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AN EPIDEMIOLOGICAL STUDY OF HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970

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CHAPTER I

INTRODUCTION

The nature of Hodgkin's disease is still the subject of much controversy. Early investigators (cited by Hoster and Dratman, 1948) noted that this disease combines features common to both inflammatory and neoplastic disorders. Recently, speculation has increased concerning the possibility of multiple etiology in Hodgkin's disease. Such speculation has been based upon diversified observations. Wright (1960), Lukes and Butler (1966), Keller et al. (1968), and Bogardus (1969) have pointed out that differences in prognosis of Hodgkin's disease are associated with variations in histological characteristics. Ultman et al. (1966), Peters (1966), and Easson (1966) found striking differences in physical manifestations at diagnosis, in clinical histories of the disease, and in its response to treatment, strongly suggestive of heterogeneity of etiologic agents. In recent years, investigators have talked about "benign Hodgkin's disease" (Harrison, 1952), and the idea has been advanced concerning a possible "cure" of this illness (Easson and Russell, 1963). Long survival of many patients with Hodgkin's disease has been reported by several investigators (cited by Henry,

1970), in sharp contrast to the rapidly fatal form which the disease usually assumes.

Some other interesting observations have been made regarding the epidemiology of Hodgkin's disease. A tendency has been noted for the disease to aggregate in families (DeVore and Doan, 1957; Razis et al., 1959). Observed "clusters", cases close together in time and space, have suggested possible infectious agents (Mazar and Straus, 1951; Gilmore and Zelesnick, 1962). Higher incidence of Hodgkin's disease has been observed in upper socio-economic, and in upper educational groups (Cohen et al., 1964). Considerable international variation in the occurrence of the disease has been regarded as particularly intriguing (MacMahon, 1966). Also, several observations have been made concerning seasonal incidence of Hodgkin's disease (Cridland, 1961; Innes and Newall, 1961).

MacMahon (1957) put forth the hypothesis that Hodgkin's disease may encompass various diseases separable by age, and having different etiologies. MacMahon based his contention on the observation that its incidence by age follows a bimodal pattern, with a first peak of clinical onset at age 15 to 34, and a second peak at age 50 years and over.

MacMahon's hypothesis has received support from various types of epidemiologic studies. Findings by Cole et al. (1968) favored the idea that several etiologic factors, operating in different areas and at different ages, may be responsible for the variations in Hodgkin's disease incidence that have been observed in different parts of the world, and in different regions of the United States. High childhood

incidence rates have been reported from Peru (Solidoro et al., 1966), and from Lebanon (Azzam, 1966). Hodgkin's disease in younger groups is almost absent in Japan, but its occurrence at older ages is comparable to that of several other European countries and the United States (MacMahon, 1957, 1966). The bimodal age curve has not been observed in Japan (MacMahon, 1966).

Hodgkin's disease has been found to differ also in various age groups with respect to clinical features (Aisenberg, 1964), histologic appearance (Keller et al., 1968), survivorship curves (Peters, 1966; Henry, 1970), and sex ratio. The 15 to 34 age group has shown a characteristic sex ratio of around 1:1, while the 50 years and over group tends to approximate a male-female ratio of 2:1 (MacMahon, 1966).

Bimodal age curves are always interesting to an epidemiologist, particularly when they refer to a chronic disease. Such curves may indicate that several diseases are being considered as a single entity, or that several etiological factors are operating at different times during the life of individuals. At the present time it is not known what factors, whether diagnostic, etiological, or other, are responsible for the bimodal age-incidence pattern shown by Hodgkin's disease. Nor is it known what factors are involved in its international and other variations. Therefore, it is worth-while to undertake exploratory studies of the subject. Such an endeavor has been the main purpose of this epidemiological study of Hodgkin's disease.

The present study was designed to be a retrospective survey of all histologically confirmed cases of Hodgkin's disease (ISC 201, 8th. revision) referred to Oklahoma City hospitals from January 1,

1965, through December 31, 1970. This investigation included two main parts: First, a description of the epidemiologic features of Hodgkin's disease as it appeared in patients admitted to Oklahoma City hospitals. Second, an exploratory case-control study which attempted to find some clue to possible factors associated with the origin of Hodgkin's disease in different age groups.

Specific Aims of This Study

The present study was specifically aimed at:

1. Describing epidemiological features of Hodgkin's disease in different age groups, and comparing such features with those observed by other investigators.
2. Exploring possible relationships between reported differences in occurrence, and in manifestation of Hodgkin's disease in the age groups 0 to 14, 15 to 34, 35 to 49, and 50 years and over, and the exposure of individuals in these age groups to particular disease-inciting factors.
3. Searching for additional evidence concerning the hypothesis that Hodgkin's disease is not a single disease, but a combination of two or more etiologically distinct entities.
4. Obtaining preliminary information to be used for formulating more specific hypotheses relating the possible etiological relationship of Hodgkin's disease with particular factors.

CHAPTER II

REVIEW OF LITERATURE

Historical Synopsis

For many years Hodgkin's disease has been a common topic of discussion in medical literature. The long history of this illness goes as far back as 1661, when Malpighi (cited by Cecil and Loeb, 1959) described what today is believed to have been the first registered case of Hodgkin's disease. However, interest in the disease really began in 1832. That year, in his report "On Some of the Morbid Appearances of the Absorbent Glands and Spleen," Thomas Hodgkin referred to seven cases of a disease which would make his name famous while challenging the minds of many a scientist (Foxon, 1966; Hardwick, 1966; Hill, 1966).

The term "Hodgkin's disease" was introduced by Wilks in 1865 after he described 15 cases, 4 of which had been previously reported by Thomas Hodgkin. Once the new syndrome was so identified, investigators started studying its nature and characteristics. Noteworthy are, among others, Greenfield (1878) and Dreschfeld (1891), pioneers in presenting a microscopic description of the disease. Outstanding contributions to the knowledge of the histopathology of the illness were made by Sternberg (1898) and Reed (1902). They share credit for the accurate study of the giant cell which today is used as a single diagnostic cri-

terion of the illness.

As more knowledge was gained concerning Hodgkin's disease, investigators started publishing their own findings and reviewing the literature concerning the subject. Comprehensive monographs appeared such as those by Chevallier and Bernard (1932), Wallhauser (1933), Jackson and Parker (1947), Hoster and Dratman (1948), and Aisenberg (1964). In 1965, an excellent set of papers dealing with all aspects of the Hodgkin's disease problem was presented in a symposium, in New York City, which was sponsored by the American Cancer Society and the National Cancer Institute.

During the last three decades research on Hodgkin's disease has been channelled mainly into three aspects of the illness: (1) its etiology, (2) the relationship between its histopathologic picture and prognosis, and (3) the therapeutic aspect. Detailed review of literature dealing with the etiology of the disease will be presented later. Among the many contributors to research on the possible relationship between the histopathologic picture of Hodgkin's disease and its etiology and prognosis were Lukes (1963, 1964, 1966, 1968), Keller et al. (1968), Newell et al. (1970), Gough (1970), and Chawla et al. (1970). The concept that Hodgkin's disease may be "curable" has gained a considerable number of followers during the last twenty years. Interesting publications have appeared dealing with the therapeutic aspect such as those by Harrison (1952), Dawson and Harrison (1961), Easson and Russell (1963), Easson (1964), Schwartz (1966), Bogardus (1969), and Henry (1970).

The Clinical Picture

Clinically, Hodgkin's has been defined as "a disease of lymphatic tissue characterized by the presence of Reed-Sternberg cells and variable proliferation of lymphocytes and histiocytes" (Cecil and Loeb, 1967). For years, investigators have been intrigued by the presence of both inflammatory and neoplastic features in this illness. Giant, multinucleated Reed-Sternberg cells are considered to be malignant and pathognomonic of the disease. The origin and nature of these cells is still the subject of much speculation. Analytic microscopic descriptions of these cells have been presented recently by different authors such as Braunstein and Gall (1962), Yang and Palmer (1963), Sinks and Clein (1966), Rappaport (1966), Bouroncle (1966), and Molander and Pack (1968). The inflammatory component is represented in many Hodgkin's disease patients by the presence of numerous cells such as lymphocytes, histiocytes, eosinophils, plasma cells, and mast cells. The role played by these inflammatory cells is still unknown, and is the subject of debate among scientists. Medical literature is rich with reports and discussions of this topic. Publications by Casazza et al. (1966), Brown et al. (1967), Lingeman (1969), Buttler (1969), and Strum et al. (1971) may be cited as examples.

A commonly accepted opinion today is that Hodgkin's disease has a single focus of origin whence it spreads to other parts of the body directly or by metastatic invasion (Kaplan, 1969). The lesion usually starts with a lymph node or a set of nodes in the same body region, but any organ or tissue may be finally involved by the illness (Kern, 1961; Craver and Miller, 1966; Horwitch, 1966; Kinnman et al.,

1969). Of interest to investigators has been the observation that cases with localized lesions show a variety of striking differences in the manifestations of the illness from cases with generalized invasion (Peters et al., 1966; Chawla et al., 1970; Rosenbaum, 1970; Smithers, 1970). In order to facilitate treatment and prognosis a staging procedure has been adopted according to the degree of dissemination of the disease. In the past the staging methods have been criticized as being highly inaccurate. However, more recently various techniques have been combined such as chest films, tomograms, laboratory tests, laparotomy, skeletal radiography, lymphangiography, and other procedures, which make the staging more reliable (Lee et al., 1964; Rosenberg, 1966; Brickner et al., 1968; Glatstein et al., 1969; Exelby, 1971; Hardin and Johnston, 1971).

Jackson and Parker (1947) recognized three main histological types of Hodgkin's disease: (1) a relatively benign paragranuloma, (2) a granuloma, and (3) a highly malignant sarcoma. This histological classification has recently been replaced by a more accurate and valuable one, which was adopted by the Rye Conference on Hodgkin's disease held in New York City in 1965 (Lukes et al., 1966a). This new system classifies Hodgkin's disease into four histological categories: (1) lymphocytic predominance, (2) nodular sclerosis, (3) mixed cellularity, and (4) lymphocytic depletion. Two main advantages have been recognized to the new classification over the traditional one. First, it is a fairly good prognostic indicator. Second, it is an easy-to-use system which reduces the inter-individual variation, and gives more consistent results when used by different observers (Keller et al.,

1968; Lukes et al., 1966b; Gough, 1970).

Mortality

Mortality and morbidity statistics are two valuable indicators to look at when studying any particular disease. They provide a picture of the disease in question as compared to other diseases, therefore making it possible to detect any trends that might have occurred, or might be occurring with time. Investigators tend to agree that mortality patterns for Hodgkin's disease have not experienced substantial changes throughout the years. Any apparent increase in death rates in recent years may be due, they say, to an overconcern in the diagnosis of the illness, or to procedural changes in its classification (Shimkin, 1955a; Clemmesen, 1965; Cowdry, 1968). In the past, Hodgkin's disease has originated a state of anxiety among people mainly because it has been considered to be a death warrant for those at the threshold of their productive years of life.

In 1965, in a statistical report, the World Health Organization stated that mortality from malignant neoplasms of lymphatic and hematopoietic tissues (ISC 200-205) had increased in all countries studied between 1953 and 1962. The same report gave mortality figures from Hodgkin's disease in the five continents around the globe, as a proportion of deaths from all malignant neoplasms. In Africa, proportional death rates for Hodgkin's disease varied from 2.2% in Mauritius to 0.1% in the United Arab Republic in 1962. The highest death rate, 1.2 per 100,000 population, was observed in South Africa. In Asia around 1% of deaths from malignant neoplasms were due to Hodgkin's disease, with rates ranging between 1.7 per 100,000 in Israel, to

0.1 per 100,000 in Ceylon. In 1962, Hodgkin's disease accounted for about 1.0% of deaths from cancer in North America. Death rates were 1.5 per 100,000 in Canada, 1.7 per 100,000 in the United States, and 0.3 per 100,000 in Mexico. Around 1.5% of all deaths from cancer were attributed to Hodgkin's disease in the Caribbean, Central, and South America in 1962, with the highest rate of 1.3 per 100,000 being observed in Puerto Rico. In Europe the proportion of deaths from Hodgkin's disease was around 1.0%. However, death rates ranged from 4.1 per 100,000 in West Berlin to 1.1 per 100,000 in Poland and Spain. During the same year Hodgkin's disease was the cause of death for about 1.0% of all cancer deaths in Oceania, with death rates approximately 1.5 per 100,000 in Australia and New Zealand. With the exception of Europe where death rates were higher in 1961 than in 1953 for nearly half the countries,the World Health Organization reported no significant changes in mortality trends.

MacMahon (1957) took international death rates from Hodgkin's disease published by the World Health Organization and adjusted them to the white population of the United States. For all ages, the countries with the highest mortality rates were the Netherlands, Denmark, Scotland, Italy, and Switzerland, the rates ranging from 2.0 per 100,000 for the Netherlands, to 1.7 per 100,000 for Switzerland. Japan showed the lowest mortality rate with 0.6 per 100,000, which is in agreement with findings by Nishiyama et al. (1970). Clemmesen (1965) noted that death rates from Hodgkin's disease in Denmark during the period 1931-1960 rose from 1.7 and 1.1 per 100,000 to 2.5 and 2.1 per 100,000 in males and females respectively. A study on Hodgkin's disease mortality in

Norway by Bjelke (1969) showed an increase in death rates during the period 1931-1955 for those under 50 years of age, and during the period 1931-1965 for those over 50 years of age.

Gordon et al. (1961) reported an apparent increase in age-adjusted death rates from Hodgkin's disease in the United States during the period 1930-1955. The rates went from 1.5 and 0.8 per 100,000 for white males and white females in 1930, to 2.4 and 1.3 per 100,000 in 1955. For non-white males and non-white females the rates rose from 0.7 and 0.5 per 100,000 in 1930, to 1.8 and 0.8 per 100,000 in 1955. MacMahon (1966) stated that the annual death rate for Hodgkin's disease in the United States from 1958 to 1962 was 2.3 per 100,000 for white males, and 1.3 per 100,000 for white females. The lifetime risk of dying from the disease before age 75 was around 2.1 per 1,000 for white males, and 1.2 per 1,000 for white females. According to Vital Statistics of the United States (1966, 1967) Hodgkin's disease accounts for 32% of all lymphomas, and causes death at an approximate annual rate of 2.0 per 100,000. Silverberg and Holleb (1971) have estimated that 3,700 persons will die of Hodgkin's disease during the current year in this country, 2,200 of which will be males and 1,500 females.

Regional differences in mortality from Hodgkin's disease were reported by Cole et al. (1968) in the United States. They observed an interesting geographic variation in incidence in younger patients in northern states as compared with other areas of the country. Such a difference in mortality rates was not observed in the older age groups. A mortality study by Martin et al. (1963) in the state of Kansas, from 1950 to 1959, showed a state death rate of 1.6 per 100,000. They ob-

served that some counties had higher rates than others. The death rates were significantly higher in urban areas, with a rate of 1.9 per 100,000, than in rural areas, with a rate of 1.2 per 100,000.

Mortality studies in the state of Oklahoma by Assal (1968), and Assal and Lindeman (1970), during the period 1956-1965, showed age-adjusted death rates for Hodgkin's disease to be over twice as high in males as in females. Annual age-adjusted death rates were 2.1 and 1.0 per 100,000 for white males and white females respectively. Rates were higher in whites than in non-whites. Some geographic variations in death rates were also noted by these investigators. They observed that high death rates for white males were more common in an area comprising Tulsa and three south-bordering counties, and in some counties extending from the southeastern to the southcentral part of the state. The highest rates for white females occurred in northeastern counties and in the northcentral region of the state. The authors reported that occurrence of Hodgkin's disease in Oklahoma seems to have remained stable during the 10-year period studied, showing only a slight increase in non-white females.

Occurrence

Hodgkin's disease has been reported from all areas of the world (Doll *et al.*, 1966). A common observed pattern is that incidence rates are higher than mortality rates. MacMahon (1966) attributes this difference, at least in part, to variations in time and area of observation. However, he adds that it is not unusual for incidence rates to be higher than mortality rates, since many Hodgkin's disease patients live long enough to have their deaths attributed to other causes.

Morbidity rates for Hodgkin's disease, per 100,000 population, for seven countries, have been published in the World Health Statistics Report (1971). Such rates ranged from 1.3 in New Brunswick, Canada, in 1965, to 5.6 in Hamburg, Germany, in 1968.

Clemmesen (1964) reported average annual incidence rates, by sex, during the period 1943-1957 in Denmark. His figures were 2.5 per 100,000 for males, and 1.8 per 100,000 for females. Bjelke (1969) found that in Norway annual incidence rates for Hodgkin's disease during the years 1953-1963 were somewhat higher than annual mortality rates during 1961-1965. He observed an incidence rate of 2.8 per 100,000 for males, and 1.8 per 100,000 for females during the period 1953-1963. Gadomska and Karewicz (1970) found that from 1961 to 1965 the incidence of lymphoma in Poland accounted for 2.1% of all malignant tumors in men, and 0.9% in women.

Reports regarding the relative occurrence of Hodgkin's disease are numerous and come from all geographic areas. Eddington and Maclean (1964) observed no significant differences in incidence rates in various areas of central and western Africa. Davies (1964) found that Hodgkin's disease represented about 16% of all lymphoreticular neoplasms in Uganda. In an editorial, The Lancet (1967) reported that Hodgkin's disease accounts for nearly 16% of all malignancies among Arabs living in Zanzibar. Olweny et al. (1971) have observed Hodgkin's to be a relatively common disease in Uganda, mainly affecting children and young adults. Occurrence of the disease in young persons is said to be relatively low in Japan (MacMahon, 1966; Haenszel and Kurihara, 1968; Stemmerman, 1970; Nishiyama and Inoue, 1970; Anderson et al.,

1970). Rowe et al. (1964) reported on 15 cases of lymphoma in tropical Central America, 9 of those cases were Hodgkin's disease. Dalldorf et al. (1969) have stated that Hodgkin's disease is the most conspicuous lymphoma in Brazilian children. The characteristic bimodal incidence pattern of Hodgkin's disease in Israel migrant populations was studied by Modan et al. (1969). Meighan (1961) and Danzinger et al. (1969) have presented information concerning the occurrence and clinical picture of Hodgkin's disease in some areas of Canada. Their findings have confirmed previous observations by Thorson and Brown (1955) that the disease constitutes a distinct entity differing from lymphosarcoma and reticulum cell sarcoma in both age and sex distribution. Talerman (1970) found that Hodgkin's disease accounted for 51% of all lymphomas in a series of 260 cases studied in Jamaica during the period 1958-1966.

In the United States, Dorn and Cutler (1955, 1958) estimated that Hodgkin's disease occurs at an annual rate of 3.5 in white males, 2.6 in white females, 2.7 in non-white males, and 1.6 per 100,000 in non-white females. The lifetime probability of being affected by the disease before age 74 is approximately 3.2 per 1,000 for males, and 2.0 per 1,000 for females. According to the World Health Statistics Report (1971), California (represented by Alameda county only) registered a Hodgkin's disease incidence rate of 3.6 for males, and 1.5 for females, in 1966. The overall county incidence rate was 2.5 per 100,000 population. During the same year, the morbidity rates in the state of Connecticut were 3.6 for males, and 2.3 for females. The overall state rate was 2.9 per 100,000.

Silverberg and Holleb (1971) have estimated that around 4,900

new Hodgkin's disease cases will be diagnosed in the United States during the year 1971, of which 2,700 cases will be among males, and 2,200 among females.

Although the occurrence of Hodgkin's disease seems to be relatively high in the United States and in certain northern European countries, and relatively low in other areas such as Australia and Japan, investigators commonly agree that these international variations are not impressive when overall rates are considered. However, more striking differences are discovered when the occurrence of the illness is studied separately in different age groups as will be seen later.

Significant changes in secular trends in the overall occurrence of Hodgkin's disease have not been observed or reported. Lancaster (1955) noted a very slight increase in mortality in Australia during the period 1920-1950. Data from Denmark published by Clemmesen (1964) show a minor increase in incidence rates for all ages between 1943 and 1957. However, when age groups are considered separately it is noted that while rates in the age group 35-50 have declined, they have increased for the age groups 15-34 and 50 years and over, remaining almost constant for the age group 0-15 years. MacMahon (1966) noted that Hodgkin's disease in the United States, during the last 15 years, has shown a decline of 20% in the age group 0-14, while it has increased by 15% in the age group 15-34, and remained constant in the 50 years and over group. He further states that:

> With the exception of the decline in rates for the 0-14 age group, and the overall increase in rates in all other age groups over several decades in the United States and England and Wales, none of the changes in time trends seem noteworthy. Perhaps all that can be said with confidence is that Hodgkin's disease appears not to be decreasing in frequency.

Age

Perhaps the most interesting epidemiological feature exhibited by Hodgkin's disease is the bimodality of its age incidence curve. MacMahon(1957) noticed that the disease showed two characteristic incidence peaks, one in the 20 to 34 year age group, and the other after age 45. He later (1966) suggested that descriptive features of the disease should be considered separately in four different age groups: 0 to 14, 15 to 34, 35 to 49, and 50 years and over. Moreover, he proposed two main hypotheses to explain this Hodgkin's disease bimodal pattern. First, that at least three subgroups of illnesses with quite distinct etiologies may be included in what today is known as Hodgkin's disease. Second, that in young adults Hodgkin's disease is a chronic granulomatous inflammation, while in persons over 50 years of age it is a neoplasm.

Bimodal age distribution curves for Hodgkin's disease have been observed in many countries such as Canada (Meighan, 1961), England and Wales, the Netherlands, Denmark, Sweden, and France (MacMahon, 1966), Italy (Cordeiro-Guerra and Bianchini, 1968), Israel (Meytes and Modan, 1969), Norway (Bjelke, 1969), Germany (Uhl and Hunstein, 1969), Poland (Gadomska and Karewicz, 1970), Jamaica (Talerman, 1970), and others. However, although the bimodality is an international feature, the incidence of the disease in different countries, and even in different areas within the same country, varies according to the age group considered. Thus Cole *et al*. (1968) found an unexplained difference in the occurrence of Hodgkin's disease in Northern and Southern United States. While mortality rates for middle-aged and elderly people in

eleven Southern states were comparable to those in the rest of the country, mortality among young adults was only half that observed in the rest of the nation. MacMahon (1966) pointed out that in Denmark the two modes in the age distribution of Hodgkin's disease have almost equal prominence. The same is true for the Netherlands. In the United States, however, the second mode is considerably larger than the first. In the Netherlands, Hodgkin's disease rates under 40 years of age are 80% higher, but rates over 40 years are 30% lower than in the United States. An interesting feature has been observed in Japan where Hodgkin's disease is practically absent in the young group, but in the old its occurrence is comparable to that in Denmark, the Netherlands, and various other countries (Anderson et al., 1970; Nishiyama and Inoue, 1970). A 19-year survey, 1938 to 1956, by Arthachinta and Ogden (1962) in Connecticut showed that the highest incidence of Hodgkin's disease occurred between the ages of 20 to 49. However, they also noted that the incidence in older groups was quite high.

Comparing urban versus rural residents in Denmark, MacMahon (1966) found that under age 15 Hodgkin's disease was more common in rural areas; over age 50, rates were higher in urban areas for females but not for males. Bjelke (1969), in Norway, found that for persons under 70 years of age, the incidence of Hodgkin's disease was higher in urban areas, and in rural areas the incidence appeared higher in densely populated than in sparsely populated areas.

Hodgkin's disease in children is relatively uncommon in the United States, particularly before 5 years of age (U. S. Vital Statistics; Fraumeni and Li, 1969; Newell, 1970). However, Miller (1966)

pointed out that an abrupt rise in mortality rates seems to occur around 11 years of age. Bailey et al., in 1961, had reported an increase in the incidence of childhood Hodgkin's disease starting at 9 years of age. These investigators have suggested that there is an increase in susceptibility to the illness beginning in late childhood which continues through adolescence and into young adulthood, particularly in males. Fraumeni and Li (1969) found some interesting variations in the geographic distribution of Hodgkin's disease deaths among white children in the United States. They observed that the West-South Central region, reported by others (Hoster, 1944; Gordon et al., 1961) to have the lowest mortality from Hodgkin's disease at all ages, was the only area with a significantly high mortality for the childhood disease. Standard mortality ratios were significantly high for Texas, Louisiana, and Arkansas, while Oklahoma had a rate lower than expected with regard to the average United States experience. These investigators noted significantly lower rates in the Pacific region of the country.

International variations in the incidence of childhood Hodgkin's disease is also a subject of interest to researchers. Already mentioned is the fact that childhood and early adulthood Hodgkin's disease is absent in Japan. However, relatively high incidence rates have been observed in certain parts of Africa (Camain and Lambert, 1964; Oettle, 1964; Davies, 1964), in Egypt (Gazayerli and Khalil, 1961), in Kenya (Linsell and Martyn, 1962), in Lebanon (Azzam, 1966), and in Peru (Solidoro et al., 1966). Teillet (1968) reported that among the "malignant tumors" Hodgkin's disease shows a lower incidence than lympho-

sarcoma and reticulosarcoma in French children. Meanwhile, Hodgkin's disease in Lebanon has shown a childhood incidence as high as 2.4 per 100,000 (Zellweger and Firzli, 1957), which is four times higher than the 0.5 per 100,000 for the same age group noted by Uddstromer (1934) in Sweden. Although data are scarce, it seems that Hodgkin's disease is also a fairly common disease in children in Uruguay (Salgado-Lanza, 1953), and in Algiers (De Perreti et al., 1963). A cancer survey of Brazilian children (Marigo et al., 1969) demonstrated a high frequency of Hodgkin's disease which accounted for 48 cases out of 103 lymphomas. Male-female ratios for the three five-year periods studied were 7:1, 2:1, and 3.3:1 respectively. The authors noted that in this instance Hodgkin's disease represented 9.2% of all childhood malignancies studied, in sharp contrast with the 3.0% proportional rate which has been commonly observed in similar surveys in England, the United States, and in some European countries.

