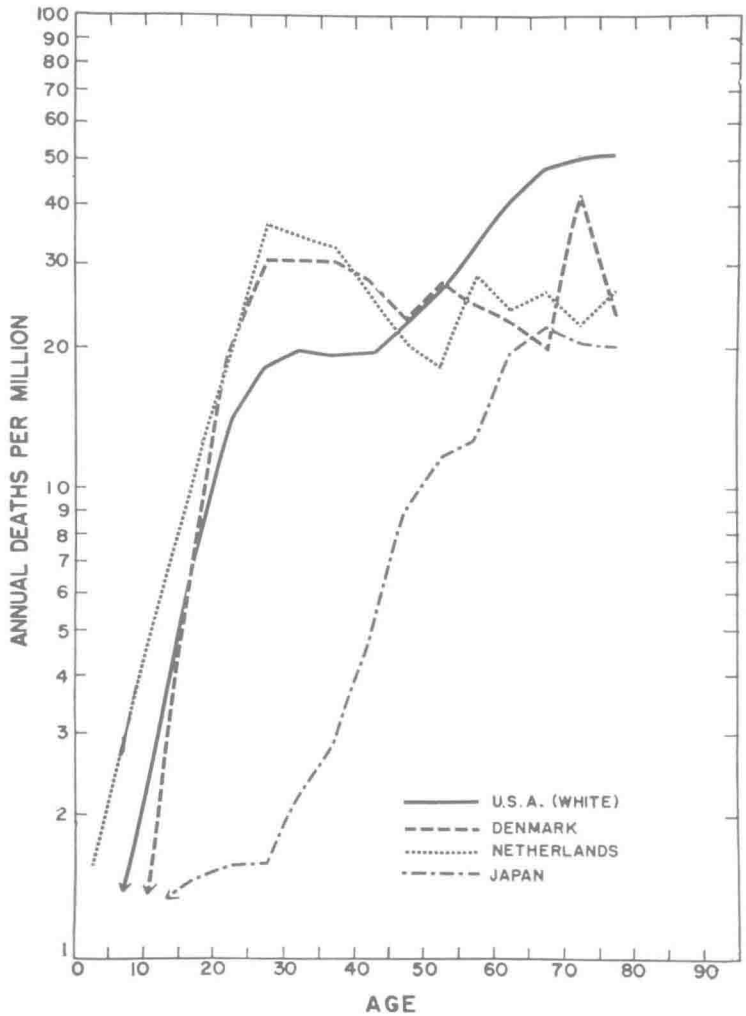

Figure 1.1 Age specific death rates from Hodgkin's disease in four countries, 1950–53. (From MacMahon, B. (1966), by courtesy of *Cancer Res.*)

and the age–specific incidence curve is characteristically bimodal. Similar bimodal curves have been observed in Great Britain (Stalsberg, 1972), Israel (Meytes and Modan, 1969), Denmark, the Netherlands (MacMahon, 1966), Northern Germany (Dörken and Singer-Bakker, 1972) and virtually every urbanised Western country where it has been sought. In Japan, the childhood age peak is clearly lacking whereas in Peru and Lebanon it predominates (Correa and O'Conor, 1971). Available data suggests that Hodgkin's disease accounts for a lower proportion of the lymphomas in Uganda than in the United States and Great Britain, but a higher proportion than found in Japan (Wright, 1973). These differences while dramatic, are difficult to intepret alone. But the evidence that Hodgkin's disease is primarily an environmentally induced malady goes beyond this point. Several studies have suggested that socio-economic factors play an important role with respect to the incidence of this disease. In the United States the disease appears to be associated with high socio-economic status among patients of 15 years of age and over (MacMahon, 1966). Unfortunately little is known about the importance of this factor for the younger age group in this country. This is a consideration of some importance since reports from other countries, especially in South America, suggest that the incidence of this disease is high among male children from poor areas (Correa and O'Conor, 1971). The importance of socio-economic factors is further suggested by the observation of three age incidence patterns for Hodgkin's disease, each apparently associated with different levels of economic development. The first pattern occurs primarily in developing countries as Peru and Columbia and is characterised by rates which are high among male children, low in the third decade of life and high in the older age groups. In urbanised countries rates are low in childhood but high for young adults and the elderly. An intermediate pattern, found in rural areas of developing countries such as Puerto Rico (Correa, 1972), is characterised by incidence rates which are somewhat higher in male children but lower in young adult males than those recorded in urbanised countries.