Most researchers agree that Hodgkin's disease in children tends to occur in the second half of childhood (Marsden and Steward, 1968). The age distribution of the disease in childhood has usually two peaks, one at 6 to 7 years, the other at 10 to 11 years. Cases of Hodgkin's disease before one year of age are very unlikely to occur, and any reported case must be carefully analyzed to avoid confusion with other affections of lymphatic organs (Teillet, 1968).

Sex

It is well established that Hodgkin's disease shows a higher incidence in males than in females, particularly in the very young group (Wallhauser, 1933; Smith, 1934; Uddstromer, 1934). MacMahon

(1957) remarked that the prevalence of the disease in males is also highly conspicuous in the age group 40 years and over.

High proportions of male patients have been found to be a common feature in most Hodgkin's disease studies. Aisenberg (1964), after reviewing mortality data from the United States, reported that 63% of white Hodgkin's disease patients were males. A high proportion of males, 58%, had been previously found by Dorn and Cutler (1958). MacMahon (1957) reported 61% males in a study in Brooklyn, New York. Clemmesen, and Busk (1947, 1964, 1965) similarly observed male proportions as high as 60% in Denmark, England, and Switzerland. Bjelke (1969) found that at all ages the incidence rates of Hodgkin's disease in males were more than 50% higher than in females in Norway. MacMahon (1966) stated that in England and Wales mortality data indicate the male proportion of deaths to be as high as 66%. Of 9 cases of Hodgkin's disease observed by Rowe and Johnson (1964) in Central America, 8 were male, and 1 female. Investigators seem to agree that the Hodgkin's disease occurrence is about twice as common in males as in females. Rubin (1964) affirmed that "although sex ratios show a greater incidence in males, there is a definite shift toward a higher proportion in females." MacMahon (1966) challenged that statement. He noted that the shift did not appear when looking at mortality data. Male proportions in the United States have remained almost unchanged since 1923; and in Denmark, Hodgkin's disease showed a male proportion of 59% during 1943-1947, increasing only to 60% in 1953-1957.

Hodgkin's disease presents another interesting feature when looking at its sex distribution in the different age categories. A

survey on the distribution and incidence of the lymphomas by Thorson and Brown (1955) showed that sex ratios were considerably lower in the younger age group than in the group 40 years and over. Uhl and Hunstein (1969), in Germany, studied a series of 315 cases occurring from 1953 to 1957. They noted that in the first peak, 16 to 35 years, Hodgkin's disease affected mainly females, while in the peak 50 to 60 years most patients were males. It appeared, therefore, that females were affected at younger ages than males. MacMahon (1966), after comparing sex ratios at different ages as reported in a variety of incidence surveys, came to the conclusion that Hodgkin's disease seems to show a characteristic male to female ratio of 1:1 in the 15 to 34 age group, and 2:1 in the age group 50 years and over.

Incidence of Hodgkin's disease in the 0 to 14 age group is characterized by a high male to female ratio. Fraumeni and Li (1969) observed an overall male to female ratio of 3:1 for white children. They noted that the male excess declined with increasing age up to age 15, from 3.5, to 3.3, to 2.9 for each succeeding age group. Miller (1966) reported that between 1950 and 1959 there were 1,484 Hodgkin's disease deaths under 20 years of age in the United States. In the 5 to 11 years age group 76% of those affected were males, thus giving a sex ratio of 3:1. After 11 years of age, a decline was observed up to age 17 when the male to female ratio was only 1.5:1. Miller also noted that mortality rates were greater for males until age 11. However, from age 11 to 19 both males and females showed about the same "absolute" increase in cases, but the "relative" increase for males was only 2.5-fold as compared with a 6.4-fold increase for females; consequently, reducing

the sex ratio after 11 years of age. A striking predominance of males, 91%, was observed by Strum and Rappaport (1970) who did a study of Hodgkin's disease in the first decade of life at the University of Chicago hospitals. They failed to find any case below age 3.

The very high male to female ratio in childhood seems to be an international feature of Hodgkin's disease. In Lebanon, Azzam (1966) observed a sex ratio approximately 2:1, in a series of 55 Hodgkin's disease cases in children. Cordeiro-Guerra and Bianchini (1968), in Italy, noted 88% males in a series of children with Hodgkin's disease. They remarked that such a percentage is "much higher than that reported at older ages." Solidoro et al. (1966) found a male to female ratio of 2.3:1 in children affected with Hodgkin's disease in Peru. The ratio decreased gradually in the older patients. The high predominance of male patients in the younger group has been reported by several other investigators, among them, Jelliffe and Thomson (1955), Razis et al., (1959), Peters and Middlemiss (1958), Hanson (1964), and Newall (1965).

In 1939, Epstein suggested that females affected with Hodgkin's disease had a better prognosis than males. Videbaek (1950) challenged that contention, and maintained that prognosis is the same for males and females. Peters et al. (1966), after performing incidence and survival studies in 323 patients, according to sex, concluded that females are more prone to develop localized lesions, while males tend to develop the generalized type of disease. They did not find any sex difference in survival rates within each disease stage beyond 10 years. Up to 10 years, they observed better survival rates for females only in stage II. MacMahon (1966) commented that if the influences of age and

sex are considered simultaneously it is likely that sex differences in survival will be greatest in young adult ages. Females, he adds, because they are more conscious of disease than males, tend to look for earlier diagnosis. This might explain the higher rates of localized lesions, the earlier age at onset, and the longer survival rates found in females than in males. However, MacMahon concludes that "more likely females suffer an innately slower developing disease in which longer duration allows greater opportunity for diagnosis in a localized stage."

Gough (1970) carried out a study on the correlation of histopathology of Hodgkin's disease with survival. He found that patients with lymphocytic predominance and the nodular sclerosis type disease had better prognosis than those with mixed cellularity or the lymphocytic depletion type. He observed also that nodular sclerosis was twice as common in females as in males, and mixed cellularity twice as frequent in males as in females. The other two types were more equally distributed between the sexes. An interesting observation was provided by Burn and Davies (1971) who did a study of Hodgkin's disease in European and African children. They noticed that African children showed a statistically significant difference in the severity of lesions (histological types with less favorable prognosis) from English, French, and Texan children. A study by Olweny et al. (1971) corroborated the previous observation. They found that in Uganda, Hodgkin's disease commonly affects children and young adults, particularly males, and is a more aggressive disease than seen elsewhere, both with respect to clinical stage and histopathology. Talerman (1970), in Jamaica, who ob-

served a male-female ratio for Hodgkin's disease of 2.6:1, noted also that the majority of the cases fell into the mixed cellularity category, while lymphocytic predominance and nodular sclerosis types were uncommon.

Race

Incidence rates of Hodgkin's disease for Negroes in the United States are lower than those for Caucasians (Lingeman, 1969). The relatively low frequency of the disease in Negroes has been a common observation in different disease studies. Mortality studies by Gilliam (1953) and Shimkin (1955) demonstrated a significantly lower mortality among Negroes than among whites in this country. In his morbidity study in Brooklyn, New York, MacMahon (1957) found only 27 Negroes among 573 Hodgkin's disease cases. Dorn and Cutler (1959) also reported low incidence rates of the disease in Negroes as compared to whites. MacMahon (1966) reviewing the vital statistics of the United States observed that in recent years, for the age group 35 to 50, the mortality rates for non-white males are closer to those for white males than rates for non-white females are to rates for white females. He could not offer any explanation for this race pattern, nor did he find substantial differences between rates for whites and non-whites in the age groups 15 to 34 and 50 years and over.

Hodgkin's disease seems to occur less frequently in Negro than in white children in the United States. Fraumeni and Li (1969) found only 46 Negroes among 359 deaths in children 1 to 15 years old, during the period 1960-1964. Other ethnic groups represented were Filipino, Chinese, Japanese, American Indian, and Eskimo, each one with

one death. Strum and Rappaport (1970) observed only 2 Negro patients out of 35 cases in their study at the University of Chicago. One of the patients was a Nigerian child, and the other American. Miller (1966) found a racial difference in death rates from Hodgkin's disease in children, but not very marked. He noted that, for the first 20 years of life, the mortality rate for white males was 3.20, and for non-white males 2.59 per 100,000. The rates for white and non-white females were 1.83 and 1.61 per 100,000 respectively.

It was previously mentioned that Hodgkin's disease seems to have a world-wide distribution, although its incidence rates vary from country to country, and even within sections of the same country. A breakdown of the occurrence of the disease in different races is not available. Most reports, some of which have been already cited, give only an account of the general picture of the disease in different countries. However, from the published literature it is possible to have at least a scant idea of the incidence of Hodgkin's disease in various ethnic groups. Well known is the common occurrence of the disease in north-european races in the Netherlands, Denmark, Switzerland, Norway, and Sweden (MacMahon, 1966; Clemmesen, 1952, 1958, 1965). Azar (1962) did a study of cancer in Lebanon and the Near East from 1953 to 1960. The ethnic groups included were Lebanese, Jordanians, Syrians, and Palestinian Arabs. He found that Hodgkin's disease accounted for 35.7% of the total number of malignant lymphomas among these groups. He further speculated that the incidence of malignant lymphomas among Arab and Near Eastern people is much higher than in Europe or the United States. Meytes and Modan (1969) studied 186 Hodgkin's disease cases in

Israel, of which 169 were Jews and 17 Arabs. They observed an annual incidence rate of nearly 2.0 per 100,000. However, they concluded that there were no significant differences in rates between the various Jewish ethnic groups, as have been observed with some other types of cancer such as breast, stomach, brain, and colon and rectum.

The Japanese have been distinguished as peculiar people with respect to the occurrence of cancer. Japan either has the highest rates, or the lowest rates for specific cancer sites in the world. After a study of lymphomas and multiple myeloma, in which they compared different aspects of these illnesses in Japan, England, and the United States, Anderson et al. (1970) summarized their findings with the following:

> Reticulum cell sarcoma is the most prevalent form of malignant lymphoma in Japan with a relative frequency (42%) that approaches Hodgkin's disease in Western series (49%). Conversely, Hodgkin's disease is the least frequently encountered form of lymphoma in Japan with a relative frequency (20%) not far removed from reticulum cell sarcoma (18%) in the West.

Hodgkin's disease has been observed to show relatively high incidence rates among other ethnic groups such as in West African Negroes living in Kampala, Uganda (Davies, 1957), in Moslems of Northern Africa (Montpellier and Mussini, 1952), and in whites of Spanish descent in Antioquia, Colombia (Correa, 1955). Gelpi (1970) studied the incidence of malignant lymphomas in the Saudi Arabs. Hodgkin's disease accounted for 35% of all cases, with the peculiarity that 11.6% of them showed abdominal involvement by the disease. Gelpi concluded that the high frequency of abdominal lymphoma in Saudi Arabs was comparable with that found in Israel among Arabs and Sephardic Jews by other investigators (Shani et al., 1969).

Time

Some speculation exists concerning possible seasonal variation in the incidence of Hodgkin's disease. Cridland (1961), and Innes and Newall (1961) noted that in England, localized Hodgkin's disease, at all ages, tended to show a peak in clinical onset during the winter months, December and January. Fraumeni and Li (1969) observed also that the disease in children in the United States showed a trend toward higher occurrence during December and January. Uhl and Hunstein (1969), in Germany, found that there was a statistically significant increase in incidence of onset of symptoms during winter, and a drop below the expected average during the summer months. If these observations were correct, Hodgkin's disease would differ from childhood leukemia which tends to have the highest occurrence rates during spring time in the United States (Fraumeni, 1963), and during summer in England (Lee, 1962). However, seasonal variation in the occurrence of the disease has not been observed in all studies. Thus in Norway, Bjelke (1969) did not find any seasonal trends in the incidence curve. He concluded that "considered as a whole, variations in the distribution of cases by month of diagnosis could easily be ascribed to chance."

Variations in cancer incidence according to month of birth have been observed (Bailar and Gurian, 1964). In the case of Hodgkin's disease, Fraumeni and Li (1969) reported that mortality rates were particularly high during 1960-1964 for children born during summer months, July and August. This observation applied especially to cases in the West-South-Central and East-North-Central regions of the United States, and it was limited to males. However, Bjelke (1969), in Norway,

found that the distribution of Hodgkin's disease cases by month of birth did not show any appreciable difference from expectation on the basis of monthly distribution of births during the period 1953-1963.

Hodgkin's disease "clustering," or the occurrence of cases close together in time and space, has received considerable attention from investigators. The possibility of time-space association has been suspected in several instances. George et al. (1965) observed the disease to occur in a pair of roommates. Gilmore and Zelesnick (1962) noted the incidence of 3 cases of Hodgkin's disease in 4 families living in adjoining houses for 13 years. Mazar and Straus (1951) reported on Hodgkin's disease affecting marital partners. Craver and Miller (1966) cited an instance in which the disease occurred within a week, in mother and son, who worked in close proximity in a room of their house.

Bjelke (1969) reported that in Norway, data from 1953 to 1963, did suggest time-space aggregation of new cases of Hodgkin's disease. Lundin et al. (1966) concluded that although in their study leukemia and lymphoma were not found to cluster in time and space, the temporal distribution of deaths from 1953 to 1962 revealed an excessive number occurring 6 to 8 years apart. Fraumeni and Li (1969) observed no clustering of childhood Hodgkin's disease in individual states in this country. However, they noted that the Southern region and the Mountain division, over a 5-year period taken together, showed both high mortality from the illness and seasonal excess in births.

The most recent, and perhaps the most interesting study so far published concerning clustering of Hodgkin's disease is the one by

Vianna et al. (1971). These investigators reported the occurrence of the disease in four students belonging to the same graduating high school class. Further inquiry among relatives and friends of these patients demonstrated an interrelationship of twelve cases of the illness in a period of about two decades, 1949-1970. Only two of the cases were familial cases. The rest were classmates, friends, or relatives linked directly or by contact to the school class.

Not all studies have proved or suggested clustering of Hodgkin's disease in time and space. An investigation of the topographical distribution of this disease in Denmark, did not show any space or time aggregation (Clemmesen et al., 1952). Similarly, an analytic study dealing with the incidence of malignant lymphomas in Connecticut (Ederer et al., 1965) failed to reveal any clustering of Hodgkin's disease in space and time.

Occupation

Hodgkin's disease has not been found to show significant predilection for any particular occupational group. The suggestion was made by Milham and Hesser (1967) that people working in the wood industry may be at higher risk of acquiring the disease. They reviewed death certificates of Hodgkin's disease patients in upstate New York, who died during the periods 1940-1953, and 1957-1964. Their conclusion was that Italian men whose work had required exposure to wood revealed a preponderance over a matched control group. However, the findings of Milham and Hesser were later refuted by two other investigators. Acheson (1967) carried out a study in England, in an area with a high concentration of the furniture industry. The total population in the

area was around one million. He found a crude annual incidence of Hodgkin's disease of 1.9 per 100,000. Incidence rates were 2.6 for males, and 1.3 for females, with a male-female ratio of 2:1. The total number of Hodgkin's disease cases was 272 from 1956 to 1965. The author concluded that all the observed rates excluded any marked increase in risk for those people having something to do with the wood industry in the area studied. Spiers (1969) after a complicated study of Hodgkin's disease in workers in the wood industry, failed also to confirm any increased risk of getting the disease. However, he clarified that "disagreements in the findings prevent the formulation of definite conclusions, since the relative risk of contracting the disease may vary from one area to another."

Other than for the wood industry, occupational studies concerning the occurrence of Hodgkin's disease have not been done. MacMahon (1957) suggested that an investigation would be worth-while in such dairy-producing countries as Switzerland, Denmark, and the Netherlands, where the disease has shown high incidence in the younger groups. He observed also that between 1943 and 1957 the incidence of Hodgkin's disease among Danish males below age 49 was higher in rural than in urban areas.

Fasal et al. (1968) did a study on the relationship between leukemia and lymphoma mortality and farm residence. They found a great similarity in the age distribution of Hodgkin's disease in rural Denmark and Norway, and mortality from the illness in California farm residents. They commented that such findings were consistent with the possible existence of a factor common to the farm environment which might be of

etiological significance. They further suggested that an analysis of farm occupations, by type of farming, could help to shed light on the nature of such a factor, if one really exists.

Other Demographic and Socio-Economic Factors

High mortality in the upper socio-economic groups is a characteristic commonly observed for all lymphomas, and Hodgkin's disease seems to be no exception. Cohen et al. (1964), studying a sample of 388 cases in the United States Army, found that patients with Hodgkin's disease showed a higher percentage in the middle occupational classes than did the controls. They reported that these socio-economic differences were highly significant. MacMahon (1966) analyzed mortality ratios for leukemia and lymphomas in males aged 20 to 64, in England and Wales, during the period 1949-1953. He observed a Hodgkin's disease mortality ratio of 142 for patients classified as "higher administrative or professional," and a mortality ratio of 87 for those classified as "unskilled workers." His results agreed with those of Cohen et al. (1964). However, MacMahon noted an incongruity in his findings. The group of clerical workers (social class III) taken separately, showed a significantly higher mortality ratio, 134, than the group of semi-skilled workers (social class III) taken as a whole whose mortality ratio was only 100. Seidman (1970) examined cancer death rates by site and sex for religious and socio-economic groups in New York City, during 1949-1951, for the 25 to 64 year old non-Puerto Rican white population. Hodgkin's disease in males showed a death rate per 100,000 population of 3.8, 3.7, and 3.8, for high, middle, and low socio-economic class respectively. The death rates for females were 2.7, 2.7, and 2.1, for

the respective high, middle, and low socio-economic group. No appreciable difference among classes was noted.

Regarding educational background, observations made so far seem to indicate that Hodgkin's disease patients have had more years of schooling than matched controls. Cohen et al. (1964) reported that the educational level of patients, as measured by number of pre-service years of schooling, was significantly higher than that of controls. LeShan et al. (1959) postulated the possibility of a relationship between Hodgkin's disease and intelligence. They observed that patients usually had obtained higher scores in the Army General Classification Test, than other enlisted men. They also noted that Hodgkin's disease patients seemed to come from occupations in which high scores in the Army General Classification Test were the common rule.

The existence of any association between religion and Hodgkin's disease is uncertain. MacMahon (1957) noted that in Brooklyn, New York, Hodgkin's disease appeared to be the cause of death nearly one and a half times more frequently in Jewish than in non-Jewish people. He found this to be true particularly for the age group over 40 years, where the percentage of Jewish deaths from Hodgkin's disease was 45.9 as compared with 32.2 for a matched sample of all deaths. Figures for the same age group in Catholics were 34.2% for Hodgkin's disease, and 42.9% for all deaths, and for Protestants the percentages were 19.9 and 24.9 respectively. MacMahon observed, however, that in the age group 0 to 39 the percentage of Jewish dying from Hodgkin's disease was not significantly higher than the percentage of Jewish deaths for all causes. He further clarifies that in each age group figures for the comparison

sample were adjusted to the age distribution of the Hodgkin's disease patients within the same group.

Seidman (1970) reported death rates per 100,000, for Hodgkin's disease, in the white population of New York City, by socio-economic class and religious affiliation. The figures he gives are as follows:

	Males			Females		
Religion	Social Class			Social Class		
	High	Middle	Low	High	Middle	Low
Jewish	3.8	6.0	4.7	3.7	---	---
Catholic	4.1	2.7	3.9	2.4	2.1	1.9
Protestant	---	3.1	2.5	---	4.1	---

Death rates for whites as a whole, by religious group, are 4.7 for Jewish, 3.5 for Catholic, and 3.1 for Protestant males. For females, the rates are 3.0 for Jewish, 2.1 for Catholics, and 2.5 for Protestants.

In regard to marital status, Cohen et al. (1964) found that Hodgkin's disease patients differed significantly from a group of matched controls. They noted that, at the time of entry into military service, the proportion of single men was higher among Hodgkin's disease patients than among controls. Bjelke (1969) reported that, although the rates were subject to large random errors, his findings demonstrated that the incidence of Hodgkin's disease in Norway, between 1951 and 1955, was higher in single women below age 55, than in women in the same age group who had ever married.

Although the above-mentioned reports bring out interesting speculations concerning the occurrence of Hodgkin's disease in diverse socio-economic groups, they are far from proving anything conclusive

about the illness. MacMahon (1966) has wisely commented that "it remains to be seen which of the closely related variables involved, socioeconomic status, educational level, intelligence, occupational class, or marital status, is most closely related to Hodgkin's disease risk."

Familial Occurrence

Investigators have observed an apparent familial tendency in the occurrence of Hodgkin's disease. Reports on the incidence of the illness in relatives are numerous, and go quite far back in time. Mac Heffey and Peterson (1934) observed Hodgkin's disease occurring simultaneously in two brothers. Smith (1934) reported on three familial cases, two sisters and a female cousin. Jackson and Parker (1947) cited the case of one sister and three brothers affected by the illness. Twenty other early reports regarding the occurrence of Hodgkin's disease in close relatives are described by Hoster and Dratman (1948).

Razis et al. (1959), reviewing the literature on the subject, found 63 instances of familial Hodgkin's disease. The analysis of data led them to conclude that a close relative of a Hodgkin's disease patient has a risk of developing the illness about three times as great as that of the general population. Their data revealed that eight pairs of close relatives developed Hodgkin's disease within a period of three years of each other. Simultaneous development of the illness occurred in a father and son, and in a brother and sister. In most cases the dates of onset were several years apart. These investigators also found two instances in which two pairs of twins were concordant for Hodgkin's disease. In a third pair of twins, both brothers acquired the illness at ages 18 and 29 respectively. In a previous study, DeVore

and Doan (1957) also had found Hodgkin's disease occurring in four pairs of close relatives. Rigby et al. (1966) carried out a case-control study of leukemia and lymphoma in the state of Nebraska. Their results showed that the incidence of these diseases was approximately two and a half times higher in the family members of the case group than in those of the control group. A study by Smithers (1967) in England showed five instances in which two brothers were affected by Hodgkin's disease. One other patient indicated that her brother had died of the same illness ten years before. Fraumeni and Li (1969) reported that in a series of 314 children they found three confirmed instances of Hodgkin's disease in close relatives. The child of an affected parent was age 6, while the disease was diagnosed between 14 and 19 years of age in two sib pairs. In a familial study by Patrassi and Menozzi (cited by Sirtori, 1969), in Italy, they found 52 families in which either two brothers, or a parent and child were affected by Hodgkin's disease.

Reports dealing with the occurrence of Hodgkin's disease in husband and wife are not easily found. In 1934, Gow described an instance in which a wife developed the disease nine years after her husband had succumbed to the illness. The peculiarity of this case was that at the middle of the nine-year interval, their 18-year old daughter had also acquired the disease. Mazar and Straus (1951) reported a case in which Hodgkin's disease in the wife started one year after her husband's death from the same illness. DeVore and Doan (1957) observed Hodgkin's disease occurring in husband and wife within a few months of each other. Lymphomas, other than Hodgkin's disease, have also been found to affect marital partners in quite unusual circumstances. A

recent report was made by Takats and Csapo (1968) concerning the occurrence of lymphomas in two couples. In each instance the disease made its appearance in both partners within a relatively short period of time.

Despite numerous reports concerning the incidence of Hodgkin's disease in close relatives, most investigators agree that a low familial case concentration is well established (Vianna et al., 1971b). MacMahon (1966) has commented that "data are still inadequate, but it seems likely that close relatives of patients with Hodgkin's disease do experience a risk of the disease that is significantly higher than that of the general population, though still small." However, as knowledge on this subject stands at the present time, it would appear that the safest position is that assumed by Razis et al. (1959) who believe that if familial concentration of Hodgkin's disease does occur, it points more to environmental than to hereditary or genetic factors. It is quite interesting that in the "extended epidemic of Hodgkin's disease" recently reported by Vianna et al. (1971a) only two of the observed cases were familial.

Etiology

In his address during the 1968-69 Harvey Lectures, Henry Kaplan remarked:

> Thomas Hodgkin, the gentle, scholarly, and philanthropic man, would undoubtedly have been astonished if he had known what a Pandora's box of controversy he was to open with his unpretentious paper "On Some Morbid Appearances of the Absorbent Glands and Spleen."

Certainly the origin and nature of Hodgkin's disease have been the subject of much discussion and debate in medical literature

for over one hundred years. Yet still today scientists are searching for a proper definition of the illness (Osborn, 1968), and, as if discouraged by the intricacy of the problem, some investigators have started to refer to the disease as "the Hodgkin's maze" (Burch, 1970).

The etiology of Hodgkin's disease is an enigma. Thomas Hodgkin (1832) apparently thought of the condition as of neoplastic nature. So did Wilks (1865) who named the illness after Hodgkin. However, investigators were not unanimous on this early opinion, and some declared their support for an infectious origin of the disease. In 1878 Greenfield did a microscopic study of affected tissue, and concluded that his pathological findings favored a diagnosis of "chronic inflammation." Sternberg (cited by Baker, 1966), in 1898, thought that Hodgkin's disease was a variety of tuberculosis. In 1904, Benda and Yamasaki (cited by Hoster and Dratman, 1948) observed the development of an invasive process in Hodgkin's disease, and they considered this to be an indication of the neoplastic nature of the illness. Two years previously, in 1902, Dorothy Reed had stated her belief in the inflammatory nature of the disease. Bunting and Yates (1914) concluded that it was probably caused by diphtheroids, while Forbus et al. (1942) pointed out that Brucellosis might be directly associated with the illness. In 1958 Bostick declared his belief in a possible viral etiology of Hodgkin's disease. Meanwhile, the confusion created by the obscure etiology of this illness has been reflected in the variety of names by which it has been referred to such as, malignant lymphoma, malignant granuloma, lymphadenoma, lymphogranuloma, lymphogranulomatosis, Hodgkin's syndrome, and other.

At the present time, the etiology of Hodgkin's disease is still a fertile field for hypotheses and conjecture. Opinions are divided mainly into those who think that the disease is neoplastic in nature, those who believe that an infectious agent may be in some way involved in its causation, and those who contend that the etiology of the illness may be of immunologic character.

Neoplastic Disease

Kaplan (1969) stated that a decisive criterion to distinguish between neoplasia and infection is whether the disease propagates in a "vertical" or in a "horizontal" fashion. Infectious disorders follow a horizontal pattern in which the responsible agent is transmitted from one cell to other nearby cells via the blood or lymph. Neoplastic conditions, on the other hand, follow a vertical pattern in which each dividing cell genetically transmits disorderly behavior to its daughter cells, and eventually to a clone of cells. Evidence regarding vertical versus horizontal propagation of the characteristic Reed-Sternberg cells is therefore necessary to decide as to the neoplastic or infectious nature of Hodgkin's disease.

Certain clinical and pathological features have led some researchers to believe that Hodgkin's disease is a neoplasm. It almost always presents a progressive and fatal course, after having spread to many parts of the body. Weakness, wasting, and anemia are usually present. The disease makes dramatic responses to X-ray treatment. The pathological picture is commonly characterized by the presence of pleomorphism, giant cells, abnormally shaped cells, and atypical mitoses (Cameron, 1968; Lukes, 1968; Kaplan, 1969; Wintrobe and Boggs, 1970).

Researchers apparently have obtained a considerable amount of support for the neoplastic hypothesis in experimental animals (Hoerni et al., 1970). Some recent chromosomal studies in humans have demonstrated the "vertical" replication of altered cells alluded to by Kaplan, therefore supporting the neoplastic nature of Hodgkin's disease. Spriggs and Boddington (1962) reported two different groups of cells in the affected lymph node of a Hodgkin's disease patient. One group of cells contained the normal diploid number of chromosomes, while the other group presented hypotetraploid metaphases. The average number of chromosomes in the abnormal cells was 83, but counts ranged from 79 to 90 chromosomes in some cells. Ricci et al. (1962), who studied seventy mitoses of Reed-Sternberg cells, found a group of cells containing 92 chromosomes. Furthermore, they observed that seven of twenty-five euploid mitoses showed an abnormal chromosome in the 17-18 group. Galan et al. (1963) also observed Reed-Sternberg cells containing 83 chromosomes. Several other investigators (Sasaki et al., 1965; Spiers and Baikie, 1966; Miles et al., 1966; Seif and Spriggs, 1967; Millard, 1968) have observed aneuploidy in mitotic cells in biopsy material from lymph nodes of Hodgkin's disease patients.

Seif and Spriggs (1967) studied a case in which they confirmed the presence of a clone of hypotetraploid cells showing two distinctive "marker" chromosomes. Kaplan (1969) pointed out, that to him, this finding represents strong evidence concerning the neoplastic nature of Reed-Sternberg cells in Hodgkin's disease. However, other investigators argue that the aforementioned studies dealt with small number of cases and karyotypes, and therefore, are far from being conclusive.

Boyd (1970), referring to a recent study, remarks that: "An analysis of the chromosomal complement of the cells in typical cases of Hodgkin's disease showed a normal chromosomal pattern in diploid cells, in this respect being quite different from the malignant lymphoma group."

Anderson and Ishida (1964) reported that the prevalence of Hodgkin's disease increased about four times in those people proximally exposed (within 1,400 meters) to the atomic bomb explosion over Hiroshima. This finding supports the concept that radiation may have acted as a carcinogen. Rappaport and Strum (1970) found vascular invasion by Hodgkin's disease in 50% of cases with lymphocytic depletion. The authors pointed out that this observation adds weight to the neoplastic theory, since vascular invasion and spread of the disease by blood vessels constitute one of the classical patterns of cancer dissemination.

Infectious Disorder

The old theory that Hodgkin's disease may be due to an infectious agent is receiving a great deal of attention at the present time. For many years investigators have been intrigued by such characteristic symptoms as night sweats, high fever, anemia, spontaneous remissions and exacerbations, leukocytosis, raised sedimentation rates, observed in many Hodgkin's disease patients, symptoms which reinforce the view that the illness is a granulomatous infection (MacMahon, 1966; Smithers, 1967; Kaplan, 1969). Reports and arguments for and against possible infectious agents have been numerous and have covered a wide range of subjects. Human and avian tuberculosis organisms, Brucella organisms, bacilli, cocci, diphtheroids, spirochaetes, yeasts, fungi,

amoebae, and viruses, have been incriminated, but up to the present time no definite proof has been obtained as to their etiological role in Hodgkin's disease (Gendel et al., 1950; Steiner, 1954; Connolly, 1963; Mayock et al., 1963; Aisenberg, 1964; Heineman et al., 1964; Nilsen et al., 1967; Walton, 1968; Barlotta et al., 1969).

Among the various infectious agents which could cause Hodgkin's disease researchers have given special consideration to viruses. In 1955, Bostick and Hanna reported that they had isolated and cultured a virus from Hodgkin's disease lymph nodes; their report did not receive further confirmation. The idea concerning the virus role in the causation of Hodgkin's disease gained strength when it was discovered that viruses were associated with certain types of cancer in animals, such as parotid gland tumors in mice, viral papillomas in rabbits, and Rous' sarcoma in chickens (Churchill and Biggs, 1968; Hinzel, 1969). Comparable human tumors have been produced also in animals by injecting them with cells from other animals recovering from virus-induced immune diseases, or with cultured lymphoma cells (Schwartz and Beldotti, 1965; Stanley and Walters, 1966). Of great interest among researchers have been the reports concerning the considerable association found between viruses and malignant lymphomas in African children (Burkitt and O'Conor, 1961; Epstein et al., 1964).

As of today, no etiological bacteria have been found, and all attempts to isolate a virus from Hodgkin's disease tissue have failed. Nevertheless, researchers believing in the possible infectious genesis of the illness continue in their effort. They seem to keep in mind the words of Kaplan (1969): "Yet, neoplasm though it be, Hodgkin's disease

must be one of the most curious neoplasms known to man". . . "the fact that the Reed-Sternberg cells are usually greatly outnumbered by a variety of other cells of obviously nonneoplastic character remains to be explained."

Investigators who recently tried to isolate a virus from Hodgkin's disease patients faced the same unlucky fate as many others before them. Yumoto and Dmochowski (1967) thought they had observed viral particles in tissues of SJL/J strain mice suffering from Hodgkin's disease-type neoplasms. However, their observation was not confirmed in a more recent investigation (Tkaczevski and Wanebo, 1969). Valladares et al. (1969) reported that they obtained particles having viral properties in a cell culture from a Hodgkin's paragranuloma. Some interesting findings were recorded by Johansson et al. (1970). These investigators studied Epstein-Barr virus antibody patterns in a group of Hodgkin's disease patients and a group of matched controls. They found that whereas Hodgkin's paragranuloma cases showed the same serological reactivity levels as the controls, Hodgkin's sarcoma cases reached high levels comparable to those seen in Burkitt's lymphoma and nasopharyngeal carcinoma. The authors commented that there is a possibility that Hodgkin's disease represents an etiologically heterogeneous group, and the significant difference in serological reactivity among the three histological groups might be more than coincidental. Similarly, elevated antibody titers to the Epstein-Barr virus in Hodgkin's disease patients were observed by Levine et al. (1971). It has been pointed out that the Epstein-Barr virus might be an etiologic agent in most cases of infectious mononucleosis (Henle et al., 1968; Stevens et al.,

1970). Of unusual interest then is the fact that Reed-Sternberg cells apparently have been observed in lymph nodes of some mononucleosis cases (Lukes et al., 1969), and that infectious mononucleosis presents unexplained epidemiological similarities with Hodgkin's disease (Smithers, 1970b).

To cover for the fact that, so far, no virus has been isolated from Hodgkin's disease patients, Sirtori (1969) has advanced his own explanatory hypothesis. The contact with a virus, he says, might have taken place during early infancy. The virus might have disappeared after having produced a moderate change in the DNA of the cell. This cellular alteration could have resulted in a gradual malignant transformation. Sirtori adds that we cannot forget that, up to the present time, nearly 60 types of viruses have been experimentally proven to possess carcinogenic power. Man could not exempt himself from the laws of nature, or make these laws to apply only in the case of Burkitt's lymphoma.

Some characteristic epidemiologic features have led researchers to speculate about the possible heterogeneous nature of Hodgkin's disease. The bimodality of the age incidence curve for this illness is perhaps one of the most intriguing problems. MacMahon (1966) put forward the hypothesis that such a bimodal curve indicates that Hodgkin's disease in young adults probably is infectious in nature, while in the elderly it is a true neoplasm. This hypothesis was challenged by Smithers (1970a) who argued that in a study of his own the different histological forms of the disease showed the same bimodal pattern exhibited by the disease as a whole. This proved to him that Hodgkin's

disease is one progressive neoplastic disorder. MacMahon et al. (1971) replied to Smithers that his findings were probably due to an erroneous impression created by figures, and that their re-examination of his data still showed that histological types with better prognosis, such as nodular sclerosis, presented highest rates in the first mode (15 to 34 years), and those with poor prognosis, as mixed cellularity and lymphocytic depletion were more frequent in the second mode (50 years and over).

Other epidemiological findings such as the rarity of Hodgkin's disease before the age of three years (Strum and Rappaport, 1970), the changes in morbidity and mortality rates in later childhood (Miller, 1966), the common initial involvement of cervical lymph nodes (Peckham and Cooper, 1969), the fact that prior appendectomy (Bierman, 1968) and tonsillectomy (Vianna et al., 1971c) apparently increase the risk of getting the disease, the clustering of cases in space and time (Vianna et al., 1971a), and the unusual infectious complications frequently accompanying the illness (Hoerni et al., 1971; Bluefarb and Caro, 1971), lead researchers to think in the possible involvement of an infectious agent in the genesis of Hodgkin's disease. Vianna et al. (1971b) have suggested that the agent may be a virus of low virulence and low infectivity that may reside in the female birth-tract; exposure to it may take place at the time of birth, and entry could be through the oral or respiratory portal.

Although reports have been published concerning the occurrence of malignant lymphoma in patient and pet (Drusin et al., 1966), and regarding an alleged clustering of lymphomas in household cats (Schneider

et al., 1967), a recent household survey (Hanes et al., 1970) failed to find any association between pets and the occurrence of Hodgkin's disease.

Auto-Immune Disorder

Almost a complement to the "infection" hypothesis is the theory that Hodgkin's disease may be the effect of an auto-immune disorder. Trentin (1956, 1957) reported the production of a variety of diseases by inoculating immunologically tolerant mice with homologous lymphoid cells. He called such disorders "homologous diseases." Characteristic manifestations in such diseases are anemia, leucocytosis, lymphadenopathy, splenomegaly, wasting , and death. The occurrence of fever has not been reported, but the depletion of lymphocytes in lymph nodes is an outstanding feature.

Kaplan and Smithers (1959) called attention to the great similarity between homologous diseases in mice and Hodgkin's disease in man. They suggested that in both instances the symptoms seem to be due to a reaction of foreign lymphoid cells against target cells in the host. In Hodgkin's disease, some lymphocytes, for a reason yet unknown, undergo antigenic deletion, while maintaining the power to produce antibodies. These antibodies react with antigens of normal lymphocytes; such reaction results in lymphocyte destruction and lymphocytic depletion. The lack of lymphocytes gives place to immunologic deficiency. Such immunologic impairment may be the reason for the high incidence of anergic responses to induced delayed cutaneous hypersensitivity that have been observed by many investigators (Aisenberg, 1962; Miller, 1967; Teillet and Schwesguth, 1968; Bernadou et al., 1970; Smith et al., 1970)

in patients with Hodgkin's disease. Supporters of the auto-immune theory believe that immunological alterations in intracellular proteins produce a distortion in cell behavior which is manifested as Hodgkin's disease.

In support of the auto-immune hypothesis, Krueger et al. (1971) recently reported that they produced lymphomas in mice under prolonged immunosuppression and persistent antigenic stimulation. Hodgkin's disease has also been observed in humans in four cases of ataxia-telangiectasia, an immunologic disorder (Peterson et al., 1965; Dugois et al., 1967). Some diseases mediated by immunologic mechanisms have been noted to occur together with Hodgkin's disease such as cerebellar degenration (Horwich et al., 1966), panaortitis (Fraumeni et al., 1967), glomerulonephritis (Brodovsky et al., 1968), and autoimmune hemolytic anemia (Pirofsky, 1968).

Another way of looking at an immune disorder as a possible etiologic factor in Hodgkin's disease has been described by Vianna et al. (1971b). These authors point out that the disease-producing agent may never reach the lymph nodes itself, and so cannot be identified. It could reside at extranodal sites where it would produce immune-complex material which, in the event of reaching the lymph nodes, might elicit their reaction. The agent, the researchers say, may be a virus held in the oropharyngeal tissue where it can remain for a long time, eventually disappearing in most persons. However, its immune-complex material could gain access to the lymph nodes of susceptible individuals by the involution or partial removal of the peripheral lymphoid tissue. Therefore, removal of adenoids and tonsils, mainly in young males, could

increase their risk of Hodgkin's disease, since they are deprived of immunocompetent organs known to produce immunoglobulins which are valuable viral antibodies in many external secretions. The authors point out also that a recent suggestion has been made concerning more efficient secretory antibody responses in females than in males, which could partially explain the higher incidence of Hodgkin's disease in males. Certain features of Hodgkin's disease such as lymphocytic transformation and cutaneous anergy could be due to cytotoxic effects or antigenic competition caused by the immune-complex material passed by the barrier-held agent. The theory proposed by Vianna et al. is fairly similar to the concept of lymphocytotoxins that has been recently advanced by Grifoni et al. (1971) to explain the etiology of Hodgkin's disease.

Justification of Present Study

From the above discussion it can be seen that Hodgkin's disease still presents one of the most interesting as well as challenging problems ever faced by medical researchers. Existent evidence is very scant, and opinions regarding the nature of this illness are highly controversial. At the same time it is most obvious that the importance of the implications involved in this subject demands an increase in research efforts to try to gain a better understanding of the enigmatic epidemiology of this disease.

MacMahon (1966) pointed out that bimodal age-curves seem to be a constant feature appearing in most descriptive epidemiologic studies so far done on Hodgkin's disease. This observation makes it desirable to study the features of the disease separately in different

age groups. The significance of the present study was thought to rest on the fact that it would be an attempt to combine descriptive and analytic epidemiologic techniques for inquiring about the possible nature of Hodgkin's disease in different age groups. So far as is known, analytic epidemiologic studies of Hodgkin's disease do not exist. Therefore, it was considered worth-while to explore the possibility of using this procedure for deriving more specific hypotheses concerning its etiology. If any valuable clue could be discovered, it would be easier to apply diverse epidemiologic methods for testing specific hypotheses concerning the nature of the disease and its prevention.

The potential of the results of this study, whether positive or negative, were viewed on the light of a comment by Cole et al., in 1968. If Hodgkin's disease really encompasses several diseases separable by age, but these continue to be considered as one, any efforts to clarify etiology, pathophysiology, or prognosis will be useless. On the other hand, if the possibility of several diseases separable by age is investigated and they are consistently found to be one entity, there will be some research inefficiency, but findings for the different age groups could then be combined with greater confidence to test specific hypotheses about a single disease.

CHAPTER III

METHODS AND PROCEDURE

Definition of a Case of Hodgkin's Disease

A case of Hodgkin's disease was defined as one which had been histologically confirmed, and was registered as such in the hospital pathological records. An attempt was made to classify each case into one of four histologic categories: lymphocytic predominance, nodular sclerosis, mixed cellularity, and lymphocytic depletion (Lukes et al., 1966a). This was done by looking at pathological slides, or, when slides were not available, by careful analysis of the biopsy microscopic description as recorded in each patient's pathological report. The histologic classification was performed by pathologists at the University of Oklahoma Medical Center.

Population Included in the Study

All histologically diagnosed cases of Hodgkin's disease treated in Oklahoma City hospitals from January 1, 1965, through December 31, 1970, were included in the study, regardless of their county of residence. Out-of-state residents were not eligible for the study. The same criteria applied to control cases.

General Plan

This study comprised two main parts:

1. A description was made, by age groups, of the epidemiologic features of Hodgkin's disease such as frequency, mortality, race and sex distribution, occupational distribution, age at onset, familial occurrence, and seasonal incidence, in patients admitted to Oklahoma City hospitals. The age groups included were: 0 to 14, 15 to 34, 35 to 49, and 50 years and over. The inclusion of the age groups 0 to 14 and 35 to 49 was mainly for purposes of completeness of the study, although it was anticipated that the number of cases in these age groups would be low as deduced from reports in former descriptive epidemiologic studies.
2. An exploratory case-control study was performed, in an attempt to find some clues on possible factors associated with the origin of Hodgkin's disease, as it manifests itself in different age groups.

Selection of the Study Group

The Hodgkin's Disease Group

The Hodgkin's disease group comprised 181 patients, living or dead, whose diagnosis was histologically confirmed, and who were admitted to Oklahoma City hospitals from January 1, 1965, through December 31, 1970. For study purposes, all cases were grouped together and divided into age categories without distinction as to the hospital where they were treated. Care was taken to crossmatch patients from all the hospitals so as to avoid duplication of cases. The Hodgkin's disease group was provided by the following Oklahoma City hospitals: Baptist Memorial Hospital, Deaconess Hospital, Mercy Hospital, Oklahoma Medical

Research Foundation Hospital, Presbyterian Hospital, Saint Anthony Hospital, South Community Hospital, University of Oklahoma Medical Center Hospital, and the Veterans Administration Hospital. Cooperation from these hospitals was secured through the hospital administrator.

The Control Group

A comparison group of 181 hospital patients matched for age (within ±1 year), race, sex, and hospital was selected as controls. The control group included patients, living or dead, who were diagnosed with any other disease except leukemia, lymphoma, and accidents (cases and controls were compared with regard to history of accidents).

The following rule was kept in the selection of the control group: A control case was defined as the next younger or the next older patient (within ±1 year) registered in the admissions list of the hospital wherefrom the Hodgkin's disease case was taken, and who fit the matching criteria. Example: If the Hodgkin's disease case was a 5-year-old white female from University Hospital, the control case could be a 4-year-old (last birthday), a 5-year-old, or a 6-year-old white female from University Hospital. Thus, both the study and the control groups, on the average, were comparable in relation to age, sex, race, and hospital distribution.

All controls were divided into age groups to be compared with their respective Hodgkin's disease age group.

The Sample Size

The purpose of this study was to draw generalizations concerning the possible nature of Hodgkin's disease in different age

groups. The sample from which such generalizations were attempted included all histologically confirmed cases of Hodgkin's disease admitted to Oklahoma City hospitals during the 6-year period 1965-1970. Review of hospital records revealed 181 Hodgkin's disease cases, all of which were included in the descriptive phase of this investigation.

The size of the control group was equal to the number of Hodgkin's disease cases, i.e., 181 patients. However, since only patients who responded to a special questionnaire (Appendix E) were used for comparison, the original number of 181 index and 181 control cases was reduced to 144 and 142 respectively. Therefore, the total sample size included 286 patients. The two groups, 144 Hodgkin's disease cases and 142 controls, were analysed with respect to differences in proportion of specific characteristics.

A sample of 144 cases and 142 controls, although small, was considered to be well definable, comparable, and of sufficient size to provide sound validity to the results. It was estimated that assigning one control to each case, 146 controls (total sample size: 292) would be needed to detect a 15% or greater difference between cases and controls when a χ^2 statistic was used. This assumed a probability of rejecting a true hypothesis (Type I error) of 10%, and a probability of accepting a false hypothesis (Type II error) of 10%.

The following formula (Dixon and Massey, 1957) was utilized to calculate the hypothetical sample size 146 cases and controls:

$$n = pq\left(\frac{c+1}{c}\right)\left[\frac{(Z_a + Z_b)^2}{(p_1 - p_2)^2}\right] \qquad \text{where,}$$

p_1 = proportion of people with the disease and the characteristic.

p_2 = proportion of people without the disease but with the characteristic.

$p = 0.50$ = the probability of having the characteristic by either the cases or the controls.

$q = 1 - p = 0.50$.

c = number of controls for each case = 1.

Z_a = risk of making an alpha (Type I) error = 0.10.

Z_b = risk of making a beta (Type II) error = 0.10.

The actual sample of size 144 cases and 142 controls was very close to the estimated hypothetical number. Therefore, it was felt that such sample was of sufficient magnitude to support valid conclusions.

Collection of Data

Four main sources were used for the collection of data in this study:

Hospital Records

Hospital records were used for properly documenting diagnoses, estimating date of onset of illness, and for learning some facts concerning the patient's present disease, past history, or family history. Special care was taken to examine records from the time of first diagnosis rather than from later hospitalizations. These procedures were uniformly followed for dealing with both the cases and the controls. Information concerning each index and control subject was recorded on a

Hospital Record Form (Appendix D) especially designed for such purpose. From this Form data were transcribed onto IBM cards, and utilized for descriptive purposes, as well as for comparisons between cases and controls.

Questionnaire

It was considered that for the purpose of this study the information that could be obtained from hospital records might not be complete. Therefore, in order to complement the hospital data, a special questionnaire (Appendix E) was designed. This questionnaire, together with explanatory letters (Appendix C), was mailed to each index and control case, inquiring about their past medical, familial, or environmental history prior to the onset of the disease in question. If the patient was dead, attempts were made to contact a member of his immediate family (spouse, parent, or child), or a close friend or neighbor. Specific information sought in the questionnaire is described below. Contact was previously established with the patients' physicians (Appendix B) explaining to them the purpose of the study, and asking for their cooperation in permitting each of their patients to receive the questionnaire.

Other Medical Records

Tumor registries, pathology records, and radiology records, when available, were used mainly as a source of reference to confirm information concerning identity of patients, diagnosis, or any other features of interest. These records were also valuable in ascertaining present address and status of some patients.

Death Certificates

Death certificates were used in some instances to ascertain information on such items as date of death, birthdate, age, sex, race, residence, clinical diagnosis, underlying cause of death, illness complications, and other available data that could be of some utility for the study.

Specific Information Sought

The information collected on each index and control case was as follows:

General Information

1. Identity of the patient: his name, sex, age, race, birthdate, and hospital where he was treated.
2. Where the patient lived at the time of onset: the county, city, farm, rural area, and street address.
3. When the patient developed the disease. The date of onset (to the nearest month) was defined as the point in time when the illness later diagnosed as Hodgkin's disease first became apparent.
4. The date of diagnosis.
5. The date of death.

Medical Information

1. Main symptoms present at onset and at diagnosis.
2. Histological type, and clinical stage of the disease at diagnosis.
3. Past illnesses of the patient such as allergies, viral

and bacterial infections, perinatal diseases, and accidents.

4. History of tonsillectomy and/or appendectomy.
5. Additional information such as any illnesses in the household or close contacts (human or animal) when the disease started.

Familial Information

1. History of the disease in the patient's immediate family such as in his spouse, parents, siblings, or children.
2. Information concerning other family cases, their age, sex, time of onset and diagnosis, relationship to the patient, and date of death.

Environmental Information

1. Approximate educational level attained by the patient.
2. If student, grade and school attended at time of onset.
3. Residence of patient at time of onset, housing conditions, general surroundings, and sanitary facilities.
4. Patient's residential history prior to onset of illness.
5. Patient's regular contacts, or special contacts at time of onset of the illness.
6. History of patient's repeated contact with animals, or special contact with animals at time of onset of the illness.
7. History of patient's exposure to radiation, medical or occupational.

8. History of patient's exposure to chemicals, toxins, or drugs.
9. History of patient's regular practice of outdoor activities such as hunting, fishing, camping, and lake or river swimming.
10. Patient's usual occupation, and occupation at time of onset of his illness. Occupation was recorded under one of nine major categories: (1) Not working, (2) Professional, (3) Managerial, (4) Non-managerial, (5) Artisan (craftsman), (6) Farm worker, (7) Oil field worker, (8) Mine and factory worker, and (9) Other occupations.

Analysis of Data

The following procedure was used to analyse the data in this study:

1. All working-forms (Hospital Record Forms and questionnaires) for both cases and controls were carefully checked for completeness.
2. The Hodgkin's disease group was used for the descriptive phase of the study. The group was analysed for those variables considered to be of some relevance according to the initial purpose of the study.
3. Index and control cases were distributed into the following age groups: 0 to 14, 15 to 34, 35 to 49, and 50 years and over.
4. Index and control cases, by age groups, were compared for specific variables relating to clinical, occu-

pational, and environmental features of the illness. Such comparisons were aimed at exploring possible increased risk of the disease in certain age groups exposed to particular factors.

5. The procedure described by Lilienfeld et al. (1967) for dealing with a disease of low incidence was used for estimating relative risks. Relative risk was defined as the ratio of the occurrence of Hodgkin's disease in those exposed to a certain variable, to its occurrence in those not exposed (MacMahon and Pugh, 1970).

6. A χ^2 test was performed in order to decide whether or not any observed difference between cases and controls was due to simple chance.

Essentially, the analytic procedure comprised the following steps:

1. Distribution of number of individuals with and without specific characteristics among cases and controls:

Characteristic	With Disease (Cases)	Without Disease (Controls)	Total
With	a	b	$a+b = M_1$
Without	c	d	$c+d = M_2$
Total	$a+c = N_1$	$b+d = N_2$	$N_1+N_2 = N$

2. Estimation of the Relative Risk. A measure of the relative risk of having Hodgkin's disease in those individuals exposed to a certain characteristic was expressed as:

$$\frac{\text{Proportion of Persons Having the Characteristic and the Disease}}{\text{Proportion of Persons Not Having the Characteristic But the Disease}} =$$

$$\frac{a/a+b}{c/c+d} = \frac{a(c+d)}{c(a+b)}$$

Since this case-control study dealt with a sample of disease and no-disease individuals, and since Hodgkin's disease is an illness of low incidence, it was assumed that, in the general population, the values of "a" and "c" are small in relation to "b" and "d", and consequently "c+d"/"a+b" in the formula could be substituted by "d/b". This gave the approximation formula that was used in this study for estimating relative risks:

$$\text{Relative Risk} = ad/bc$$

A relative risk value equal to 1.0 was interpreted as indicating that Hodgkin's disease and a specific characteristic were not associated in this study. Relative risk values within the range 1.0 to 2.0 were interpreted as "moderately increased," while values above 2.0 were considered as "highly elevated." Relative risk values less than 1.0 were considered as indicative of a negative association between the disease and a characteristic.

3. Test of Significance. The χ^2 statistic was used to test whether any observed difference in the risk of Hodgkin's disease between the group with the characteristic and the group without the characteristic was significant or not. The expression used was:

$$\chi^2 = \frac{\left\{|ad - bc| - \frac{N}{2}\right\}^2 N}{(N_1)(N_2)(M_1)(M_2)}$$

This expression is applicable to fourfold tables with one

degree of freedom. The term N/2 is a correction factor which is needed to increase the validity of the test when dealing with a small sample size.