Leaving international comparisons for studies in specific regions, other important differences become apparent. Thus, MacMahon (1966) showed that between 1943 and 1957 the incidence of Hodgkin's disease among Danish males under 49 years of age, was higher in rural regions than in capital and suburban regions. Similar observations have been made by Dörken and Singer-Bakker (1972) in Northern Germany, and Fasal *et al.* (1968) noted that incidence rates are higher at younger

ages among Californian male farm workers and Norwegian male rural residents. Still other studies have demonstrated significant variations in Hodgkin's disease mortality rates for different regions of the United States. Cole *et al.* (1968) studied eleven contiguous southern states from 1949–54 and 1959–61 and found mortality rates in young adults to be significantly lower than those recorded in the North. This 'Southern pattern' appeared to be characterised then by mortality rates approximating the national average for the older age groups but below it for the young adult age group. These intriguing observations raise a question of fundamental importance: what were the characteristics of the childhood mortality pattern in the South? This is partially answered by Fraumeni and Li (1969) who found higher childhood mortality rates in this region than in the North, albeit during a slightly different time period. The high childhood–low young adult–high older age group pattern suggested by these studies corresponds best to that observed for developing countries. Are the different age distributions observed in various small countries primarily a reflection of the multiplicity of patterns occurring in different regions of a large country? Unfortunately this crucial question has not been satisfactorily answered at present. The obvious implication of the international, regional, socio-economic and urban–rural differences observed however, is that all these factors are interrelated and might be explained by differing interactions between environment and host.

The results of various migration studies would also appear to be consistent with an environmental interpretation in Hodgkin's disease. In a recent study (Figure 1.2), age–specific mortality rates for Japanese-Americans were found to be higher than those for Japan (Mason and Frauneri, 1974). This excess in mortality was statistically significant for the 15–34 and 50 and older age groups. Haenszel and Kurihara (1968) found standard mortality rates for Isei males and females to be more closely aligned to those for United States' whites than for Japanese. Furthermore, there does not appear to be any significant difference in mortality rates between whites and Japanese living in Hawaii (Blaisdell and Boxer, 1971). Meytes and Modan (1969) found no significant difference in the incidence of Hodgkin's disease among various Israeli migrant populations, but they did observe that the bimodality was more pronounced for American, European and Asiatic born Jews than for those born in Africa.

The results of time-space cluster analysis in Hodgkin's disease have been quite variable. Thus reports by Gilmore and Telesnick (1962),

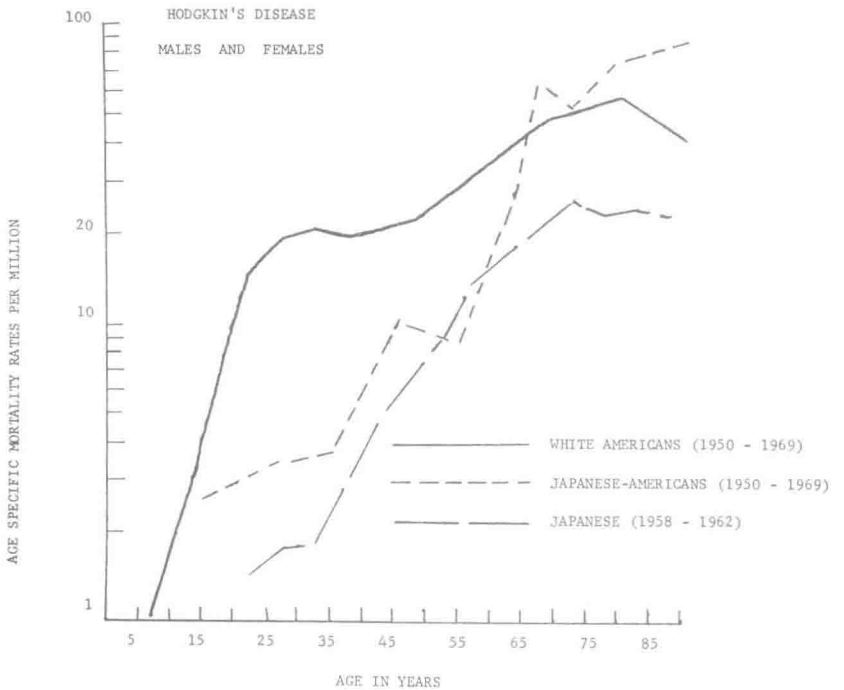

Figure 1.2 Mortality rates for Hodgkin's disease among US White and Japanese populations (1950–69) and native Japanese (1958–62) (From Mason, T. J. and Fraumeni, J. F. (1974) by courtesy of *Lancet*)

Clemmesen *et al.* (1952) and Bjelke (1969) would suggest that this phenomenon does occur whereas the more elaborate studies conducted by Alderson and Nayak (1971) found no overall evidence of clustering. Why should these discrepancies exist? While it is possible that clustering does not occur in Hodgkin's disease, the negative results obtained might be due in great part to the various time-space co-ordinates being rather arbitrarily chosen, the different age groups studied and the methods of analysis employed. Perhaps at this point it would be worth while to mention the obvious: all that encompasses the biologic world, including patients with Hodgkin's disease, is bound in time and space and each of these parameters represent a continuum of multiple points. If the reasonable assumption is made that Hodgkin's disease might have relatively specific aetiologic time and space co-ordinates, one is immediately confronted with two alternate approaches: either to continually select different co-ordinates at random from a pool of overwhelming combinations or to critically examine reported groupings of this disease for

probable co-ordinates, despite the fact that the biologic significance of these groupings remains to be determined. The latter choice would appear to be the more logical one, but has yet to be employed. More will be said about the problems encountered in applying time-space cluster analysis to Hodgkin's disease in Chapter 2.

Evaluation of familial aggregates of Hodgkin's disease provides another means of crudely dissecting genetic disorders with a definite age association from those primarily environmental in aetiology. Thus, if the interval between diagnoses or onsets of illness is shorter than the age (at diagnosis or onset) difference between two sibs, an environmental interpretation is favoured (MacMahon, 1966). Although there have been numerous reports of familial Hodgkin's disease, mostly sib–sib pairs (MacMahon, 1966; Razis *et al.*, 1959; DeVore and Doan, 1957), unfortunately the time interval between cases is not stated. While the most detailed study of this type, that of Razis and his colleagues (1959), presents evidence to favour environmental rather than genetic factors, it has been pointed out that certain biases might account for these results. In any hospital based study that employs a review of medical records to detect familial cases, it is possible that cases occurring within a short time interval would most likely be remembered and thus recorded in preference to more distant ones. Furthermore, the statement of a patient with Hodgkin's disease that he has a relative with the same disease is unacceptable unless the diagnosis can be confirmed histologically. One method of avoiding these confounding factors is to use tumour registries or regional hospital surveys to identify familial cases with similar surnames, over long periods of time. This approach is limited by the fact that it can not identify all familial cases, but it can be used as an objective means of determining the age and time intervals between such cases. A recently conducted study of this type (Vianna *et al.*, 1974) identified twenty-three familial pairs with Hodgkin's disease all of which were reassessed histologically. Analysis of these pairs showed that the time interval between diagnoses was shorter than the age interval, thereby suggesting that environmental factors might be more important than genetic. Taken together, the implication of these studies and the international, regional and socio-economic differences observed seems clear; environmental factors undoubtedly play a major role in the aetiology of Hodgkin's disease.

OTHER LYMPHORETICULAR DISORDERS

In contrast to Hodgkin's disease, our knowledge of the epidemiology of the other lymphomas is quite limited. One major reason for this is the difficulty encountered in the classification of this group of disorders. For example, the histologic features of reticulum cell sarcoma are not pathognomonic and it is frequently difficult to distinguish this disorder from certain types of lymphosarcoma (Oéttlé, 1964). Furthermore, the validity of any histologic classification depends upon a certain constancy of morphology and cell types. Custer and Bernhard (1948) claimed that transitions from one type of lymphoma (including Hodgkin's disease) to other types occurs with some frequency. In contrast, Gall and Mallory (1942) and Rappaport (1966) were impressed with the general constancy of the various types of lymphoma. While the latter view is generally accepted, a more detailed classification which considers not only architecture and cell type but also recent immunologic concepts, will be required before this matter can be evaluated sufficiently. Despite these limitations, available evidence does suggest the importance of environmental factors in the non-Hodgkin's lymphomas. They apparently occur with a greater frequency and at earlier ages in Egypt than in America or European countries (El-Gazayerli *et al.*, 1962). In Uganda, there is a relatively high proportion of reticulum cell sarcoma (Table 1.1) and low proportion of lymphosarcoma and Hodgkin's disease when compared to the United States. The distribution of malignant lymphomas in Great Britain is similar to that observed in the United States (Wright, 1973), but the pattern in Japan (Anderson *et al.*, 1970) is more closely aligned with that of Uganda (Table 1.1). In Latin American countries, the