The level of significance used was the 0.10 level. Therefore, χ^2 values greater than 2.706 (as calculated from the study values) were interpreted as being significant. In other words, such estimated values indicated that an observed association between Hodgkin's disease and a characteristic might be real, and not merely the product of simple chance. A significant χ^2 value at the 0.10 level was considered to show that there were less than 10 chances in 100 that an observed relative risk could occur by chance alone.

When comparing cases and controls, all ages 15 years and over combined, it was noted that, in some instances, discrepancies in proportions did not follow the same direction in all age groups. In such cases, a χ-statistic test described by Maxwell (1967) was employed to estimate probability values. This test allows the signs of discrepancies to be taken into account when combining results from various fourfold tables. The expression used was:

$$\text{Test of Significance} = \frac{\Sigma \sqrt{\text{Uncorrected } \chi^2}}{\sqrt{n}}$$

. The result is referred to The Normal Curve.

The Fisher's Exact Probability Test, as explained by Siegel (1956), was utilized to estimate probability values when comparing cases and controls in the age group 0 to 14. Such test is indicated when dealing with very small number of cases.

CHAPTER IV

RESULTS I

Descriptive Study

The first objective of the present study was the description of epidemiological features of Hodgkin's disease in patients admitted to Oklahoma City hospitals. Results obtained in the descriptive phase of this investigation are presented in this chapter.

The Hodgkin's Disease Patients

Review of records from the nine participating hospitals revealed 181 new Hodgkin's disease cases diagnosed between January 1, 1965, and December 31, 1970. All 181 cases were included in the descriptive phase of this study. Table 1 gives the number and percentage of cases registered in each hospital. Total cases reported by each hospital apparently depended upon the size and type of hospital, and medical services available. Of all cases, 45.8% were diagnosed at three hospitals affiliated with the University of Oklahoma Medical Center: the University Hospital, the Oklahoma Medical Research Foundation, and the Veterans Administration Hospital.

Of the 77 counties in the state of Oklahoma, 47 were represented in this study. However, most counties were represented only with 1 or 2 cases. As expected, 76 (42%) of the total number of

TABLE 1

NEW CASES OF HODGKIN'S DISEASE DIAGNOSED IN OKLAHOMA CITY HOSPITALS, FROM JANUARY 1, 1965, THROUGH DECEMBER 31, 1970

NAME OF HOSPITAL	NUMBER OF PATIENTS AND YEAR OF DIAGNOSIS							
	1965	1966	1967	1968	1969	1970	Total	Percent
Baptist Memorial	3	2	1	6	4	4	20	11.0
Deaconess	1	0	0	1	1	2	5	2.7
Mercy	2	5	1	2	6	5	21	11.7
Presbyterian	5	3	5	2	4	2	21	11.7
Saint Anthony	5	4	6	4	5	3	27	14.9
South Community	0	0	1	1	1	1	4	2.2
Oklahoma Med. Res. Foundation	0	1	1	3	2	5	12	6.6
University	15	11	9	6	12	6	59	32.6
Veterans Administration	0	5	1	3	2	1	12	6.6
TOTAL	31	31	25	28	37	29	181	100.0

patients came from Oklahoma county. This is the county where all nine participating hospitals are located; it includes about 25% of the total population of the state. The relatively few patients from other counties suggest that a considerable number of Hodgkin's disease cases occurring throughout the state are not seen in Oklahoma City hospitals. Therefore, it is believed that the number of cases included in this study does not reflect the true incidence of Hodgkin's disease in the state of Oklahoma.

Table 2 shows the distribution of the 181 Hodgkin's disease cases by sex, race, and year of diagnosis. The number of new cases diagnosed each year remained about constant during the six-year period studied. A decrease in new cases was noted, however, in 1967, and an increase in cases in 1969. The yearly trend in new cases diagnosed between 1965 and 1970 is visible in Figure 1.

Medical records of Hodgkin's disease patients were abstracted during the month of December, 1970. At that time, 110 (61%) of the patients were alive, and 71 (39%) were dead. Table 3 shows the proportion of patients surviving by year of diagnosis. It was interesting to observe that of 31 patients who were diagnosed in 1965, 11 were still alive on December 31, 1970. Similarly, 16 out of 31 cases diagnosed in 1966 were living on December 31, 1970. The percentage of surviving patients was considerably higher in the younger than in the older groups.

Age

Descriptive features of Hodgkin's disease were analysed separately in the age groups 0 to 14, 15 to 34, 35 to 49, and 50 years and

TABLE 2

NEW CASES OF HODGKIN'S DISEASE DIAGNOSED IN OKLAHOMA CITY HOSPITALS, BY YEAR, SEX, AND RACE, 1965-1970

SEX AND RACE	YEAR OF DIAGNOSIS						
	1965	1966	1967	1968	1969	1970	Total
All Races	31	31	25	28	37	29	181
Male	15	17	15	15	20	21	103
Female	16	14	10	13	17	8	78
White	28	31	23	27	33	28	170
Male	14	17	14	15	17	20	97
Female	14	14	9	12	16	8	73
Nonwhite	3	0	2	1	4	1	11
Male	1	0	1	0	3	1	6
Female	2	0	1	1	1	0	5
Sex Ratio							
All races	0.93	1.21	1.50	1.15	1.17	2.62	1.32
Whites	1.00	1.21	1.55	1.25	1.06	2.50	1.32
Nonwhite	0.50	----	1.00	----	3.00	----	1.20

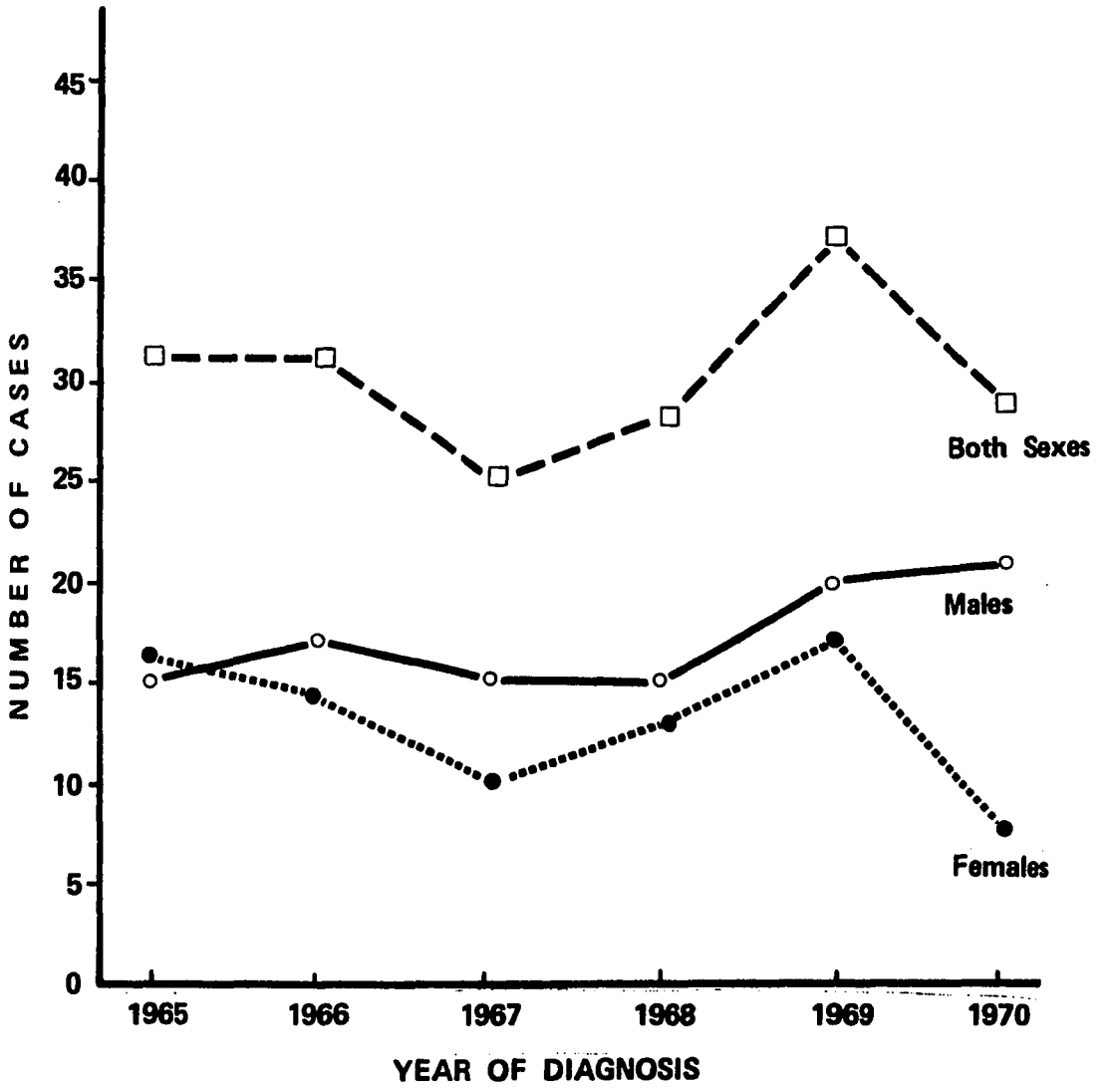

Fig. 1.--New cases of Hodgkin's disease diagnosed in Oklahoma City hospitals, by sex and year, January 1, 1965, through December 31, 1970.

TABLE 3

STATUS OF 181 HODGKIN'S DISEASE PATIENTS ON DECEMBER 31, 1970,
BY AGE, SEX, AND YEAR OF DIAGNOSIS, 1965-1970

AGE AND SEX	Total in Age Group	YEAR OF DIAGNOSIS, AND STATUS OF PATIENT ON DECEMBER 31, 1970												% of Total in Age Group	
		1965		1966		1967		1968		1969		1970			
		L*	D*	L	D	L	D	L	D	L	D	L	D	L	D
0 - 14															
Males	5	2	1	0	0	1	0	0	0	1	0	0	0	80.0	20.0
Females	4	0	0	1	0	0	0	1	1	1	0	0	0	75.0	25.0
15 - 34															
Males	30	2	0	4	0	9	2	3	0	5	2	3	0	87.0	13.0
Females	30	3	1	2	2	2	3	3	0	7	1	5	1	73.3	26.7
35 - 49															
Males	24	0	4	1	2	0	2	1	3	3	1	7	0	50.0	50.0
Females	10	2	1	0	0	1	1	3	1	1	0	0	0	70.0	30.0
50+															
Males	44	1	5	3	7	1	0	3	5	2	6	10	1	45.4	54.6
Females	34	1	8	5	4	1	2	2	2	5	2	2	0	47.1	52.9
TOTAL	181	11	20	16	15	15	10	16	12	25	12	27	2	61.0	39.0

(*) L = Living; D = Dead.

over. The sistribution of the 181 patients according to age is given in Table 4. The larger concentration of cases occurred in the age groups 15 to 34, and 50 years and over. The age group 35 to 49 showed a number of cases intermediate between the two other age groups. Only 9 cases were observed in the age group 0 to 14 years. A single case, a 4-year old male, was found younger than age 5. The mean age at the time of onset of symptoms was 10, 22, 42, and 64 years, for each of the four age groups respectively.

Age-sex distribution of cases showed a bimodal pattern. This bimodality is clearly seen in Figure 2, especially for males and females separately. The peak of the first mode occurred in the age group 15 to 24, for males, females, and for both sexes combined; the peak of the second mode occurred in the age group 45 to 54 for males, and 65 to 74 for females. However, for both sexes combined there appeared to be two peaks for the second mode, one in the age group 45 to 54, and the other in the age group 65 to 74, perhaps reflecting the occurrence of the second peak in each of the sexes.

Figure 2 shows also that, for both sexes, the first peak of the age curve was considerably higher than the second. This might indicate that Hodgkin's disease is more frequent, within a specific age period, in the younger than in the older group. However, it is recognized that the curve represents only the absolute number of cases and not incidence rates. The latter would probably tend to reduce the prominence of the first age peak, while increasing the peak in the older group.

Table 4 indicates that age segregates the total number of

TABLE 4

AGE, SEX, AND RACE DISTRIBUTION, SEX RATIO, AND MEAN AGE OF 181 NEW CASES OF HODGKIN'S DISEASE AT TIME OF ONSET, 1965-1970

SEX AND RACE	AGE GROUP				
	0-14	15-34	35-49	50+	All Ages
All Races	9	60	34	78	181
Male	5	30	24	44	103
Females	4	30	10	34	78
White	9	56	31	74	170
Male	5	28	22	42	97
Female	4	28	9	32	73
Non-white	0	4	3	4	11
Male	0	2	2	2	6
Female	0	2	1	2	5
Sex ratio					
All races	1.25	1.00	2.40	1.29	1.32
Whites	1.25	1.00	2.44	1.31	1.32
Non-white	----	1.00	2.00	1.00	1.20
Mean Age - All races					
Both sexes	10	22	42	64	----
Males	8	24	42	65	----
Females	13	21	43	64	----

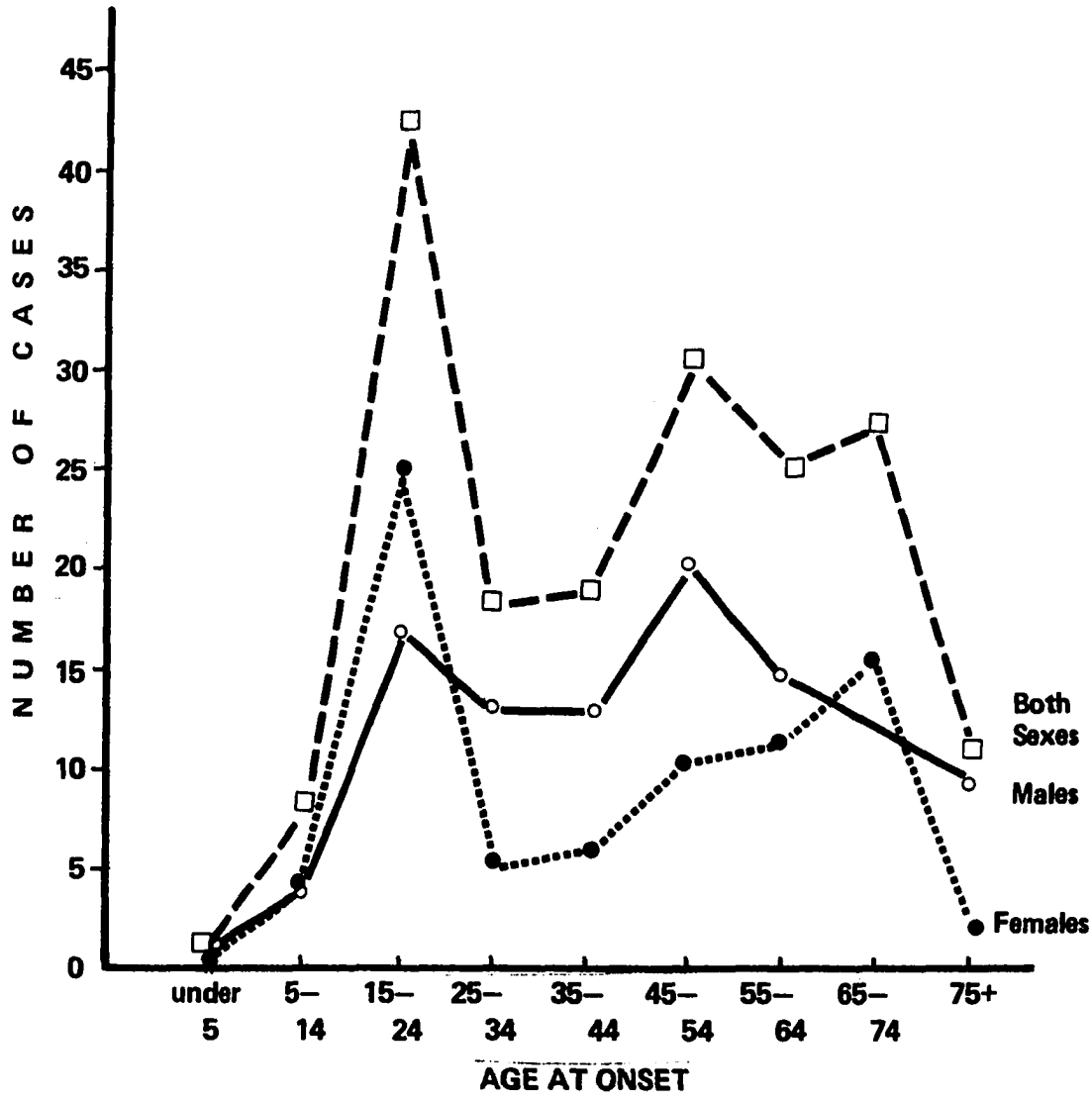

Fig. 2.--Sex and age distribution of 181 new cases of Hodgkin's disease diagnosed in Oklahoma City hospitals, 1965-1970.

Hodgkin's disease cases into two main groups. Those two age groups are the 15 to 34 years, and the 50 years and over. To ascertain whether the age group 0 to 14 should be considered separately from the group 15 to 34 is difficult, due to the small number of cases found in the first decade of life. However, the rapid increase in the number of cases after age 10, tends to support the idea that Hodgkin's disease in children is related to the disease in young adults. The age group 35 to 49 seems to occupy a transitional position, in which the disease might share epidemiological features with both the younger and the older groups.

Sex and Race

The high proportion of males reported by other investigators was also supported in this study. As shown in Table 2, 103 or 57% of all cases were males, as compared with 78 or 43% females. Table 2 and Figure 1 show that the number of male cases diagnosed each year was higher than the number of female cases. This was particularly true for the year 1970 when only 8 new female cases were diagnosed, in sharp contrast with 21 new male cases. The reason for the striking decline in females diagnosed during the year 1970 is not known. Errors in reporting by Oklahoma City hospitals might be suspected, although it results difficult to explain why such errors would affect only females. Personnel in medical records departments were most cooperative in reporting any new cases. Therefore, the reason for the significant decrease in female cases during 1970 remains obscure. Looking at Figure 1, it would appear that Hodgkin's disease in males is increasing, while it is decreasing in females. Male to female sex ratios given in Table

2 further confirm the preponderance of males over females. Furthermore, such sex ratios give the impression that, from 1965 to 1970, there has been an increasing representation of male cases diagnosed at Oklahoma City hospitals.

Table 4 demonstrates the sex distribution of the 181 cases by age group. The number of male and female patients was about equal in the age categories 0 to 14, and 15 to 34 years. In the age groups 35 to 49 and 50 years and over, the number of male cases was considerably higher than the number of females. These differences are reflected in the male to female sex ratio for each age group. Sex ratios of 1.25 and 1.00 were observed in the age groups 0 to 14 and 15 to 34, in contrast with sex ratios of 2.40 and 1.29 in the 35 to 49 and 50 years and over groups. High male to female ratios in the older groups have been a common observation in various Hodgkin's disease surveys. The findings in the present study are consistent with those observations.

Figure 2 shows that the bimodality by age was exhibited by both sexes. The male to female sex ratio was lower in the first mode than in the second. In the first mode females reached a higher peak than males. Conversely, the age peak for males was higher than for females in the second mode; furthermore, the peak for females occurred at an older age than for males. Recalling that in the age group 15 to 34 the number of male and female cases was equal, it is interesting to speculate why there were 25 female cases diagnosed between ages 15 to 24, as compared to only 17 male cases.

The distribution of cases according to sex and race is shown in Tables 2 and 4. Of the 181 cases, only 11 or 6.7% were non-white.

All such cases were Negro patients; 6 of them were male, and 5 female. Sex ratios for non-whites were about equal for all age groups. For whites, sex ratios were 1.25 and 1.00 for the age groups 0 to 14 and 15 to 34 respectively; quite different from male to female ratios of 2.44 and 1.31 observed in the 35 to 49 and 50 years and over groups.

The condition of the patients according to age and sex, by December 31, 1970, is given in Table 3. In the age groups 0 to 14 and 15 to 34 years, males had better survival after diagnosis than females. However, in the age groups 35 to 49 and 50 years and over, the proportion of living females was higher than the proportion of surviving males.

The Clinical Picture

The clinical picture of Hodgkin's disease in this series of cases varied considerably according to age group and sex of the patients. Table 5 presents the distribution of the 181 cases, by age and sex, in relation to illness manifestation at the time of admission to the hospital, as recorded by attending physicians. Systemic symptoms such as fever, pruritis, and night sweats, were less common in the younger than in the older groups. The same was true in the case of anemia, splenomegaly, and hepatomegaly. The percentages at the bottom of Table 5 indicate that the manifestations of the disease were less severe in the younger than in the older groups. Also, looking at males and females separately, it appeared that females experienced a less severe disease than did males in all age groups, except in the group 15 to 34 years.

Table 6 presents the distribution of cases, by age and sex,

TABLE 5

DISTRIBUTION OF 181 NEW CASES OF HODGKIN'S DISEASE, BY AGE AND SEX, ACCORDING TO ILLNESS MANIFESTATION AT TIME OF HOSPITAL ADMISSION, 1965-1970

ILLNESS MANIFESTATION	AGE GROUP AND SEX												All Ages	
	0 - 14			15 - 34			35 - 49			50+				
	M*	F*	T*	M	F	T	M	F	T	M	F	T	Both Sexes	%
Fever	3	0	3	7	8	15	4	3	7	14	11	25	50	27.6
Pruritis	0	0	0	1	1	2	2	1	3	7	5	12	17	9.3
Night sweats	0	0	0	7	5	12	2	1	3	12	10	22	37	20.4
Anemia	0	0	0	3	2	5	2	2	4	7	12	19	28	15.4
Splenomegaly	2	0	2	3	6	9	7	3	10	10	6	16	37	20.4
Hepatomegaly	2	0	2	0	4	4	3	2	5	13	11	24	35	19.3
None of the above symptoms	2	4	6	17	13	30	11	5	16	13	13	26	78	43.0
Percent of total in age group with none of the above symptoms			66.6			50.0			47.0			33.3		
TOTAL CASES	5	4	9	30	30	60	24	10	34	44	34	78	181	

(*) M = Males; F = Females; T = Total, males and females.

according to clinical stage and site of involvement at the time of diagnosis. A considerable difference in the extent of the disease in the younger and the older groups was evident. The percentage of patients with localized disease, particularly stage I, was relatively high in the 0 to 14 and 15 to 34 age groups, as compared to the age groups 35 to 49 and 50 years and over. Stages II and III showed nearly equal percentages of patients in all age groups. However, the most advanced stage of the illness, stage IV, involved an appreciably higher percentage of patients in the 35 to 49 and 50 and over age groups, than in the younger groups. The difference in disease involvement among the four age groups can be readily seen in Figure 3. It is of interest to note that in the most advanced stages of the disease, stages III and IV, the number of females was smaller than the number of males.

As in other Hodgkin's disease studies, a high proportion of cervical node involvement in stage I of the illness was observed in this investigation.

The distribution of patients, by age and sex, in regard to histological type at the time of diagnosis is given in Table 7. The difference between the younger and the older groups with respect to type of lesion, is obvious in the table. The proportion of patients with lymphocytic predominance and nodular sclerosis types, was much higher in the age groups 0 to 14 and 15 to 34 than in the groups 35 to 49 and 50 years and over. On the other hand, the less favorable histologic types, mixed cellularity and lymphocytic depletion, showed higher proportions in the older groups, particularly the 50 years and over, than in the younger ages. The distribution of patients by type of

TABLE 6

DISTRIBUTION OF 181 NEW CASES OF HODGKIN'S DISEASE, BY AGE AND SEX, ACCORDING TO STAGE AND SITE OF INVOLVEMENT AT TIME OF DIAGNOSIS, 1965-1970

STAGE	SITE OF INVOLVEMENT	AGE GROUP AND SEX*												All Ages	
		0 - 14				15 - 34				35 - 49				50+					
		M	F	T	%	M	F	T	%	M	F	T	%	M	F	T	%	M&F	%
I	One lymphatic region																		
	Cervical	2	1	3		7	10	17		3	2	5		8	6	14		39	
	Mediastinal	0	0	0		0	1	1		1	0	1		0	0	0		2	
	Axillary	0	0	0		2	0	2		1	0	1		1	0	1		4	
	Abdominal	0	0	0		0	0	0		0	0	0		0	0	0		0	
	Inguinal	1	0	1		0	0	0		0	0	0		0	0	0		1	
	Total			4	44.5			20	33.3			7	20.6			15	19.2	46	25.4
II	Two or more regions on same side of diaphragm	1	1	2	22.2	4	9	13	22.0	5	2	7	20.6	7	6	13	16.7	35	19.3
III	Lymph nodes on both sides of diaphragm	1	2	3	33.3	13	7	20	33.3	7	3	10	29.4	13	10	23	29.5	56	30.9
IV	Any organ or tissue other than lymph node	0	0	0	0.0	3	3	6	10.0	7	3	10	29.4	15	10	25	32.0	41	22.6
	Unspecified site	0	0	0	0.0	1	0	1	----	0	0	0	0.0	0	2	2	----	3	0.0
	TOTAL CASES	5	4	9		30	30	60		24	10	34		44	34	78		181	

(*) M = Males; F = Females; T = Total, males and females.

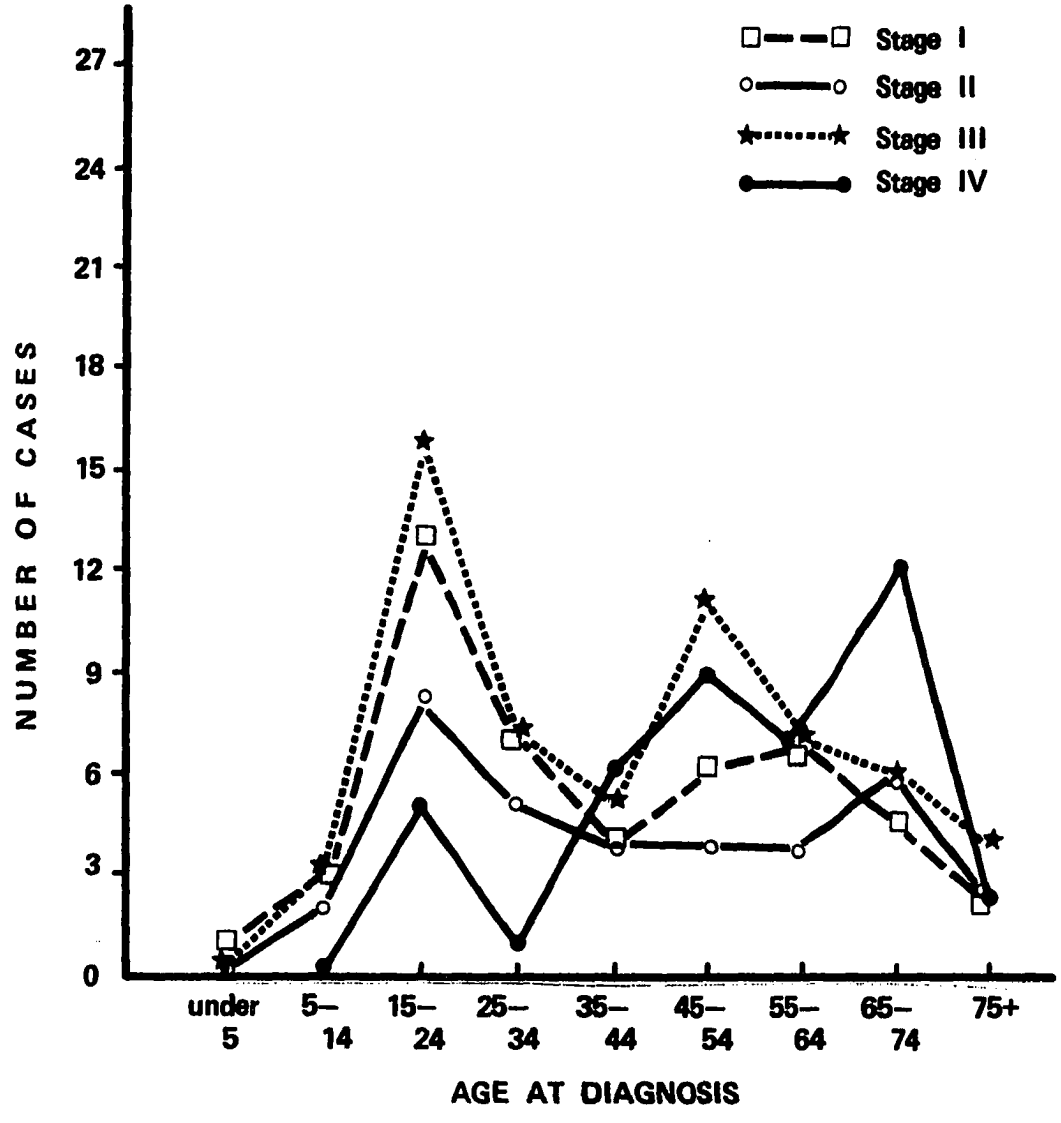

Fig. 3.--Age and clinical stage at diagnosis of 181 new cases of Hodgkin's disease admitted to Oklahoma City hospitals, 1965-1970.

TABLE 7

DISTRIBUTION OF 181 NEW CASES OF HODGKIN'S DISEASE, BY AGE AND SEX, ACCORDING TO HISTOLOGICAL TYPE, 1965-1970

SEX AND HISTOLOGICAL TYPE	AGE GROUP									
	0 - 14		15 - 34		35 - 49		50+		All Ages	
	#	%	#	%	#	%	#	%	#	%
Lymphoc. Predom.	4	44.4	18	30.0	4	11.7	18	23.0	44	24.3
Males	3		11		2		11		27	
Females	1		7		2		7		17	
Nodular Sclerosis	3	33.3	21	35.0	11	32.3	9	11.5	44	24.3
Males	1		10		7		4		22	
Females	2		11		4		5		22	
Mixed Cellularity	1	11.1	14	23.3	9	26.4	27	34.6	51	28.1
Males	0		5		8		16		29	
Females	1		9		1		11		22	
Lymphoc. Deplet.	1	11.1	6	10.0	7	20.5	20	25.6	34	18.7
Males	1		3		5		12		21	
Females	0		3		2		8		13	
Type not available	0	0.0	1	1.6	3	8.8	4	5.1	8	4.4
Males	0		1		2		1		4	
Females	0		0		1		3		4	
TOTAL	9	100.0	60	100.0	34	100.0	78	100.0	181	100.0

lesion is illustrated in Figure 4. By looking at both Table 7 and Figure 4, an obvious difference between males and females can be observed. In the lymphocytic predominance type, males tend to outnumber the females in both the younger groups and the 50 years and over group. Lesions of the nodular sclerosis type are equally distributed between the two sexes. Yet, in the histologic types with the poorest prognosis, i.e., mixed cellularity and lymphocytic depletion, the number of females is far less than the number of males in the age groups 35 to 49 and 50 years and over. The disparity between the sexes, however, is not so marked in the younger groups.

Table 8 was designed to demonstrate the correlation found in this study, between histological type and clinical stage of Hodgkin's disease. The table shows that, in the case of lymphocytic predominance, the number of patients in each clinical stage followed a descending pattern from stage I to stage IV. The reverse occurred with the lymphocytic depletion type of lesion. Nodular sclerosis showed almost twice as many patients with stage I and II disease, as it did with stage III and IV. However, mixed cellularity included nearly twice as many cases of disease in stages III and IV, as of cases with disease in stages I and II. These findings show a correlation between more favorable types of lesions and less advanced stages of Hodgkin's disease, and viceversa.

Figure 5 illustrates the age distribution of patients according to duration of symptoms prior to diagnosis of Hodgkin's disease. No major differences among the four age groups could be identified. The average length of onset was about 2 months for all patients. A sharper decline in the number of cases diagnosed 2 months after onset was noted

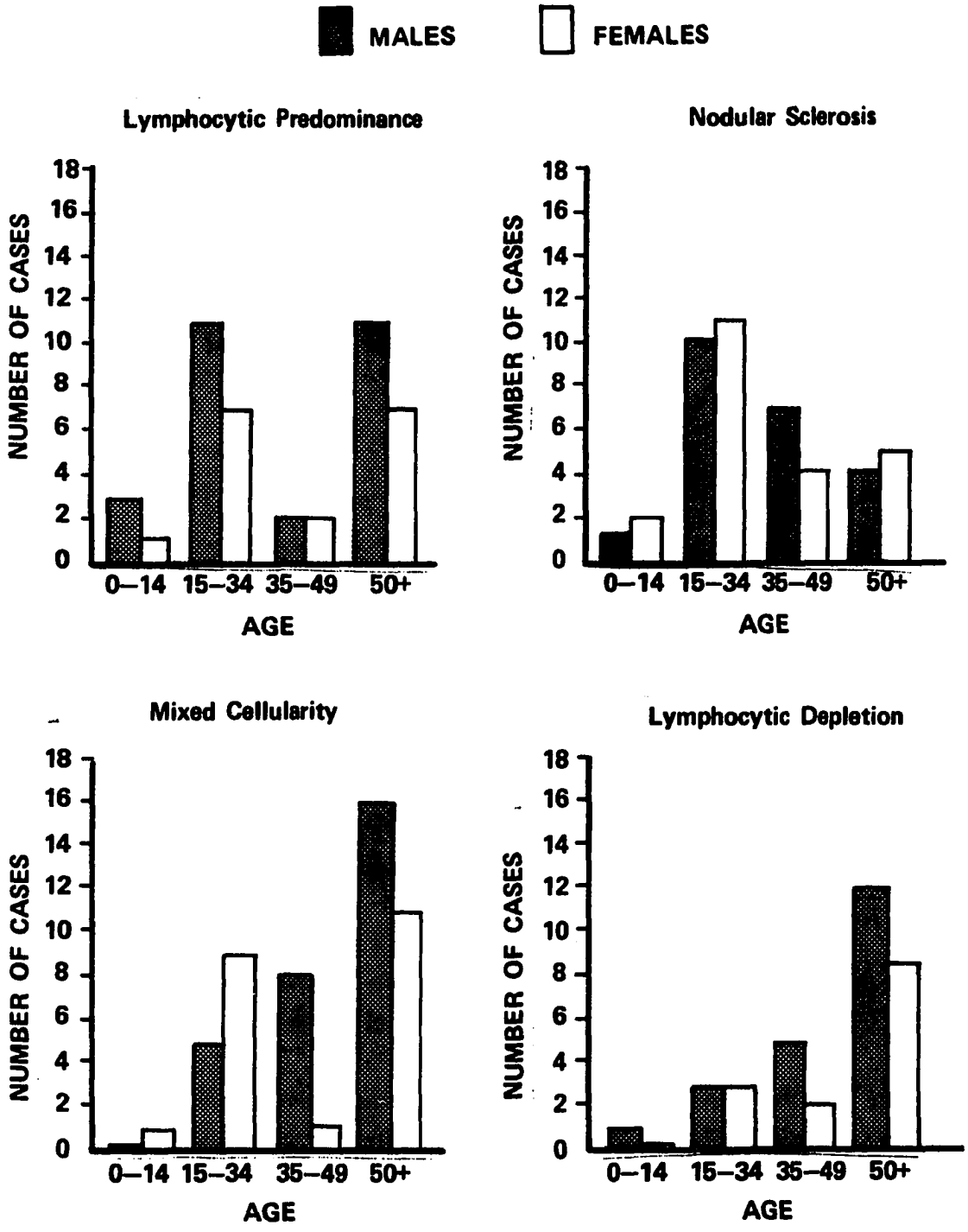

Fig. 4.--Age, sex, and histological type at diagnosis of 181 new cases of Hodgkin's disease admitted to Oklahoma City hospitals, 1965-1970.

TABLE 8

DISTRIBUTION OF 181 NEW CASES OF HODGKIN'S DISEASE, BY AGE GROUP, ACCORDING TO HISTOLOGICAL TYPE, AND CLINICAL STAGE AT DIAGNOSIS, 1965-1970

HISTOLOGICAL TYPE[a]	AGE GROUP AND CLINICAL STAGE																			
	0 - 14				15 - 34				35 - 49				50+				All Ages			
	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
Lymphocytic predominance	4	0	0	0	11	4	2	1	2	1	1	0	5	4	7	2	22	9	10	3
Nodular sclerosis	0	2	1	0	5	7	9	0	3	3	3	2	4	3	1	1	12	15	14	3
Mixed cellularity	0	0	1	0	4	1	6	3	2	1	4	2	5	5	7	10	11	7	18	15
Lymphocytic depletion	0	0	1	0	0	1	3	2	0	0	1	6	1	1	6	12	1	2	11	20
TOTAL	4	2	3	0	20	13	20	6	7	5	9	10	15	13	21	25	46	33	53	41

[a]Histological type was not available in 8 cases.

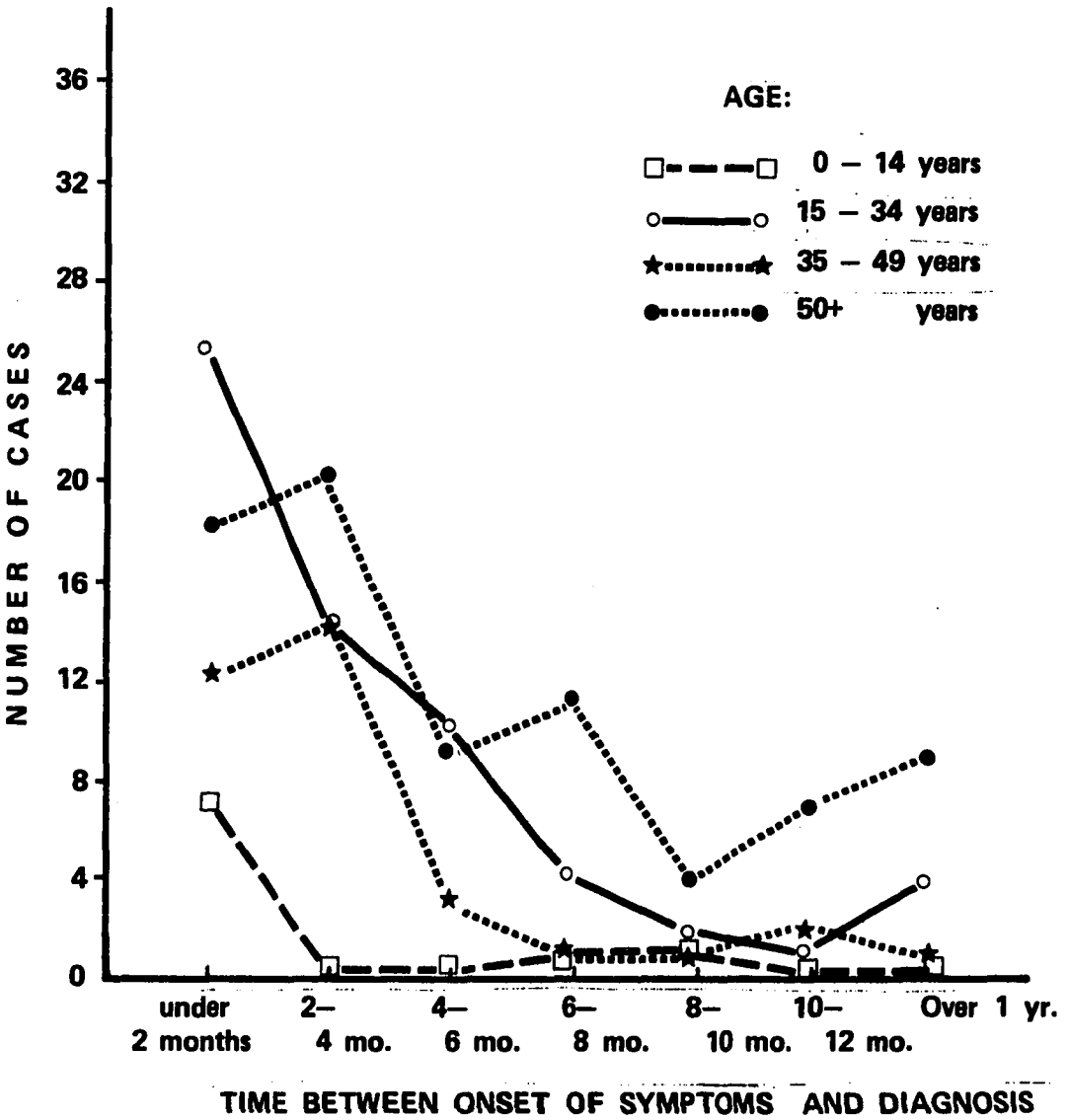

Fig. 5.--Duration of illness onset in 181 new cases of Hodgkin's disease admitted to Oklahoma City hospitals, 1965-1970.

in the age group 15 to 34, as compared with the 50 years and over group, but the difference was not remarkable.

Season of Birth and Season of Onset

Table 9 gives the distribution of the 181 Hodgkin's disease cases, by age group, according to their month of birth. Considering the group as a whole, it was found that 60.2% of the patients were born during fall and winter months (October, November, December, January, February, and March), and 39.8% were born during spring and summer.

Some variations with regard to month of birth were observed when the four age groups 0 to 14, 15 to 34, 35 to 49, and 50 years and over were considered separately. Table 9 shows that of the 9 cases in the age group 0 to 14, 8 were born during fall and winter. The birth trend for the age group 15 to 34 was high during the months of January, February, and March; it dropped considerably during the summer months, and regained its original peakings during October, November, and December. The birth trend for the age group 15 to 34 differed appreciably from that for the age groups 35 to 49 and 50 years and over. In these two age groups, as Table 9 demonstrates, the number of births, by months, showed less striking variations throughout the year. In what ways, or for what reasons, Hodgkin's disease may be associated with the month of birth, is an intricate problem. Studies with larger series of cases, susceptible of more sensitive analysis, are needed to determine whether the findings in this study are valid, or the mere products of chance.

Hodgkin's disease cases were also analysed with respect to month of illness onset; their distribution, by age group, is presented

TABLE 9

DISTRIBUTION OF 181 NEW CASES OF HODGKIN'S DISEASE, BY AGE GROUP, ACCORDING TO MONTH OF BIRTH, 1965-1970

MONTH OF BIRTH	AGE GROUP					
	0 - 14	15 - 34	35 - 49	50+	Total	%
January	3	8	3	9	23	12.7
February	0	7	4	4	15	8.3
March	2	6	3	10	21	11.6
April	1	5	3	6	15	8.3
May	0	0	3	8	11	6.1
June	0	4	3	8	15	8.3
July	0	1	2	5	8	4.4
August	0	4	2	5	11	6.1
September	0	3	2	7	12	6.6
October	2	6	4	5	17	9.4
November	0	8	4	7	19	10.5
December	1	8	1	4	14	7.7
TOTAL	9	60	34	78	181	100.0

in Table 10. The table shows that the proportion of patients reporting the onset of their illness during fall and winter months, was higher than the proportion declaring the beginning of their disease during other months. It is interesting to observe that the age groups 15 to 34 and 50 years and over, show a similar trend, that is, toward maximum occurrence of illness onset during fall and winter. There are too few cases in the age group 0 to 14 to see any definite trend in month of onset. The group 35 to 49 shows a slightly higher frequency of disease onset during spring and summer months.

Education

Information concerning education was obtained from medical records and questionnaires. No data were available on 21 cases or 11.6% of the total number of patients. The distribution of cases, by age group, in regard to education completed at the time of onset of Hodgkin's disease is given in Table 11. The table shows that 58 patients or 32.0% of the total cases, had completed their high school. Only 6 patients or 3.3% of the total, reported no education at all. No special trends that might help to establish a relationship between education of the patient and Hodgkin's disease, are visible in the educational data obtained in this study. However, if the completion of high school, college, and/or a professional career were to be taken as a basis for measuring the educational level attained by the patients, then, it could be said that patients in the age group 15 to 34 had better educational background than those in the other age groups. There were 42, or 70.0% of the total number of patients in the age group 15 to 34, who had completed either high school, college, or a

TABLE 10

DISTRIBUTION OF 181 NEW CASES OF HODGKIN'S DISEASE, BY AGE GROUP, ACCORDING TO MONTH OF ONSET, 1965-1970

MONTH OF ONSET	AGE GROUP					
	0 - 14	15 - 34	35 - 49	50+	Total	%
January	1	9	4	14	28	15.5
February	0	4	2	5	11	6.1
March	0	6	1	7	14	7.7
April	0	5	1	4	10	5.6
May	0	2	7	3	12	6.6
June	0	3	5	4	12	6.6
July	3	3	2	6	14	7.7
August	1	6	2	4	13	7.2
September	0	3	2	7	12	6.6
October	2	3	4	9	18	9.9
November	1	9	2	5	17	9.4
December	1	7	2	10	20	11.1
TOTAL	9	60	34	78	181	100.0

TABLE 11

DISTRIBUTION OF 181 NEW CASES OF HODGKIN'S DISEASE, BY AGE GROUP, ACCORDING TO EDUCATION COMPLETED AT TIME OF ONSET, 1965-1970

EDUCATION COMPLETED	AGE GROUP 0 - 14	15 - 34	35 - 49	50+	Total	%
Grade school	5	1	5	20	31	17.1
Junior High	0	13	6	11	30	16.6
High school	0	31	12	15	58	32.0
College	0	8	3	5	16	8.9
Graduate, or Professional	0	3	2	5	10	5.5
Vocational school	0	2	1	6	9	5.0
None	4	0	0	2	6	3.3
Not reported	0	2	5	14	21	11.6
TOTAL	9	60	34	78	181	100.0

professional career. This figure could be considered as high if it is compared with only 17 patients, or 50.0% in the age group 35 to 49, and 25 patients, or 32.0% in the 50 years and over group.

Usual Occupation

Patients were distributed, by age group, into ten occupational categories as listed in Table 12. The highest percentage (28.7) of patients fell in the not-working category, which comprised mainly retired individuals, the disabled, housewives, and students. The next highest percentage was for managerial workers, secretaries, administrators, bookkeepers, and other white-collar people holding similar jobs. The managerial group constituted 22.1% of all cases (including 9 whose occupation could not be determined). Following in descending order were the artisan workers with 9.9%, the farm workers with 8.8%, and individuals such as military personnel, caretakers, tailors, waitresses, with 8.3%. There were no miners in the caseload.

The number of cases in particular occupations, as Table 12 shows, revealed some differences among the various age groups. The proportion of professional and managerial workers was higher in the age group 15 to 34 than in the older groups. In the age group 15 to 34 there were 21 professional or managerial workers, representing 35% of the total cases in the age group. Such figures were higher than the 11 cases or 32%, and 18 cases or 23%, found in the 35 to 49 and 50 years and over groups respectively, for the same occupations. The largest number, 16, and the largest proportion, 47%, of non-managerial, artisan, and "other" workers occurred in the age group 35 to 49. When the numbers of farmers and oil field workers were combined, it was found

TABLE 12

DISTRIBUTION OF 181 NEW CASES OF HODGKIN'S DISEASE, BY AGE GROUP, ACCORDING TO USUAL OCCUPATION, 1965-1970

USUAL OCCUPATION	AGE GROUP 0 - 14	15 - 34	35 - 49	50+	Total	%
Professional	0	3	2	5	10	5.6
Managerial	0	18	9	13	40	22.1
Non managerial	0	4	5	3	12	6.6
Artisan (craftsman)	0	5	6	7	18	9.9
Farm worker	0	1	2	13	16	8.8
Oil field worker	2	2	2	5	9	5.0
Mine worker	0	0	0	0	0	0.0
Other[a]	0	5	5	5	15	8.3
Not working	9	22	3	18	52	28.7
Not reported	0	0	0	9	9	5.0
TOTAL	9	60	34	78	181	100.0

[a]Military, civil service, caretakers, watchmen, tailors, cooks, nurses aid, waitresses.

that they accounted for 18 cases or 23%, in the age group 50 years and over. However, in the age group 35 to 49 there were only 4, or 11%, and in the age group 15 to 34, only 3 cases, or 5% of the total in the age group. The highest proportion of cases, 37%, in the not-working category was recorded in the age group 15 to 34. For the same occupational category the age group 35 to 49 showed a proportion of 9%, and the group 50 years and over a proportion of 23%.

No attempt was made in this study to obtain a clear-cut idea of the socio-economic condition of the patients. A glance at the last column on the right in Tables 11 and 12 would only suggest that the majority of the patients did not come from the lowest strata of society. The proportion of patients who completed high school, college, or professional training, and the proportion of patients in professional or managerial occupations, was fairly large. However, the figures alone are not sufficient to support firm conclusions for or against the socio-economic background of the patients.

Marital Status

Table 13 presents the distribution of the 181 Hodgkin's disease patients, by age group, according to their marital status at the time of illness onset. Of the total number of cases, 62.4% were married, as compared to only 24.3% who were single or never married. There were also 9.4% widow patients, 2.8% divorced, and 1.1% whose marital status could not be determined. No special trend in regard to marriage experience was observed when the age groups were considered separately.

TABLE 13

DISTRIBUTION OF 181 NEW CASES OF HODGKIN'S DISEASE, BY AGE GROUP, ACCORDING TO MARITAL STATUS AT TIME OF ONSET, 1965-1970

MARITAL STATUS	AGE GROUP 0 - 14	15 - 34	35 - 49	50+	Total	%
Single	9	27	4	4	44	24.3
Married	0	31	25	57	113	62.4
Divorced	0	1	4	0	5	2.8
Widow	0	1	0	16	17	9.4
Separated	0	0	0	0	0	0.0
Not reported	0	0	1	1	2	1.1
TOTAL	9	60	34	78	181	100.0

Familial Occurrence

Of the 181 Hodgkin's disease cases there were 25 who reported the occurrence of the same illness in close members of their family. However, in 10 instances the reports were extremely dubious since the words "Hodgkin's disease" were never mentioned either in the medical records, or in the answers to the questionnaire. In most cases, the respondents referred to the illness under the generic term "cancer." Therefore, in Table 14 only 15 cases are included. Those are cases in which the words "Hodgkin's disease" were used by the proband when narrating his family's medical history to the attending physician. Personal contact, by telephone, was obtained with 7 of the 15 patients (probands) or their relatives, to try to confirm the family history of Hodgkin's disease. By all information gathered from medical records, questionnaires, and telephone conversations, it appeared that the 15 reported instances of familial Hodgkin's disease were accurate; nevertheless, doubts still exist since pathological records could be obtained for the relatives of only two of the 15 cases.

The 15 cases, and the relatives in whom Hodgkin's disease allegedly occurred, are described in Table 14. Case 1 was a 12-year old male whose uncle acquired the disease at the age of 23. At the present time, the disease is in remission in both individuals. Case 2 is the nephew of case 6. Both persons are living and described their present health status as "excellent." The aunt of case 3 died of Hodgkin's disease at the age of 45. Her daughter (proband's cousin) was reported to have acquired the illness at around age 20; however, no other information was available. Case 4 reported that his maternal uncle died of

TABLE 14

OCCURRENCE OF HODGKIN'S DISEASE IN FAMILY MEMBERS OF 181 PATIENTS ADMITTED TO OKLAHOMA CITY HOSPITALS, 1965-1970

Case Number	PROBAND		RELATIVES AFFECTED BY HODGKIN'S DISEASE	
	Age at Onset	Sex	Relationship to Proband	Age at Onset
1	12	Male	Uncle	23
2	17	Male	Uncle	39
3	22	Male	Aunt, and cousin	40, 20
4	26	Male	Uncle	25
5	37	Male	Cousin	20
6	39	Male	Nephew	17
7	51	Male	Cousin, and aunt	21, 35
8	68	Male	Father	47
9	19	Female	Cousin	8
10	21	Female	Cousin	22
11	25	Female	Father	40
12	49	Female	Father, uncle, and cousin	50, ?, ?
13	59	Female	Mother, sister, and cousin	70, 50, ?
14	70	Female	Son	?
15	79	Female	Son	39

Hodgkin's disease at the age of 29. The wife of case 5 stated that a female cousin of her husband has Hodgkin's disease at the present time. Case 5 died at age 38. An aunt and a female cousin of case 7, dead at age 51, reportedly died also of Hodgkin's disease at ages 39 and 27 respectively. Case 8, a 68-year old male, said that his father had suffered from Hodgkin's disease since age 47; he did not give any further information. Case 9 was a female of 19 years of age whose cousin died of Hodgkin's disease at age 10. Case 10 was a female dead at age 23. Her 24-year old male cousin is presently afflicted with Hodgkin's disease. Case 11, a 25-year old female, reported that her father acquired the same illness at around age 40.