Table 1. 1. Distribution of various lymphomas based on reports from different countries

	Hodgkin's disease (%)	*Lymphosarcoma* (%)	*Reticulum cell sarcoma* (%)
United States			
Gall and Mallory (1942)	37·0	35·6	20·4
Jackson and Parker (1947)	32·6	43·3	19·6
Mollander and Pack (1963)	34·6	30·2	22·3
Japan			
Anderson *et al.* (1970)	16·2	14·3	64·4
Uganda			
Wright (1973)	18·5	19·2	23·7

frequency of Hodgkin's disease appears to be higher than that of reticulum cell sarcoma and lymphosarcoma (Besuschio, 1974). In Africa and New Guinea, the Burkitt lymphoma is very common (Krüger and O'Conor, 1972), in the United States and Great Britain it is quite rare and in tropical regions of Latin America, the incidence of this tumour is low to moderate (Besuschio, 1974). Interesting regional differences have also been observed for certain lymphomas. In Kyadondo County, Uganda, the overall incidence of lymphosarcoma is low when compared to Western countries, but rates for males with this disorder and Hodgkin's disease are higher in the Northern Province (Figure 1.3) than in Buganda, where medical facilities are better (Amsel and Nabembezi, 1974). These international and regional differences and the observation that the standard mortality ratios for Isei males and females are more similar to those for the white population in the United States (Haenszel and Kurihara, 1968), regardless of age, suggest that environmental factors are important in the group of disorders.

Figure 1.3 Map of Uganda showing the four provinces, Kyadondo County, and the capital, Kampala (from Amsel, S. and Nabembezi, J. S. (1974), by courtesy of *J. Nat. Cancer Inst.*)

International studies have also made us aware of specific features of the non-Hodgkin's lymphomas in certain areas. There is a close overlap of the Burkitt tumour belt with the classical malaria zones in Africa (Daldorf *et al.*, 1964; Burkitt, 1969). Is this mere coincidence or does the malaria parasite act as a chronic antigenic stimulus or immunosuppressive agent which sets the stage for the Burkitt tumour (Krüger and O'Conor, 1972)? Lymphomas occur with great frequency among individuals under 20 years of age in Egypt. Is this possibly due to some relationship with chronic bilharziasis, which produces a marked reticulum cell proliferation in nodes draining active lesions (El-Gazayerli *et al.*, 1962)? There is a high frequency of intestinal lymphoma which appears to be related to high IgA levels in Arabs (Ramot and Many, 1972). Does chronic parasitic infection stimulate the gastrointestinal tract and ultimately lead to the development of intestinal lymphoma? In South America, splenic, follicular and nasal lymphomas appear to occur with undue frequency (Weiss and Morón, 1962; Andrade and Waldeck, 1971). Could this be due to customs specific to this area or environmental factors which tend to localise these disorders? These questions are worthy of further investigation. They all raise the possibility that specific environmental factors in certain areas might affect the incidence and/or mode of presentation of certain lymphoreticular disorders. The possibility must be considered that the same type of lymphoma may be associated with different factors in various parts of the world. For example, chronic parasitism may be a major predisposing factor to intestinal lymphomas in Arabian countries, but in Western countries, oeliac sprue might act in this capacity (Harris *et al.*, 1967).

In considering the lymphatic leukaemias, a major problem has been the fact that many previous studies did not treat each subtype separately. This is unfortunate since several studies (Court Brown and Doll, 1961; MacMahon and Clark, 1956; Fraumeni *et al.*, 1971) have suggested that each subtype has certain distinctive features. In general, leukaemia in Western countries has an age incidence peak before the fifth year of life, declines gradually during the middle years and then increases sharply with advanced age. In contrast, leukaemia in Uganda is not characterised by a childhood peak and rates decline after the age of 65 years (Amsel and Nabembezi, 1974). The absence of this early age peak is undoubtedly reflective of the low incidence of acute lymphatic leukaemia in this country (Amsel and Nabembezi, 1974; Templeton, 1973). In addition to the differences in leukaemia patterns that have been observed, other studies suggest the potential importance of