Case 12 was a 49-year old female whose medical records registered the history of Hodgkin's disease in three other members of her family. Her father succumbed to the illness at the age of 54; an uncle and a cousin (father's side) also died of Hodgkin's disease at an unknown age. Case 13 was the most unusual case of Hodgkin's disease found in this study. It was a female who died at the age of 59. The medical records of this woman showed a history of Hodgkin's disease in three members of her family. Her mother and sister died of the disease at ages 78 and 56 respectively. A cousin (mother's side) also died of the same illness at an unknown age. Furthermore, medical records registered a long history of "allergies" in various other members of the family. A relative of the proband stated: "we are extremely concerned about the occurrence of Hodgkin's disease in our family." Case 14, a female dead at age 71, reported the occurrence of Hodgkin's disease in one son. She had 11 other children. The occurrence of the illness in

a son was reported also by case 15, a 79-year old female who is alive. Her son died at age 41.

Examining the list of probands with affected relatives in Table 14, it is observed that there was 1 in the age group 0 to 14; 6 in the age group 15 to 34; 3 in the age group 35 to 49; and 5 in the age group 50 years and over. The total number of affected relatives was 21. However, the age at onset of the disease was not available for 4 of them. The distribution of the 17 relatives whose age was known was 1, 7, 6, and 3, for the respective 0 to 14, 15 to 34, 35 to 49, and 50 and over age groups. The mean difference, in years, between the age at onset in the proband, and the age at onset in his relative or relatives was estimated. An average 11-year difference was obtained for the group 0 to 14; a 10-year difference for the age group 15 to 34; a 13-year difference for the 35 to 49 age group; and an average difference of 21 years for the age group 50 years and over.

Status of the Hodgkin's Disease Patients at the Time This Study Was Concluded, (Aug. 31, 1971)

All contact with the Hodgkin's disease patients in this study was lost around August 31, 1971. Up to that time efforts were made to determine the condition of all patients, whether living or dead, even of those who did not respond to the questionnaire. This was done by looking at dates of clinic appointments, obtaining information from tumor registries, calling the patients or their relatives, inquiring about the patients from county administrators, and in a few instances by calling the patient's former employer, or his insurance company. Information concerning the patient's status was obtained for all cases but four.

Table 15 presents the distribution of the cases, by age, sex, and histological type at diagnosis, according to their condition on August 31, 1971. Twelve cases are not included in the table; four of them because the condition of the patient could not be determined, and the other eight, because their histological type was not available.

Of the 169 cases included in Table 15, 86 or 50.9% were alive, and 83 or 49.1% were dead. If the histological types are considered, it will be seen that there was a striking difference between the percentage of patients alive in the lymphocytic predominance and nodular sclerosis types, and the percentage alive in the mixed cellularity and lymphocytic depletion categories. The percentage of patients alive in the first two types were 68.2% and 81.8% respectively, by contrast to 36.7% and 6.3% in the last two histologic categories.

Differences in survival were also noted among the four age groups. In the 0 to 14 age group, 6 or 66.7% of the cases were still living by August 31, 1971. A high proportion of patients, 43 or 72.0%, were also alive in the age group 15 to 34. However, the percentage of patients alive in the older groups, was not as high as in the younger ages. Table 15 shows that in the age group 35 to 49, only 17, or 54.0%, of the patients were still alive. The smallest percentage of surviving patients was observed in the age group 50 years and over. Only 20, or 29.0%, of the patients in this group, were still living by August 31, 1971. These results point out to a direct correlation of lower age with the lymphocytic predominance and nodular sclerosis types, and of higher age with the mixed cellularity and lymphocytic depletion categories. It was mentioned above that the number of females in the

TABLE 15

STATUS OF 169[a] HODGKIN'S DISEASE PATIENTS AT TIME OF CONCLUSION OF PRESENT STUDY, BY AGE, SEX, AND HISTOLOGICAL TYPE, 1965-1970

AGE AND SEX	HISTOLOGICAL TYPE											
	Lymphocytic Predominance		Nodular Sclerosis		Mixed Cellularity		Lymphocytic Depletion		All Types			
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	%	Dead	%
0 - 14	3	1	3	0	0	1	0	1	6	66.7	3	33.3
Male	3	0	1	0	0	0	0	1	4		1	
Female	0	1	2	0	0	1	0	0	2		2	
15 - 34	17	1	19	2	6	8	1	5	43	72.0	16	28.0
Male	10	1	9	1	3	2	1	2	23		6	
Female	7	0	10	1	3	6	0	3	20		10	
35 - 49	3	1	10	1	3	6	1	6	17	54.0	14	46.0
Male	1	1	6	1	3	5	1	4	11		11	
Female	0	0	4	0	0	1	0	2	6		3	
50+	7	11	4	5	9	16	0	18	20	29.0	50	71.0
Male	4	7	1	3	7	8	0	11	12		29	
Female	3	4	3	2	2	8	0	7	8		21	
TOTAL	30	14	36	8	18	31	2	30	86		83	
Percent	68.2	31.8	81.8	18.2	36.7	63.3	6.3	93.7	50.9		49.1	

[a]Status not known in 4 cases; histological type not available in 8 cases.

lymphocytic depletion and mixed cellularitv histologic types, was smaller than the number of males. This difference in number seems to be reflected in the slightly better survival experience of females over males, in the age groups 35 to 49, and 50 years and over.

CHAPTER V

RESULTS II

Case-Control Study

The second objective of the present investigation was to explore possible relationships between Hodgkin's disease and suspected disease-inciting factors, in the age groups 0 to 14, 15 to 34, 35 to 49, and 50 years and over. To accomplish this, an epidemiological case-control study was designed and performed as explained in Chapter III.

The Index and Control Groups

Table 16 presents the number of Hodgkin's disease cases and the number of controls that were included in the study. The table also shows how the two groups were derived.

Of the 181 cases and their matched controls whose medical records were abstracted, the questionnaire was not sent to 3 cases and 1 control because permission was denied by their attending physicians. Therefore, the number of questionnaires mailed to cases and controls was 178 and 180 respectively. Response to the questionnaire was obtained from 144 or 81% of the cases, and from 142 or 78.9% of the controls. Nonrespondents accounted for 15.1% of the cases, and 15.6% of the controls. An open refusal to answer the questionnaire was received from 2 cases, and from 4 controls. Also, the mailing address of 5 cases

TABLE 16

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
DERIVATION OF THE INDEX AND CONTROL GROUP, AND TOTAL SAMPLE SIZE

INFORMATION	CASES		CONTROLS	
	Number	%	Number	%
Hospital records abstracted . . .	181		181	
Permission to send questionnaire denied by physician	3		1	
Questionnaires mailed	178	100.0	180	100.0
Questionnaires filled out	144	81.0	142	78.9
No reply.	27	15.1	28	15.6
Refusals.	2	1.1	4	2.2
Not located	5	2.8	6	3.3
Patients used for comparison . .	144		142	
Total sample size	286			

and 6 controls could not be obtained. Only patients who answered the questionnaire were used for comparison; consequently, the index and control groups consisted of 144 and 142 cases, respectively. The total sample size was 286 patients.

The distribution of the 144 Hodgkin's disease cases, and their 142 matched controls, by age and sex, is given in Table 17. The table shows that 81 or 56.2% of the cases, and 78 or 55.0% of the controls were male. There were 63 or 43.8% females in the index group, and 64 or 45.0% females in the control group. These figures show that the percentage of males and females was nearly equal in both groups.

The distribution of the sexes in each of the four age groups was quite similar, although more discrepant than for the two groups as a whole. Males and females were about equally represented in both index and control cases, in the age groups 0 to 14, 15 to 34, and 50 years and over. However, in the age group 35 to 49, the percentage of males was higher for index cases than for controls, while the opposite was true for females. For unknown reasons, the loss of patients due to any of the factors outlined in Table 16, showed more discrepancies in the age group 35 to 49 than in any of the other age groups.

The total number of patients who responded to the questionnaire in each age group, regardless of sex, was used for comparisons between cases and controls. No appreciable differences were observed in the proportion of respondents from each of the nine participating hospitals. Table 17 indicates that the total number of patients in the index and control groups, as well as in each of the four age groups, was reasonably comparable.

TABLE 17

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
DISTRIBUTION OF 144 CASES AND 142 MATCHED CONTROLS,
BY AGE AND SEX

AGE AND SEX	CASES		CONTROLS	
	Number	%	Number	%
0 - 14				
Both sexes	8	100.0	8	100.0
Males	4	50.0	4	50.0
Females	4	50.0	4	50.0
15 - 34				
Both sexes	50	100.0	51	100.0
Males	23	46.0	26	51.0
Females	27	54	25	49.0
35 - 49				
Both sexes	25	100.0	24	100.0
Males	19	76.0	15	62.5
Females	6	24.0	9	37.5
50+				
Both sexes	61	100.0	59	100.0
Males	35	57.4	33	56.0
Females	26	42.6	26	44.0
All ages				
Both sexes	144	100.0	142	100.0
Males	81	56.2	78	55.0
Females	63	43.8	64	45.0

Seasonal Factors and Hodgkin's Disease

The possibility of seasonal variations in Hodgkin's disease has been considered by various investigators. Such possibility was suggested also by findings in the descriptive phase of the present study. Therefore, it was deemed worth-while to compare cases and controls with respect to season of birth and season of onset, to explore potential season-disease relationships.

In the descriptive phase of this investigation it was observed that Hodgkin's disease cases showed higher trends of birth and illness onset during fall and winter months than during spring and summer (Tables 9 and 10). Therefore, for comparing cases and controls by age groups, it was thought advisable to group the seasons into fall and winter (October, November, December, January, February, and March), and spring and summer.

Table 18 describes the distribution of cases and controls according to season of birth. In the age group 0 to 14 years, 7 cases and 5 controls were born during fall and winter. An apparent increased relative risk of Hodgkin's disease (4.20) in those born during the colder months was noted. However, the Fisher's Exact Test applied to the figures ruled out any association between the illness and season of birth in this age group. Due to the small number of index and control cases, comparisons within the age group 0 to 14 years should be interpreted with caution. It was stated in the descriptive section of this study, that Hodgkin's disease in the first 14 years of life shows various similarities with the disease in young adults. This fact must be born in mind when assessing the real significance of the findings

TABLE 18

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY SEASON OF BIRTH

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Born during fall and winter[a]	7	5	4.20	P> .20
Born during spring and summer	1	3		
15 - 34				
Born during fall and winter	37	23	3.46	P< .01
Born during spring and summer	13	28		
35 - 49				
Born during fall and winter	14	8	2.54	P> .15
Born during spring and summer	11	16		
50+				
Born during fall and winter	32	26	1.40	P> .20
Born during spring and summer	29	33		
All ages, 15 years and over[b]				
Born during fall and winter	83	57	2.11	P< .01
Born during spring and summer	53	77		

[a]October, November, December, January, February, and March.

[b]Additive χ^2 test with 3 degrees of freedom.

obtained in the 0 to 14 age group presented in subsequent tables.

The comparison of cases and controls by season of birth in the other three age groups is also shown in Table 18. A greatly increased risk (3.46) of Hodgkin's disease in individuals born during fall and winter months was noted in the 15 to 34 age group. A possible association between season of birth and disease, in this age group, was suggested by a highly significant probability value. The age group 35 to 49 years also showed a high risk for those born during fall and winter; however, the probability of a season-disease relationship was not significant. The relative risk of Hodgkin's disease in those born during fall and winter was mildly increased (1.40) in the age group 50 years and over, although the probability of a season-disease association was not significant at the critical region of 10% adopted in this study. Interesting differences in relative risk and in probability values, between the age groups 15 to 34 and 50 years and over, are evident in Table 18.

After comparing cases with controls for specific attributes in each of the age categories, a comparison of the two groups as a whole was performed, using the additive χ^2 test, in which all patients over 15 years of age were included. The purpose of this overall comparison was to inquire about possible associations of Hodgkin's disease with a particular factor when all three age groups were taken together, even if no association was found when individual age groups were considered.

In regard to season of birth, Table 18 shows that there were 83 cases and 57 controls born during fall and winter months. The ob-

served relative risk was 2.11; the difference in the risk of Hodgkin's disease between those individuals born during the colder months, and those born during spring and summer was statistically significant at the .01 level. These findings are suggestive of an association between Hodgkin's disease and season of birth, particularly in the age group 15 to 34 years.

The comparison of the 144 cases and their 142 matched controls, by age group, with respect to season of illness onset is presented in Table 19. Seasons were grouped as explained previously. A decreased risk of illness onset during fall and winter months was noted for the age groups 0 to 14 and 35 to 49 years. The relative risk values were 0.14 and 0.47 for each age group respectively. However, the probability that the onset of Hodgkin's disease is less likely to occur during fall and winter, than in other seasons in these two age groups, was not statistically significant.

A moderately increased risk of Hodgkin's disease onset during fall and winter was found for the age groups 15 to 34 and 50 years and over. Relative risk values were 1.83 for the 15 to 34 age group, and 1.60 for the 50 years and over group. These results, however, were not statistically significant. By the same token, when all ages over 15 years were compared, it was found that illness onset occurred during fall and winter in 80 cases and 69 controls. This produced a mild increase in relative risk, which could easily be the product of chance.

Surgery, Trauma, Allergy, and Hodgkin's Disease

Some suggestions have been made concerning possible roles that appendectomy and/or tonsillectomy might play in the development of

TABLE 19

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY SEASON OF ILLNESS ONSET

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Onset during fall and winter[a]	4	7	0.14	P> .20
Onset during spring and summer	4	1		
15 - 34				
Onset during fall and winter	31	24	1.83	P> .15
Onset during spring and summer	19	27		
35 - 49				
Onset during fall and winter	10	14	0.47	P> .20
Onset during spring and summer	15	10		
50+				
Onset during fall and winter	39	31	1.60	P> .20
Onset during spring and summer	22	28		
All ages, 15 years and over[b]				
Onset during fall and winter	80	69	1.34	P> .20
Onset during spring and summer	56	65		

[a]October, November, December, January, February, and March.

[b]Additive Chi ($\sqrt{\chi^2}$)-test to account for results in opposite directions.

Hodgkin's disease. In view of such suggestions it was thought advisable to compare cases and controls in this study in regard to presence or absence of any of those surgical procedures at the time of onset. The distribution of the 144 cases and their matched controls, by age group, with respect to presence or absence of tonsillectomy and/or appendectomy at the time of onset of their illness, is given in Table 20.

Table 20 demonstrates that in the age group 0 to 14 years there were 3 cases and 2 controls who had had tonsillectomy and/or appendectomy. The relative risk of Hodgkin's disease, therefore, was found to be moderately increased by either procedure. However, the Fisher's Exact Test indicated that the observed differences between cases and controls, in this instance, could be ascribed to chance, since a large probability value was obtained. Different results were observed when patients in the age group 15 to 34 were compared. There were 34 cases and 20 controls, aged 15 to 34, who had had tonsillectomy and/or appendectomy prior to onset of their illness. This represented a difference of 29% between cases and controls. Such a difference was reflected by a highly increased relative risk (3.29) of Hodgkin's disease in those who had experienced either procedure. Furthermore, a strong association between tonsillectomy and/or appendectomy and Hodgkin's disease in the age group 15 to 34 was suggested by a highly significant statistical probability value.

There was also a 31% difference in the proportion of cases and controls age 35 to 49 who had had one or both procedures. In this age group, the risk of Hodgkin's disease in those who had had surgery was almost four times as high as the risk in those without either oper-

TABLE 20

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY APPENDECTOMY AND/OR TONSILLECTOMY

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CON-TROLS	RELATIVE RISK	P VALUE
0 - 14				
Tonsillect. and/or appendect.	3	2	1.8	P> .20
None of these surgeries	5	6		
15 - 34				
Tonsillect. and/or appendect.	34	20	3.29	P< .01
None of these surgeries	16	31		
35 - 49				
Tonsillect. and/or appendect.	17	9	3.54	P< .10
None of these surgeries	8	15		
50+				
Tonsillect. and/or appendect.	30	20	1.89	P< .15
None of these surgeries	31	39		
All ages, 15 years and over[a]				
Tonsillect. and/or appendect.	81	49	2.55	P< .01
None of these surgeries	55	85		

[a]Additive χ^2 with 3 degrees of freedom.

ation. The difference was statistically significant at the .10 level. The age group 50 years and over differed from the other two age groups. The relative risk, although moderately increased for those who had had surgery, was appreciably lower than for ages 15 to 34 and 35 to 49. The difference in surgical experience between cases and controls in the 50 years and over group was not significant at the .10 level. When age groups were combined, it was observed that 81 cases and 49 controls had undergone tonsillectomy and/or appendectomy. The difference in proportion was 23%, with a risk of Hodgkin's disease about three times greater in those having undergone surgery. The probability value was significant at the .01 level.

Trauma or injury has been associated with certain types of tumors, such as sarcoma of bone and gliomas of the brain. In the present study, cases and controls were compared with respect to history of injuries received within 10 years prior to onset of their illness. Only injuries for which medical attention was sought by the patient were included. Table 21 shows the distribution of cases and controls, by age group, according to injury history. No clue to any possible associations between Hodgkin's disease and trauma, in any age group, was found. Relative risk values, for the different age groups, as well as for all ages combined, were close to unity. Small differences registered between cases and controls were found not to be significant.

It was said in Chapter II, that speculations have existed for many years concerning the possible role of hypersensitivity reactions in Hodgkin's disease. To explore this subject, cases and controls in the present study were compared with respect to their allergy history.

TABLE 21

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY INJURIES PRIOR TO ILLNESS ONSET

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Presence of injuries[a]	1	1	1.00	---
Absence of injuries	7	7		
15 - 34				
Presence of injuries	20	19	1.12	P> .20
Absence of injuries	30	32		
35 - 49				
Presence of injuries	12	12	0.92	P> .20
Absence of injuries	13	12		
50+				
Presence of injuries	23	26	0.77	P> .20
Absence of injuries	38	33		
All ages, 15 years and over[b]				
Presence of injuries	55	57	0.92	P> .20
Absence of injuries	81	77		

[a]Only injuries received within 10 years prior to illness onset.

[b]Additive Chi ($\sqrt{\chi^2}$)-test to account for results in opposite directions.

Only patients with allergies of five or more years duration were used for comparison. The results are shown in Table 22. The age group 0 to 14 years experienced a highly increased risk of Hodgkin's disease in those with allergy history. The relative risk value for this age group was 9.0. However, due to the extremely small numbers in this age group, the probability value was not statistically significant, although it was borderline.

The number of cases and controls who reported a history of allergy in the age group 15 to 34 years was 21 and 22 respectively, and the relative risk was nearly one. The difference in the proportion of patients with or without allergy history was not significant. Similarly, no difference with respect to presence or absence of allergic reactions prior to onset of their illness was found, between cases and controls, in the age group 35 to 49. Yet, in the age group 50 years and over, cases showed 35 patients who reported allergy histroy, in contrast with only 22 of the controls. This represented a 20% difference between both groups. This difference was statistically significant. The relative risk of Hodgkin's disease in this age group was over twice as high in those with a history of allergy as it was in those without such history. Only an 8% difference between cases and controls in regard to allergy history was observed when all ages were combined, and the difference was not statistically significant. The likelihood of any association between Hodgkin's disease and allergy was minimal, when all ages were considered.

Environment and Hodgkin's Disease

The influence that exposure to environmental factors may ex-

TABLE 22

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY ALLERGY HISTORY PRIOR TO ILLNESS ONSET

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Presence of allergies[a]	6	2	9.00	P< .15
Absence of allergies	2	6		
15 - 34				
Presence of allergies	21	22	0.95	P> .20
Absence of allergies	29	29		
35 - 49				
Presence of allergies	13	14	0.77	P> .20
Absence of allergies	12	10		
50+				
Presence of allergies	35	22	2.26	P< .05
Absence of allergies	26	37		
All ages, 15 years and over[b]				
Presence of allergies	69	58	1.35	P> .20
Absence of allergies	67	76		

[a]To plants, foods, drugs, chemicals, or animal products, for at least 5 years prior to illness onset.

[b]Additive Chi ($\sqrt{\chi^2}$)-test to account for results in opposite directions.

ert in the development of Hodgkin's disease has been a topic for much speculation and debate. In an effort to explore this subject further, various environmental factors were selected in the present investigation, and cases and controls of different age groups were compared with respect to their exposure to such variables.

Table 23 presents the distribution of cases and controls, by age group, with regard to history of exposure to chemicals before onset of their illness. "Regular exposure to chemicals" was defined as any contact with such substances as insecticides, paints, glues, solvents, or plant sprays, daily, or at least once a week during one or more years. In the age group 0 to 14 years, the relative risk of Hodgkin's disease was found to be over twice as high in those who had had any exposure to chemicals, as in those who had not experienced such exposure. However, the difference in the proportion of cases and controls who reported chemical exposure was not statistically significant. Likewise, no major difference between cases and controls was observed in the age group 15 to 34. In the age group 35 to 49, on the other hand, there were 15 cases and 8 controls who reported history of exposure to chemical products. This represented a difference of 27% between cases and controls. Again, the difference was not statistically significant, although the probability value was close to the borderline, and the observed relative risk value in this age group was 3.0. Cases did not differ significantly from their matched controls in regard to exposure to chemicals in the age group 50 years and over. The comparison of the two groups, all ages combined, produced a moderately increased risk of Hodgkin's disease for those with a history of chemical exposure, but

TABLE 23

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY CHEMICAL EXPOSURE PRIOR TO ILLNESS ONSET

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Exposure to chemicals[a]	2	1	2.30	P> .20
No exposure to chemicals	6	7		
15 - 34				
Exposure to chemicals	17	14	1.36	P> .20
No exposure to chemicals	33	37		
35 - 49				
Exposure to chemicals	15	8	3.00	P< .15
No exposure to chemicals	10	16		
50+				
Exposure to chemicals	23	18	1.38	P> .20
No exposure to chemicals	38	41		
All ages, 15 years and over[b]				
Exposure to chemicals	55	40	1.60	P> .15
No exposure to chemicals	81	94		

[a]To insecticides, paints, glues, solvents, or plant sprays, daily, or at least once a week, during one or more years.

[b]Additive χ^2 with 3 degrees of freedom.

the difference in the proportion of patients with such history was slight, and not statistically significant.

Table 24 compares the cases and controls with respect to regular contact with animals prior to illness onset. "Regular contact" was defined as any association with domestic or farm animals, daily, or at least once a week, during one or more years. Comparison of cases and controls in the age group 0 to 14 years gave a highly increased relative risk for those who reported a histroy of animal exposure. However, the high risk value, apparently depended more on the small number of patients involved, than in a real difference between cases and controls, which was not statistically significant. Regular contact with animals was reported by 36 cases and 22 controls in the age group 15 to 34 years. The difference in the proportion of individuals exposed to animals was 29%. This difference was statistically significant at the .01 level. Moreover, the risk of Hodgkin's disease for those exposed to animals in this age group was over three times as high as the risk for those reporting no exposure.

In the age group 35 to 49 there was a 22% difference in the proportion of cases and controls with history of animal exposure. This difference was not statistically significant. Nevertheless, the relative risk in this age group was estimated as 2.86. It is interesting to observe that in the age group 50 years and over, the difference in the proportion of cases and controls with a history of regular contact with animals was only 16%, and this difference was also not significant at the .10 level. The relative risk of Hodgkin's disease in those who had had regular contact with animals in this age group was moderately

TABLE 24

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY HISTORY OF CONTACT WITH ANIMALS

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Regular contact with animals[a]	7	4	7.00	P> .20
No contact with animals	1	4		
15 - 34				
Regular contact with animals	36	22	3.39	P< .01
No contact with animals	14	29		
35 - 49				
Regular contact with animals	20	14	2.86	P> .15
No contact with animals	5	10		
50+				
Regular contact with animals	37	26	1.96	P< .15
No contact with animals	24	33		
All ages, 15 years and over[b]				
Regular contact with animals	93	62	2.51	P< .01
No contact with animals	43	72		

[a]Domestic or farm animals, daily, or at least once a week, during one or more years.

[b]Additive χ^2 with 3 degrees of freedom.

high, although not as high as for the 15 to 34 years age group.

Another suggestion of a possible association between Hodgkin's disease and regular contact with animals was obtained when cases and controls, all ages combined, were compared. History of exposure to animals was registered by 93 cases and 62 controls. This difference was statistically significant at the .01 level. For all ages, it was found that patients with history of contact with animals had a relative risk two and a half times as high as the risk of those without such contact.

Cases and controls were also compared in regard to regular practice of hobbies away from home prior to onset of their illness. "Regular hobby practice" was defined as any outdoor activity, such as hunting, fishing, camping, lake or river swimming, carried out by the patient weekly or several times a month, during one or more years. The results, by age, are given in Table 25. In the age group 0 to 14 years, 7 cases and 3 controls reported regular hobby practice. The difference was not significant, although the probability value fell close to the .10 region. A very high relative risk value (11.7) was observed in this age group; however, one must keep in mind the small number of cases. A 22% difference in the proportion of cases and controls who practiced outdoor activities, was noted in the age group 15 to 34 years. The difference was statistically significant at the .05 level. For this age group, the risk of Hodgkin's disease was over twice as high in those with a history of regular hobby practice as in those without such history.

The proportion of cases and controls who reported regular

TABLE 25

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY PRACTICE OF OUTDOOR ACTIVITIES

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CON-TROLS	RELATIVE RISK	P VALUE
0 - 14				
Regular hobby practice[a]	7	3	11.7	P< .15
No hobby practice	1	5		
15 - 34				
Regular hobby practice	36	26	2.47	P< .05
No hobby practice	14	25		
35 - 49				
Regular hobby practice	17	10	2.97	P< .15
No hobby practice	8	14		
50+				
Regular hobby practice	29	21	1.64	P> .20
No hobby practice	32	38		
All ages, 15 years and over[b]				
Regular hobby practice	82	57	2.05	P< .02
No hobby practice	54	77		

[a]Camping, hunting, fishing, lake or river swimming, once a week, or at least once a month, during one or more years.

[b]Additive χ^2 with 3 degrees of freedom.

hobby practice in the age group 35 to 49 differed by 27%. Although this difference was not statistically significant, the result was borderline. The observed relative risk in the age group was 2.97. In the age group 50 years and over, 29 cases and 21 controls reported regular hobby practice, which represented a proportional difference of 12%, and could be accounted for by chance. Furthermore, the relative risk of Hodgkin's disease in those who practiced outdoor activities regularly, was only moderately increased in the 50 years and over group. For all ages combined, the relative risk of the illness was twice as high in individuals with history of regular hobby practice, than in those who did not report such history. The proportional difference between cases and controls in regard to hobby practice was 18%. This difference was statistically significant at the .02 level.

A report was published (Gilmore and Zelesnick, 1962) about the occurrence of 3 cases of Hodgkin's disease in individuals living in the same frame house over a period of 13 years. Hence, it was thought appropriate in the present study, to compare cases and controls with regard to type of construction, whether wood or other, of the house where they lived prior to onset of their disease. This comparison appears in Table 26. Statistical values estimated for each of the four age groups, as well as for all ages combined, gave no hint of association between Hodgkin's disease and type of construction. In fact, wood construction was reported more often by controls than by cases. However, in no instance was the proportional difference between the two groups statistically significant.

Table 27 presents results obtained by comparing cases and

TABLE 26

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY TYPE OF CONSTRUCTION OF THEIR HOUSE

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Wood construction	7	7	1.00	---
Other types	1	1		
15 - 34				
Wood construction	23	31	0.55	P> .15
Other types	27	20		
35 - 49				
Wood construction	10	12	0. 67	P> .20
Other types	15	12		
50+				
Wood construction	35	37	0.80	P> .20
Other types	26	22		
All ages, 15 years and over[a]				
Wood construction	68	80	0.67	P> .20
Other types	68	54		

[a]Additive χ^2 with 3 degrees of freedom.

TABLE 27

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY LOCATION OF THEIR HOUSE

AGE GROUPS AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Farm, or outside city limits	1	2	0.42	P> .20
Within city limits	7	6		
15 - 34				
Farm, or outside city limits	11	10	1.15	P> .20
Within city limits	39	41		
35 - 49				
Farm, or outside city limits	5	4	1.25	P> .20
Within city limits	20	20		
50+				
Farm, or outside city limits	21	7	3.90	P< .01
Within city limits	40	52		
All ages, 15 years and over[a]				
Farm, or outside city limits	37	21	2.01	P< .05
Within city limits	99	113		

[a]Additive χ^2 with 3 degrees of freedom.

controls respecting the location of the house where they lived at the time of illness onset. Patients were divided into two categories, namely those residing on a farm, ranch, or outside city limits, and those living in urban areas, within city limits. No remarkable differences were observed between cases and controls, in relation to place of residence, in the first three age groups. In the age group 50 years and over, there were 21 cases and 7 controls who lived on a farm or outside city limits at the time their illness made its appearance. Index and control cases differed by a proportion of 23%, a difference which was statistically significant at the .01 level. Also, it was noted that patients who lived on farms or outside city limits experienced a relative risk of Hodgkin's disease nearly four times as high as the risk for patients who lived within city limits. The comparison of all patients over 15 years of age demonstrated that there were 37 Hodgkin's disease cases, and 21 controls, who lived on a farm or outside city limits at the time their illness began. The proportional difference between the two groups was 12%. This difference was statistically significant at the .05 level. Furthermore, the relative risk value for all ages was 2.01; this value suggested an appreciably higher risk of Hodgkin's disease for rural residents.

Occupation and Hodgkin's Disease

The classification used in the present study for recording occupation of the patients was described in Chapter III. In the comparison of cases and controls, occupational categories were combined according to their similarity in the type of tasks involved. Table 28 shows the distribution of index and control cases with respect to pro-

TABLE 28

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY PROFESSIONAL AND MANAGERIAL OCCUPATION

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Professional and managerial	0	0	0.00	---
Other occupations	0	0		
15 - 34				
Professional and managerial	21	8	3.89	P< .01
Other occupations	29	43		
35 - 49				
Professional and managerial	8	7	1.14	P> .20
Other occupations	17	17		
50+				
Professional and managerial	15	17	0.80	P> .20
Other occupations	46	42		
All ages, 15 years and over[a]				
Professional and managerial	44	32	1.52	P> .20
Other occupations	92	102		

[a]Additive Chi ($\sqrt{\chi^2}$)-test to account for results in opposite directions.

fessional and managerial occupation. The largest number of professional and managerial workers among the Hodgkin's disease patients was observed in the age group 15 to 34 years. Within the managerial category, the single group with the major number of patients was the clerical group. Table 28 indicates that 21 cases and 8 controls reported their occupation as professional or managerial in the age group 15 to 34. This represented a proportional difference between index and control cases of 27%, which was statistically significant at the .01 level. Moreover, the relative risk for those in professional or managerial occupations in the age group 15 to 34, was nearly four times as high as the risk of Hodgkin's disease in other occupational groups.

It was of interest to observe that neither in the age group 35 to 49, nor in the group 50 years and over, was there any significant difference between cases and controls in the proportion of professional and managerial workers. Nor was a significant difference found between cases and controls when all ages were compared. However, at all ages, professional and managerial workers did show a moderately increased risk of Hodgkin's disease.

Table 29 presents the findings obtained when comparing cases and controls in regard to non-managerial, artisan, and "other" occupations. It is readily seen that both groups were similar in the proportion of patients reporting any of these occupations.

The comparison of index and control cases in relation to number of farmers and oil field workers in each group, is given in Table 30. In the age group 15 to 34, the risk of Hodgkin's disease in farmers and oil field workers was considerably increased. However,

TABLE 29

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY NON-MANAGERIAL, ARTISAN, AND "OTHER"[a] OCCUPATION

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Non-managerial, artisan, "other"	0	0	0.00	---
Other occupations	0	0		
15 - 34				
Non-managerial, artisan, "other"	11	17	0.56	P> .20
Other occupations	39	34		
35 - 49				
Non-managerial, artisan, "other"	11	11	0.93	P> .20
Other occupations	14	13		
50+				
Non-managerial, artisan, "other"	15	16	0.88	P> .20
Other occupations	46	43		
All ages, 15 years and over[b]				
Non-managerial, artisan, "other"	37	44	0.76	P> .20
Other occupations	99	90		

[a]Military, civil service, nurses aid, caretakers, waitresses, cooks, tailors.

[b]Additive χ^2 with 3 degrees of freedom.

TABLE 30

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY FARMING, AND OIL-FIELD OCCUPATION

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Farmers and oil-field workers	0	0	0.00	---
Other occupations	0	0		
15 - 34				
Farmers and oil-field workers	2	1	2.08	P> .20
Other occupations	48	50		
35 - 49				
Farmers and oil-field workers	4	3	1.33	P> .20
Other occupations	21	21		
50+				
Farmers and oil-field workers	17	6	3.41	P< .05
Other occupations	44	53		
All ages, 15 years and over[a]				
Farmers and oil-field workers	23	10	2.52	P< .10
Other occupations	113	124		

[a]Additive χ^2 with 3 degrees of freedom.

these results might be influenced by the small size of the numbers in each one of the upper cells. A very small proportional difference (3%) was observed between cases and controls in this age group, which was not statistically significant. Similarly, no particular differences in regard to farming or oil field working were noted between cases and controls, in the age group 35 to 49 years. In contrast, there were 17 cases and 6 controls who reported these occupations in the age group 50 years and over. That represented a 17% difference in the proportion of farmers or oil field workers in both groups. This difference was statistically significant at the .05 level. A relative risk of Hodgkin's disease over three times higher for farmers and oil field workers than for individuals in other occupations was observed in the 50 years and over group. Such relative risk was still very high when cases and controls, all ages combined, were compared. Furthermore, the difference in the proportion of farmers and oil field workers in both groups was statistically significant when all ages were considered.

Table 31 demonstrates that there were more non-working patients in the control than in the index group. This was true for each age group separately, as well as for all ages combined. The reason for this difference between cases and controls is not clear. Looking at relative risk values it would appear that not-working individuals had a better chance of escaping Hodgkin's disease than working people. Yet, the difference between cases and controls with respect to the proportion of not-working patients was not significant in any of the age groups; although it came close to significance in the age group 15 to 34 years. The implications in these results are not clear.

TABLE 31

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS.
NON-WORKERS AT THE TIME OF ILLNESS ONSET

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Not working	8	8	0.00	---
Working	0	0		
15 - 34				
Not working	16	25	0.50	P< .15
Working	34	26		
35 - 49				
Not working	2	3	0.60	P> .20
Working	23	21		
50+				
Not working	14	20	0.58	P> .20
Working	47	39		
All ages, 15 years and over[a]				
Not working	32	48	0.55	P> .15
Working	104	86		

[a]Additive χ^2 with 3 degrees of freedom.

Smoking and Hodgkin's Disease

Cigarette smoking has been found to be associated with several diseases. An attempt to explore possible relationships between smoking and Hodgkin's disease was made in the present study. Cases and controls were compared as to smoking history of one or more packs of cigarettes per day, prior to onset of their illness. The distribution of the 144 Hodgkin's disease cases and their 142 matched controls, according to smoking habits, is shown in Table 32. The most remarkable feature appearing in the table is the consistent minority of smokers in the case group, as compared with the control group. In the age group 15 to 34 years there were 11 smokers among the cases, and 24 smokers among the controls. The difference in the proportion of smokers between the two groups was 25%, which was statistically significant at the .02 level. The observed relative risk value (0.32) appeared to indicate that smokers were in appreciably less danger of contracting Hodgkin's disease than non-smokers. Differences in the proportion of smokers among cases and controls were not significant in the age groups 35 to 49 and 50 years and over. Nevertheless, the relative risk values were considerably decreased in both age groups.

Comparison of all age groups combined showed 37 smokers among the cases, and 59 smokers among the controls. There was a 17% difference in the proportion of smokers between both groups. This difference was statistically significant at the .02 level. The relative risk value for all ages was 0.47, again suggesting that the hazard of Hodgkin's disease was less for smokers than for non-smokers.

TABLE 32

HODGKIN'S DISEASE IN OKLAHOMA CITY HOSPITALS, 1965-1970.
COMPARISON OF 144 CASES AND 142 CONTROLS,
BY CIGARETTE SMOKING HABITS PRIOR TO ILLNESS ONSET

AGE GROUP AND ATTRIBUTE COMPARED	CASES	CONTROLS	RELATIVE RISK	P VALUE
0 - 14				
Smokers of 1 pk./day, or more	0	0	0.00	---
Non-smokers	8	8		
15 - 34				
Smokers of 1 pk./day, or more	11	24	0.32	P< .02
Non-smokers	39	27		
35 - 49				
Smokers of 1 pk./day, or more	10	15	0.40	P> .15
Non-smokers	15	9		
50+				
Smokers of 1 pk./day, or more	16	20	0.69	P> .20
Non-smokers	45	39		
All ages, 15 years and over[a]				
Smokers of 1 pk./day, or more	37	59	0.47	P< .02
Non-smokers	99	75		

[a]Additive χ^2 with 3 degrees of freedom.

CHAPTER VI

DISCUSSION

The third and fourth objectives of the present study were corollaries of the first two. Its third purpose was to search for additional evidence supporting the hypothesis that Hodgkin's disease may encompass two or more etiologically distinct entities with different age distributions. Further, this study contemplated the possibility of using obtained information for formulating hypotheses regarding the etiology of Hodgkin's disease. With these objectives in mind, a discussion of the results described in Chapters IV and V is presented below.

The Descriptive Study

It was previously mentioned that this study dealt with Hodgkin's disease cases admitted to nine Oklahoma City hospitals. Consequently, it was not expected to include all cases occurring throughout the state of Oklahoma. It is believed, however, that the sample obtained was of reasonable size, quite definable, and fairly representative of the Hodgkin's disease population. It is recognized that this study, like any epidemiological study of this nature, faced many hazards with respect to the accuracy of the data. Retrieval of records by all hospitals may not have been complete. Attending physicians may

have misrecorded medical information concerning their patients. Much of the data gathered from medical records depend upon the memory and reliability of the informant. Completeness of data is a serious problem in all epidemiological studies based on medical records. An attempt to cope with this problem was made in this investigation by obtaining additional information through questionnaires.

Efforts were made to minimize as much as possible the introduction of bias in this study, and no gross evidence was detected of extraneous factors that could seriously jeopardize the validity of the results. However, the author recognizes that there are many potential sources of error upon which the findings could be impugned, and which demand for caution in drawing definite conclusions.

The value of descriptive epidemiologic studies in tracking down the various pathways through which a disease may reach human populations is well established. The description of how a disease manifests itself, and when, where, and who, are affected, is usually an essential step to be taken upon which more definitive studies can be designed in an attempt to discover the true nature of the illness. Hodgkin's disease has not been exempted to the use of this methodology, and in recent years much insight into its epidemiology has been gained. The descriptive phase of the present study attempted to add to the knowledge already acquired, by studying epidemiological features of Hodgkin's disease in Oklahoma City hospitals, and looking for agreement or disagreement with findings of other investigators.

A feature of Hodgkin's disease that has greatly aroused the curiosity of epidemiologists, is the bimodality of its age incidence

curve, first described by MacMahon, in 1957, and subsequently confirmed by other researchers (Meighan, 1961; Meytes and Modan, 1969; Uhl and Hunstein, 1969; Talerman, 1970). As stated in Chapter IV, the bimodal age distribution of Hodgkin's disease was quite evident in the present study. The highest concentrations of cases occurred at ages 15 to 34, and 50 years and over. The disease was very rare in early childhood, and also had a low incidence for the ages 35 to 49 years. Interestingly, a sharp increase in the number of cases took place from around age 9 up to age 24; only one case was found before age 5.

The cause of the abrupt rise in Hodgkin's disease cases starting in mid-childhood is obscure. Exposure to particular environmental agents at this age, or changes in host susceptibility, have been proposed as possible explanations (Miller, 1966). Reference was made earlier to the high prominence of the first age peak observed in this study, indicating an over-concentration of cases in the age group 15 to 24 years. Figure 2 shows that the peak was significantly less marked in the second mode, and it extended for a longer age period than it did in the first mode. It would be interesting to find out if the same age features appear in a large scale incidence study in the state of Oklahoma. In incidence surveys in the United States it has been consistently found that the second mode is larger than the first. Only in Denmark have the two modes appeared about equal in prominence, while in Japan the first mode is practically absent (MacMahon, 1966; Nishiyama and Inoue, 1970). The age distribution curve observed in this study supports the concept of dual etiology in Hodgkin's disease. It could be that the illness is of an infectious nature in the younger

ages, while it is a chronic neoplastic process in older people.

Results concerning sex and race distribution of Hodgkin's disease were also in close agreement with findings of other workers (Aisenberg, 1964; MacMahon, 1966; Uhl and Hunstein, 1969; Fraumeni and Li, 1969). The overall observation was a great preponderance of males as compared with females. However, interesting variations were present in the various age groups. The absence of female cases up to age 9 years was conspicuous. From age 9 to 24 years there were more females than males. After age 25, the number of females showed a sharp decline, while males maintained a relatively high level up to age 34. The reasons behind these male-female differences in the younger group are disputable. It could be that females look for diagnosis earlier than males (Jelliffe and Thomson, 1955), or that males age 9 to 24 were under-represented in this study. However, the possibility exists also of an environmental disease-inciting factor, with which both sexes could come in contact during their first two decades of life. Perhaps the differences in the way both sexes are affected by such factor, and the larger number of females involved between ages 9 and 24, depend upon age-sex dissimilarities in the potential to combat infection, physiological make up, physical or recreational activities, social interests, occupation, or diverse habits of life.

A point of great interest is also the high male to female ratio in the age groups 35 to 49 and 50 years and over, contrasting with a sex ratio of 1:1 observed in the age group 15 to 34. Looking at the second mode in Figure 2, one receives the impression that a new disease starts around age 35, in which more males than females are in-

volved, and which follows a prolonged course throughout older ages, particularly in females.

The frequency of Hodgkin's disease cases among Negroes was significantly low in the present study. Why Negroes appear to be spared by this illness is a question still awaiting an answer which could give better insight into factors involved in the causation of the disease. Rates for Negroes are closer to rates for whites in the older than in the younger groups (MacMahon, 1966). If the dual infectio-neoplastic concept of Hodgkin's disease were to be relied upon, it could be hypothesized that in the younger ages, Negroes due to socio-economic, or other reasons, may be less exposed than whites to particular environments which host the infectious agent. It may be, also, that prolonged exposure to a specific infectious agent, and long-lasting subclinical infection, make the immunologic potential higher in Negroes than in whites. In the older groups, on the other hand, it may be that the opportunities of exposure to a carcinogen are about equal for both races. Properly designed epidemiological studies are needed to test these hypotheses.

Clinical features of Hodgkin's disease as observed in the present investigation were largely compatible with findings by other workers (Peters, 1966; Eason, 1966; Keller et al., 1968; Bogardus, 1969; Strum et al., 1970; Gough, 1970). Manifestations of the illness were much less severe in the age groups 0 to 14, and 15 to 34 years, than in the older groups.

The four age groups studied were quite peculiar in regard to clinical stage at diagnosis. Stages I and II were common in the age

groups 0 to 14 and 15 to 34 years, decreasing at older ages. A reverse trend was observed for the most advanced stage of the disease, stage IV. A glance at Figure 3 will show that if stages I and II were combined, and compared with stages III and IV combined, the age curves would cross. While the curve for stages I and II would show a high peak in the 15 to 34 age period, decreasing thereafter, the age curve for stages III and IV will increase from a low peak in the younger groups, to a highly prominent peak in the group 50 years and over. These findings suggest that two diseases with different courses are being intermixed.

Complementary to the previous observation was the finding that histological types with apparently better prognosis (Lukes, 1964; Gough, 1970; Chawla et al., 1970; Henry, 1970) were more common in the 0 to 14, and 15 to 34 age groups, than in the older groups. An interesting triple correlation was detected in this study, among age (under 35), histologic type (lymphocytic predominance and nodular sclerosis), and the less advanced stages (I and II) of Hodgkin's disease. Also, even though this investigation was not designed to study survival, a look at Tables 3 and 15 suggests that the major proportion of survivors are among younger patients, and among patients with disease of the lymphocytic predominance and nodular sclerosis types. The author is aware of the various potential sources of error, and of the different ways that these findings could be interpreted. Yet, variations in clinico-epidemiologic features of Hodgkin's disease among the four age groups, were sufficiently noticeable in this study, not to be ascribed to simple chance or error. Rather, they are strongly suggestive of the

heterogeneity of the illness.

Associations of Hodgkin's disease with season, if existent, are not clear. High mortality rates were observed by Fraumeni and Li (1969) among children born during summer months. Bjelke (1969) did not find any association between the distribution of the disease and month of birth. The study in Oklahoma City hospitals demonstrated a relationship between Hodgkin's disease and birth during fall and winter, only for the age group 15 to 34, and possibly for the group 0 to 14 years of age. As to season of onset, results of this study, in part, were in harmony with those obtained by others (Cridland, 1961; Innes and Newall, 1961; Uhl and Hunstein, 1969). Higher frequency of illness onset during fall and winter occurred in the age groups 15 to 34, and 50 years and over. The present findings did not agree with those of Fraumeni and Li (1969), who observed higher onset of childhood Hodgkin's disease during winter months. A reason for such disagreement could be the small number of childhood cases in the present survey.

Two subjects for speculation are apparent in the seasonal trends observed in this study. First, why Hodgkin's disease onset in the age group 35 to 49 was higher during spring and summer months. Second, why the two age groups 15 to 34 and 50 years and over, which for most variables have occupied opposite ends of the spectrum, showed similar trends in regard to season of onset of the disease. It could be postulated that these observations merely reflect random variability, or the lack of representativeness of this Hodgkin's disease sample. However, it could also be hypothesized that the age group 35 to 49 constitutes the meeting-point for two illnesses of different origin

and courses. Higher onset of the illness during fall and winter in the age group 15 to 34, might be due to particular infectious agents present in the environment during colder months. The apparent higher onset of the disease during colder months in the age group 50 years and over, on the other hand, could be the effect of older age and its sequelae. Older people might be more prone to develop different kinds of disorders leading them to look for medical consultation during winter months. In this instance, Hodgkin's disease could be taken as the main cause of the complaints, when in reality it might have been latent for a long time. Akin with this type of thinking is the fact that, in the present study, several cases were observed in old people who experienced the "first symptoms of Hodgkin's disease" together with some other illness, or immediately following an injury. Surprisingly, some old patients died only a few weeks after their first hospitalization, and autopsy revealed an extensively disseminated stage IV Hodgkin's disease.

The descriptive study did not reveal any clues suggestive of associations between Hodgkin's disease and socio-economic class. However, the proportion of patients who completed high school, college, or professional careers, was higher in the 15 to 34 age group than in the older ages. These findings are of interest, and harmonize with observations by Cohen et al. (1964). Possible inter-relationships between Hodgkin's disease and educational, or socio-economic background of the individual may be a topic that warrants further study and confirmation.

This study did not suggest any connection between Hodgkin's

disease and particular occupations, as reported by others (Milham and Hesser, 1967). However, professional and managerial workers were represented in higher proportion in the age group 15 to 34, than in the other age groups. Conversely, a larger proportion of non-managerial, artisan, and "other" workers was observed in the group 35 to 49. As in the case of educational background of the patients, it is felt that these results merit further study and discussion. If a consistent association between Hodgkin's disease and professional or managerial occupations were observed solely for the 15 to 34 age group, it might constitute a valuable clue to be utilized for building new hypotheses concerning distinct etiologies in the younger and the older groups, depending upon their degree of exposure to selected environmental factors.

The occurrence of Hodgkin's disease in close relatives has been well documented (DeVore and Doan, 1957; Razis et al., 1959; Rigby et al., 1966; Smithers, 1967; Fraumeni and Li, 1969). Opinions as to what could be the cause of such family concentration of the disease are conflicting. Some have proposed a possible genetic or hereditary mechanism, but most workers prefer to think about potential environmental factors involved. Detailed description of 15 instances in which familial occurrence of Hodgkin's disease was observed in this study was presented earlier. Interestingly, there were 6 cases in which father, mother, or son were affected. In the rest of the cases the disease made its appearance in uncles, cousins, or nephews of the proband, what seems to point more to environmental, than to genetic or hereditary factors. Perhaps properly designed case-control studies are needed to

confirm the validity of these observations.

Although the numbers are too small to draw valid conclusions, it is interesting to observe that the number of Hodgkin's disease cases with affected relatives followed a bimodal pattern, more probands being observed in the 15 to 34, and 50 years and over groups, than in the other two age groups. Yet, such bimodal distribution was not present in the affected relatives. If Hodgkin's disease were a single entity having a bimodal age distribution, one would expect this bimodality to appear both in probands and relatives. Conversely, the presence of age bimodality in the probands, and its absence in the relatives, might suggest that two different diseases are present, one acting in the younger, and the other in the older groups.

A further point of interest was the mean length of time elapsed between onset of the disease in the proband, and its onset in the relatives, in the four age groups. An appreciable contrast existed between an average length of 11 and 10 years in the age groups 0 to 14, and 15 to 34, and a length of 13 and 21 years in the 35 to 49, and 50 years and over groups. Again, these findings may suggest that two diseases with different incubation periods are operating in younger and older people. Future research might give the appropriate answer to these speculations.

The Case-Control Study

A case-control study is a valuable epidemiologic tool for exploring possible etiologic determinants of a disease. Review of the literature did not reveal any instance in the past, in which this methodology has been used in the study of Hodgkin's disease. The utili-

zation of such a technique was attempted in the present investigation. Cases and controls were compared, by age groups, in relation to selected variables. The priority given to the selected attributes depended, partly, upon observations in descriptive studies by other researchers, and partly, upon suggestions obtained in phase one of the present investigation. A detailed description of the results obtained in the case-control study was presented in Chapter V. Comments made earlier in regard to potential sources of error in the descriptive data, are applicable to findings obtained when comparing cases and controls. However, efforts were made to minimize, as much as possible, the introduction of bias. With the exception of tonsillectomy and appendectomy, and possibly allergies, all variables selected for comparison were those which, by themselves, did not appear to increase the probability of hospitalizing an individual. The logic behind this procedure was the willingness to avoid the detection of spurious relationships between Hodgkin's disease and particular variables. Such danger has been long recognized in case-control studies of hospital patients (Berkson, 1946).

The total group of cases and controls was necessarily eroded by the loss of patients. However, the response percentage was considerably high from both groups. A look at Table 17 would indicate that the total number of index and control cases, 144 and 142 respectively, was close to the size expected, and therefore, suitable for comparison under the pre-established conditions of the study.

The significant discrepancy between cases and controls with regard to season of birth in the age group 15 to 34 years, and the

highly increased risk of Hodgkin's disease for those born during fall and winter, poses an interesting question. The fact that the difference was not significant, and the relative risk was appreciably lower in the age group 50 years and over, enhances the suspicions concerning the nature of Hodgkin's disease in both age groups. In view of these data, the idea of an environmental agent, active during certain months, and operating during the fetal or neonatal period (Fraumeni and Li, 1969), looks attractive. If such agent exists, it would still be necessary to decide how it reaches its host, how long the incubation period is, whether there are any susceptibility patterns determining the responses of the host, or other contributing factors that trigger the onset of the disease. The last and most important question concerns the nature of the agent itself. Differences observed in this study among the four age groups with respect to season of birth, deserve further exploration in future case-control studies.

Differences between cases and controls with respect to season of onset of their illness were not significant. Yet, the moderately higher risk of illness onset during fall and winter for the 15 to 34 and 50 years and over groups agreed with findings of other investigators (Cridland, 1961; Innes and Newall, 1961). One wonders if the increased risks may not be due to different reasons in both age groups. As was discussed earlier, the idea that readily comes to mind is that in the younger group, such elevated risk of illness onset during the colder months could be etiologically related, while in the elderly it could be simply a reflection of the cumulative effects of age. The transition period from "one type" of Hodgkin's disease in the younger group, to

the "other type" of illness in the elderly, could be implicit in the significantly decreased risk of illness onset during the colder months, observed in the age group 35 to 49.

This investigation detected a remarkable difference between Hodgkin's disease cases and their matched controls in regard to presence or absence of appendectomy and/or tonsillectomy, prior to onset of their disease. Similar findings have been reported by other investigators (Bierman, 1968; Vianna et al.; 1971c). What most excites the curiosity in the present findings are the variations noted among the four age groups. A highly significant difference between index and control cases with respect to lymphoid tissue operations was present in the age group 15 to 34. The striking dissimilarity was reflected in a threefold increased relative risk value. Contrariwise, in the age group 50 years and over, the divergence between cases and controls was not statistically significant. Bridging the gap between the two age groups was the age category 35 to 49 years, in which the contrast between index and control cases was less marked than in the younger group, but more pronounced than in the older ages. These results are indicative of a possible association between Hodgkin's disease and tonsillectomy and/or appendectomy, particularly during early and middle adulthood. The nature of such an association constitutes a fertile field for hypotheses and research. Epidemiologists, virologists, immunologists, and other medical sciences personnel working together, perhaps could find an answer as to what defensive role do tonsils and/or appendix play against Hodgkin's disease inciting factors.

The exploratory nature of this study led to a comparison of

cases and controls with respect to history of accidental injuries and allergies. A great similarity was observed between the two groups in regard to presence of injuries before illness onset. In the case of allergies, the almost statistically significant difference between cases and controls in the age group 0 to 14 years, and the high relative risk of Hodgkin's disease in those with allergy history, suggest the need for further investigation in this area, with a larger number of cases.

Cases and controls were significantly disparate with respect to allergy history in the age group 50 years and over. The possibility of an association between allergies and Hodgkin's disease in the older groups should not be excluded, and merits further exploration. Mention was made in Chapter IV, of an instance found in this study, in which the proband and three relatives affected with Hodgkin's disease registered a long allergy history. Furthermore, such history extended to other members of their family. All the disease-affected individuals were over age 50 (age was not available for one case) when Hodgkin's disease appeared. This is only one family and, obviously, it could be an exception. It might happen, however, that more of these "exceptions" could be brought into the open in future case-control studies.

A further point for comment is the fact that no disparity between cases and controls was observed in the age groups 15 to 34 and 35 to 49 in regard to allergy history. The tendency, repeatedly observed in this study, for the younger and older groups to run in opposite directions, was again manifested in this instance. Such a tendency is suggestive of the heterogeneous nature of Hodgkin's disease.

Comparison of cases and controls in the four age groups, as to their exposure to chemical substances before illness onset, did not produce any major differences. Results of this study, therefore, do not support an association between Hodgkin's disease and chemical exposure.

The most striking discrepancies between the 15 to 34 age group and the group 50 years and over appeared when comparing cases and controls with respect to some environment-related variables. Index and control cases in the age category 15 to 34 years, showed a highly significant difference in regard to history of contact with animals. Such a difference was not significant in the 50 years and over group. Relative risk values were also markedly discrepant for both age groups, being highly increased in the younger group, and only moderately elevated in the older ages. Results from comparing cases and controls in the age group 0 to 14, tended to approximate those in the 15 to 34 age category, while findings in the group 35 to 49 resembled more closely those in the older ages. Disparities between the younger and the older groups followed almost identical patterns to those just explained, when cases and controls were compared as to practice of hobbies away from home.

Findings in this study concerning regular contact with animals, and regular practice of outdoor activities, are certainly interesting. In first place, they offer strong support to the hypothesis that Hodgkin's disease might be a combination of two etiologically distinct entities, one acting in the younger ages, and the other in older groups. Secondly, these results provide solid suggestions of possible

involvement of infectious agents in the genesis and development of Hodgkin's disease in younger people. Perhaps this is valuable preliminary information which could be utilized in formulating and testing specific hypotheses regarding environmental exposure, and subsequent development of the illness. It seems appropriate to emphasize here, that the potential role of viruses in the etiology of Hodgkin's disease is a subject justifying an increase in research efforts. The implications of the findings in this study gain further strength from recent observations (Eisinger et al., 1971; Zygiert, 1971) of Hodgkin's disease cases in which viral involvement was highly suspected.

Hodgkin's disease cases in the present investigation, did not differ from their matched controls in regard to the type of construction of the house where they lived at the time of onset. However, some dissimilarities were noted between the two groups when they were compared with respect to house location at the time their disease started. Interestingly, a highly significant discrepancy between index and control cases appeared only in the age group 50 years and over. Individuals living in farms or outside city limits, in this age group, showed a relative risk of Hodgkin's disease nearly four times higher than the risk of those living within city limits. Again, the divergence between the oldest age group, and those aged 15 to 34 is striking. In the other age groups, numbers were too small to support valid conclusions.

Various reasons could be adduced to explain disparities between the 15 to 34 and 50 years and over groups in regard to place of residence. Under-representation of farmers among the controls in the age group 50 years and over is a strong possibility. Older patients

with Hodgkin's disease in rural areas may be referred to Oklahoma City hospitals for care, while those with other illnesses are treated locally (although, when looking at Table 27, one wonders why this would not be true also for the younger groups). Observed differences might merely reflect differential mobility patterns of cases and controls. There is also the possibility of misinformation. Yet, still another reason comes to mind, in view of other findings in this study that have been previously described. It could be that farm environment plays quite distinct roles in the etiology of Hodgkin's disease in the younger and in the older groups. Temporary exposure to certain environments (not necessarily rural residence) might be sufficient in younger people to come in contact with an etiologic agent of possible infectious nature. Older individuals, although living in farm environments, could be resistant to such agent, either by acquired immunity through prolonged exposure, or by other reasons. Conversely, older people living in farm areas could be exposed to other factors inciting Hodgkin's-like diseases, to which young people are less exposed, or are not susceptible. Case-control studies dealing with each one of these age groups separately, might give a more sensitive appraisal of the validity of this type of thinking.

The contrast so often observed in this investigation between the younger and the older groups appeared again when cases and controls were compared in regard to professional and managerial occupations. Index and control cases differed significantly in the age group 15 to 34 years; such discrepancy was not evident in the 35 to 49, and 50 years and over groups. Furthermore, the relative risk of Hodgkin's

disease in the 15 to 34 age group was highly increased, but not so for the older groups. These results once more are suggestive of the heterogeneous nature of Hodgkin's disease in younger and older people. By looking at Tables 28, 29, 30, and 31, one would tend to believe that the type of occupation is not, in itself, an etiologic factor in Hodgkin's disease. Rather, it affords the individual according to his age, sex, socio-economic and educational background, personal interests, and life habits, the opportunity to come in contact with particular disease-inciting factors.

Findings in the present study indicated that Hodgkin's disease cases smoked considerably less than their matched controls. However, the disparity in the proportion of smokers among cases and controls was significant only in the age group 15 to 34 years, and for all ages combined. It is interesting to observe that negative associations have been reported also between smoking and brain tumors (Choi et al., 1970), and between smoking and cold-injury (Schuman, 1955). Yet, the validity and implications of the findings in this study are not clear. Perhaps smoking habits are associated with other behavioral patterns of the individuals affected by Hodgkin's disease. If such activities as outdoor hobbies were found to be related with the illness in younger patients, one might hypothesize that such practices serve the individual to release his tensions, thus setting aside the need for smoking. To make wise interpretations of these results is difficult; at best, they might provide starting points for more specific and sensitive research.

A synoptic consideration of the findings obtained in this

study supports the heterogeneity of Hodgkin's disease. Numbers were too small in the age group 0 to 14 to warrant any definite conclusions. Nevertheless, it was obvious that the illness exhibited great similarity in its manifestations in childhood, and in the 15 to 34 age group. Any definite statement regarding the age group 35 to 49 requires great caution. Hodgkin's disease in this age group showed certain characteristics not observed in any of its adjacent age groups, although in most instances its features greatly resembled those of the oldest group. Disparities in epidemiologic features of Hodgkin's disease in the age groups 15 to 34 and 50 years and over were pronounced. Such discrepancies were suggestive of a different disease in both age groups. Findings were also consistent with the possibility of an environmental agent, perhaps infectious, operating in the younger groups.

CHAPTER VII

SUMMARY

An epidemiologic study of Hodgkin's disease was conducted utilizing new cases admitted to nine Oklahoma City hospitals from January 1, 1965, through December 31, 1970. The study was developed in two phases: First, a descriptive analysis of 181 patients whose hospital records were abstracted, and second, a retrospective study in which 144 Hodgkin's disease cases were compared with 142 matched controls.

The study was developed around four objectives, the main one being the search for possible relationships between Hodgkin's disease and particular disease-inciting factors, in each of the age groups 0 to 14, 15 to 34, 35 to 49, and 50 years and over.

The main findings of this study were as follows:

1. Descriptive features of Hodgkin's disease were largely compatible with those reported by other investigators in the United States, as well as in other areas of the world. The most salient characteristics of the illness were, the bimodality of its age distribution curve, and its contrasting clinico-pathologic features in the younger and the older groups.
2. A significant association between Hodgkin's disease and

season of birth, with a high risk of the disease for those born during fall and winter months, was observed only in the age group 15 to 34.

3. A significant relationship between appendectomy and/or tonsillectomy and Hodgkin's disease was observed in the age groups 15 to 34 and 35 to 49. This relationship was not significant in the oldest group. On the other hand, a significant association of Hodgkin's disease with allergies was observed only in the group 50 years and over.
4. Contact with animals, and the practice of outdoor activities, were strongly associated with Hodgkin's disease in the age group 15 to 34. This relationship was not significant in the two older age groups. These findings may support the infectious (perhaps viral) hypothesis for the younger ages.
5. Hodgkin's disease showed a significant association with professional and managerial occupations in the age group 15 to 34. This association was not significant in the other age categories. Conversely, a significant relationship of the illness with farm work was observed only in the age group 50 years and over. The possible implications of these findings were discussed.
6. Residence in farm areas or outside city limits was found to be significantly associated with Hodgkin's disease only in the age group 50 years and over.

7. Cigarette smoking was observed to be less common among Hodgkin's disease cases than among their matched controls.
8. An almost consistent discrepancy between the younger and the older groups, particularly between the age group 15 to 34 and 50 years and over, was evident in this study. Epidemiological features of Hodgkin's disease in the age group 0 to 14 years, were quite similar to those in the age group 15 to 34, while the age category 35 to 49 simulated more closely the 50 years and over group. However, no definite conclusions can be made about the age groups 0 to 14 and 35 to 49, due to the small number of cases.

Results of this study support the conclusion that Hodgkin's disease may encompass at least two etiologically distinct entities, one operative in the age group 0 to 35 years, and the other in the group 50 years and over. The age group 35 to 49 might serve as the meeting point for these two illnesses. Environmental factors, possibly of infectious nature, are suspected as being involved in the causation of the illness in the younger ages. However, much research is still needed for elucidating these suspicions, and for tracking down essential sequences of events that might lead an individual to an encounter with the etiologic agent. It is hoped that findings in this study may provide starting points for such research.

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APPENDIXES

APPENDIX A

LETTER TO HOSPITAL ADMINISTRATORS

The University of Oklahoma Medical Center
School of Health
Department of Biostatistics
and Epidemiology

November 11, 1970

Mr.
Hospital
Address

Dear Sir:

Mr. Francisco Serrano is a Ph.D. student in the Department of Biostatistics and Epidemiology, School of Health, at the University of Oklahoma Medical Center, who is interested in pursuing a research project in Hodgkin's disease. He has given me your name as one who he has contacted, and I would like to take this opportunity to express my appreciation for your cooperation and explain Mr. Serrano's situation.

He has proposed an investigation of Hodgkin's disease utilizing the Oklahoma City hospitals to identify the cases. He is submitting a protocol to his Advisory Committee which consists of members from this department as well as a physician from the Veterans Hospital, and a physician from the Oklahoma Research Foundation. Upon approval by this committee, Mr. Serrano will be able to start gathering his data. At that time, and if you wish, I believe it would be appropriate for Mr. Serrano and I to discuss any aspects of his research with you.

He has received permission from nine hospitals to use their records to obtain the needed data on the cases with Hodgkin's disease, one of which was your hospital. In order to carry out these needed epidemiologic studies it is necessary to be able to use the hospital records, and I appreciate your cooperation in this matter. I would like to reassure you that the data will be used for statistical purposes only, that we are aware that we must work through the physician

APPENDIX A -- Continued

LETTER TO HOSPITAL ADMINISTRATORS

if the study requires contacting the patient, and that we hope to inconvenience you or your staff as little as possible. Thus, we would be delighted to discuss these areas and others with which you have concern, in order that you may be assured that we understand the problems involved, and will follow the most appropriate course of action.

Thank you again for your cooperation, and if you have any questions regarding this matter please do not hesitate to call me. My telephone number is 236-1366, Extension 138.

I look forward to meeting you in the near future.

Sincerely,

Dr. Paul S. Anderson, Jr.
Professor and Chairman
Department of Biostatistics
and Epidemiology

PSA/mm

APPENDIX B

LETTER TO ATTENDING PHYSICIANS

The University of Oklahoma Medical Center
School of Health
Department of Biostatistics
and Epidemiology

November__, 1970

Dr.
Address

Dear Dr.

In recent years much concern has been expressed regarding the possible etiology of Hodgkin's disease. Two main currents of thinking have developed: one, advocating the purely neoplastic nature of the disease, the other, suggesting an infectious process.

The Department of Biostatistics and Epidemiology of the University of Oklahoma Medical Center is sponsoring a case-control study of Hodgkin's disease in Oklahoma City hospitals. The main purpose of the study is to look for additional clues concerning the etiology of Hodgkin's disease. All histologically confirmed cases admitted to Oklahoma City hospitals over the period January 1, 1965, through December 31, 1970, are included in the study.

The Hodgkin's disease cases (180), and their controls, have been already identified from hospital records. As you well know, the information gathered from medical records is not sufficient for this type of study; therefore, it is imperative to collect additional data by other means. A letter and questionnaire (copies of which are enclosed) will be sent to each Hodgkin's disease patient, and to each control. You will note that there is no mention of the disease under study, and both, cases and controls, receive the same letter.

APPENDIX B -- Continued

LETTER TO ATTENDING PHYSICIANS

Our records indicate that you were the attending physician of some of the patients that we are using in our study. Enclosed please find a list in duplicate of your patients. We will greatly appreciate that, if you have no objection, you sign one copy and mail it back to us as soon as you have a free moment. Since our sample is relatively small your cooperation and permission to approach all your patients through this questionnaire will be most helpful. The information gathered on each patient will be treated as strictly confidential, and will be used for research only.

This study is being supervised by Dr. Paul S. Anderson, Jr., Chairman of the Department of Biostatistics and Epidemiology, Dr. Paul T. Condit, Head of the Cancer Section, Oklahoma Medical Research Foundation, Dr. Robert D. Lindeman, Director of the Renal Section, Veterans Administration Hospital, and Drs. Nabih R. Assal, Katherine B. Sohler, and Stanley Silberg, of the Department of Biostatistics and Epidemiology, at the University of Oklahoma Medical Center.

Thank you again for your cooperation, and if you have any questions please do not hesitate to call me, or any of the aforementioned study committee members. The telephone number to call is 236-1366, Extension 138.

Sincerely,

Francisco Serrano

Dr. Paul S. Anderson, Jr.
Professor and Chairman
Department of Biostatistics
and Epidemiology

FS/mm

Enclosure:

APPENDIX C

LETTER TO PATIENTS

The University of Oklahoma Medical Center
School of Health
Department of Biostatistics
and Epidemiology

November___, 1970

Name
Address

Dear

We are writing from the University of Oklahoma Medical Center. As you well know, the University of Oklahoma Medical Center is continuously doing research on different diseases. The only purpose of this research is to try to understand the nature of such diseases, so that better help and service can be offered to suffering people. Through this letter we are asking you a favor. We will very much appreciate it if you will help us in one of our studies by simply filling out the enclosed questionnaire. Your help is very important for the success of our study.

On top of the first page of the questionnaire you will find the name of a patient, and a date when he was hospitalized in one of the Oklahoma City hospitals. The patient named in the questionnaire (yourself, or a relative or friend of yours) has been selected for participation in our study. The purpose of this study is to look for different factors that may contribute to the occurrence of disease. Once those factors are discovered it will be much easier to prevent disease, or to offer better help to patients. We will appreciate it very much if you will fill out the questionnaire for us. The doctor who was an attending physician of the patient named in the questionnaire is aware of our study, and has granted us permission to send

APPENDIX C -- Continued

LETTER TO PATIENTS

this questionnaire to you.

We know that you are most willing to cooperate with us in the fight against disease, and will give us the information we need. If you do not have the exact answer to a question, or do not remember exact dates, please write your best estimate. If for any reason you are not able to fill out the questionnaire by yourself, please ask a relative or friend of yours to help you in filling it out. Your reply will be held strictly confidential and will be used for research purposes only. The identity of persons will not be disclosed for any purpose. This will be the only help that we will need from you for our study.

Since our study uses a very small number of cases your answer to the questionnaire is most essential. Even if you do not have the exact answer to every question please give your best estimate, and try to mail the completed questionnaire within five days in the enclosed self-addressed envelope which requires no stamps. Just drop it in a mail box.

Your cooperation and prompt attention to this request will be greatly appreciated, and you can be sure that the few minutes you will take for filling out this questionnaire will contribute very much to the search for a happier and healthier life for yourself, your relatives, or your fellow human beings.

Thank you again for your cooperation, and if you have any questions please do not hesitate to call us. The telephone number to call is 236-1366, Extension 138, Oklahoma City.

Sincerely,

Francisco Serrano

Dr. Paul S. Anderson, Jr.
Professor and Chairman
Department of Biostatistics
and Epidemiology

FS/mm

Enclosure:

APPENDIX D

HOSPITAL RECORD FORM

HOSPITAL	Case #	NAME OF PATIENT	
Patient's Condition Alive | Dead	Address at Onset		County
Race | Sex	Present Address		County
Date of Birth (Age)			
Date of Admission	Nearest Relative		
Date of onset	Attending Physician		
Date of Diagnosis	Referred By		
Date of Death			

CLINICAL INFORMATION

Main Symptoms at Onset	Major Past Infections	Fungal Diseases	
		Allergies	
Main Symptoms at Diagnosis	Surgeries	Injuries	
Mouth or Nose Disorders Before Onset	Sick Persons (or Animals) in Household	Stage-Histol. Type	
		Biopsy	Autopsy

APPENDIX D -- Continued

FAMILIAL INFORMATION

Name	Sex	Age	Date of Onset	Date of Diagn.	Date Death	Present Health or Cause of Death
Parents						
Siblings						
Spouse						
Children						
Other Relatives						

ENVIRONMENTAL INFORMATION

Patient's Usual Occupation	Housing Conditions at Onset
Patient's Occupation at Onset	
Approximate Education	Regular Social Contacts
If Student, School and Grade at Onset	
Past Residence	Special Contacts at Onset

APPENDIX D -- Continued

ENVIRONMENTAL INFORMATION

Regular Contact With Animals	Exposure to Radiation
Special Contact With Animals at Onset	Exposure to Chemicals or Drugs
Special Dietary Habits	Church Attended
COMMENTS	

APPENDIX E

QUESTIONNAIRE

Name of Patient _____

Date This Patient Was Hospitalized _____

PLEASE NOTE: If the patient named above is filling out this questionnaire please check here _____
If any person other than patient is filling out this questionnaire, please:

a) Explain why _____
b) Give your name _____ Phone _____
Address _____
c) Relationship to patient _____

1- To the best of your knowledge, did the patient named above suffer from any of the following illnesses or conditions before the date of hospitalization shown above?

Illnesses	Yes	No	Age When Illness Started	Conditions	Yes	No	Age When Condition Started
Tuberculosis	___	___	_____	Sinusitis	___	___	_____
3-day measles	___	___	_____	Hay fever	___	___	_____
German measles	___	___	_____	Asthma	___	___	_____
Mumps	___	___	_____	Jaundice	___	___	_____
Smallpox	___	___	_____	Hives	___	___	_____
Fever blister	___	___	_____	Mouth ulcers	___	___	_____
Shingles	___	___	_____	Nose ulcers	___	___	_____
Viral hepatitis	___	___	_____	Eczema	___	___	_____
Rheumatic fever	___	___	_____	Skin problems	___	___	_____
Fungus disease	___	___	_____	(Explain)	_____		
(Explain)	_____				_____		
	_____				_____		

2- Did the patient have any accident before the above date of hospitalization? Yes_____ No_____
If yes, did the patient look for any medical treatment after the accident? Yes_____ No_____
What kind of accident was it? Car___ Home___ Fall___
Farm___ Industry___ Other___
Please explain _____

APPENDIX E -- Continued

QUESTIONNAIRE

What part of the body was involved at the time of the accident?
Head___ Neck___ Mouth___ Throat___ Back___ Chest___
Abdomen___ Other (Explain)_____
Approximate date the accident happen: Month_____ Year_____

3- Did the patient have any allergy before the above date of hospitalization? Yes_____ No_____
If yes, to what was he allergic? plants___ foods___ drugs___
chemicals___ animal hair___ other (explain)_____
_____
Around what age did the allergy start?_____
How long (months, years) did it last?_____

4- Before the above date of hospitalization, did the patient use continuously any of the following products?

Products	Daily	At Least Once A Week	Name of Product, and About How Long (months, years) Was It Used
Tonics	___	___	_____
Vitamins	___	___	_____
Hormones	___	___	_____
Blood thinners	___	___	_____
Antibiotics	___	___	_____
Tranquilizers	___	___	_____
Diuretics	___	___	_____
Other drugs	___	___	_____

5- Before the above date of hospitalization, was the patient regularly exposed to any of the following substances?

Substances	Daily	At Least Once A Week	Name of Substance, and About How Long (months, years) Exposed
Insecticides	___	___	_____
Garden sprays	___	___	_____
Paints	___	___	_____
Solvents	___	___	_____
Cleaning liquids	___	___	_____
Detergents	___	___	_____
Printing inks	___	___	_____
Glues	___	___	_____
Other chemicals	___	___	_____

APPENDIX E -- Continued

QUESTIONNAIRE

6- Before the above date of hospitalization, did the patient engage in special hobbies at home? (Example: carpentry, toy assembling, stamp collection, etc.) Yes_____ No_____
If yes, what was the patient's hobby?_____
How often did the patient practice his hobby? daily___
at least once a week___ at least once a month___
About how long (months, years) did the patient have this hobby?___
_____

7- Did the patient engage in any of the following recreational activities away from home? camping___ hunting___ fishing ___
lake or river swimming___ scouting___ other_____
_____
How often did the patient practice these activities?
at least once a week___ at least once a month___
at least once a year___
About how long (months, years) did the patient practice these activities?_____

8- Did the patient have any contact with an apparently sick animal during the 12 months before the beginning of the illness for which he was hospitalized the date above? Yes___ No___
If yes, what animal was it? dog___ horse___ cat___ rabbit_
parakeet___ chickens___ other (explain)_____
What signs of illness did the animal show?_____

9- Did the patient have any contact with animals any time before the above date of hospitalization? Yes___ No___
If yes, how often was the contact? daily___ at least once a week___ at least once a month___ about once a year___
Where was such contact with animals? at home___ at work___
during vacation___
With what animals did the patient have contact?
a) At home_____
b) At work_____
c) During vacation _____
Approximately how long (months, years) did the contact last?_____

10- Were rats and mice commonly found in the vicinity of the house where the patient lived?
rats: Yes___ No___ mice: Yes___ No___
Did rats and mice come inside the house, or into premises outside the house?
rats: Yes___ No___ mice: Yes___ No___

APPENDIX E -- Continued

QUESTIONNAIRE

11- Was the patient exposed to any kind of radiation or cobalt treatment before the above date of hospitalization? Yes___ No___
If yes, what part of the body was treated?_____
What was the approximate duration (months, years) of the treatment?_____
What was the approximate date when treatment started?_____

12- Up to the above date of hospitalization what was the highest grade of regular school that the patient had completed?
None___ Grade school___ Junior high___ High school___
College___ Graduate or professional___ Other (explain)___
_____

13- What was the usual occupation of the patient just before the above date of hospitalization?_____
Did the patient have any other occupation during the past 10 years or more besides the one mentioned above? Yes___ No___
If yes, please list other occupations and their approximate dates:

Occupation	Approximate Dates
_____	_____
_____	_____
_____	_____

14- Please describe the dwelling in which the patient lived just before the beginning of the illness for which he was hospitalized the date above:
a) Type of dwelling (one family, trailer, etc.)_____
b) Type of construction (wood, brick, etc.)_____
c) Type of water supply (city, well, etc.)_____
d) Type of toilet (indoor, outdoor, etc.)_____
e) How many bed-rooms were there in the house?_____
f) How many persons lived in the same house with the patient?_____

15- Where was the house located? (Please mark one space)
On a farm or ranch _____
Residential area, within city limits _____
Residential area, outside city limits _____
In an industrial area _____
Other location (explain)_____
_____

APPENDIX E -- Continued

QUESTIONNAIRE

16- Before the above date of hospitalization, did the patient have any particular preference for certain type of foods? (Example: raw, non-processed milk, dry meats, etc.) Yes___ No___
If yes, what were those foods?_____

_____

Did the patient eat such foods daily?___ several times a week___
Around what age did the patient start eating such foods?_____

17- Have there been any other members of the patient's family suffering from the same disease for which he was hospitalized the date above? Yes___ No___
If yes, who were the other members? (Please do not give names):

Relationship to Patient	Age	Sex	Age the Illness Began

18- How would you say is the patient's health status at the present moment?
Excellent___ Very good___ Good___ Not too good___
Patient died (date) Month_____ Year_____

THANK YOU VERY MUCH FOR FILLING OUT THIS QUESTIONNAIRE

We will greatly appreciate it if you help us to the success of this study by mailing this questionnaire back to us within five days. Just put it in the self-addressed envelope which needs no stamps. Again, THANK YOU VERY MUCH!