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S.L. Glaser
(Ph.D. Thesis)

November 1984

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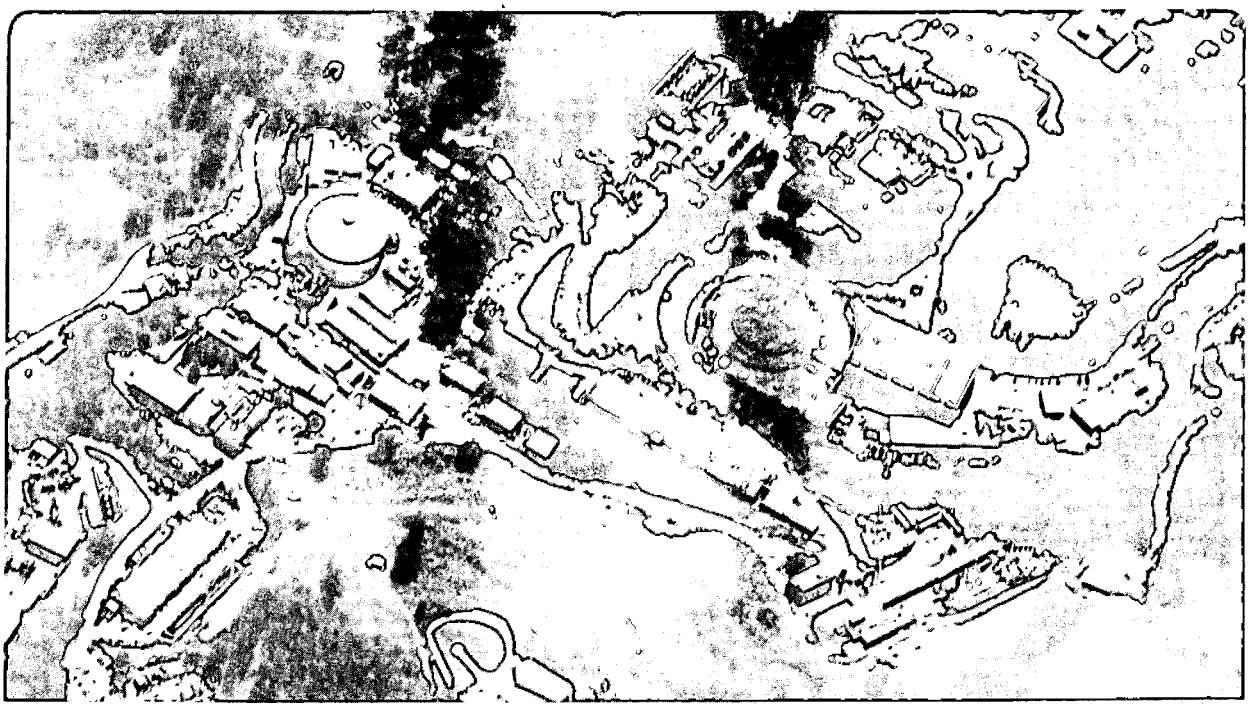

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HODGKIN'S DISEASE INCIDENCE IN THE UNITED STATES BY AGE, SEX, GEOGRAPHIC REGION AND RYE HISTOLOGIC SUBTYPE

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November 1984

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Hodgkin's Disease Incidence in the United States by Age, Sex, Geographic Region and Rye Histologic Subtype

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Sally Louise Glaser

Hodgkin's Disease Incidence in the United States by Age, Sex, Geographic Region and Rye Histologic Subtype

Sally Louise Glaser

Abstract

Hodgkin's disease (HD) incidence in whites is described by age, sex, Rye histologic subtype and time period for ten United States locations, using recently available data with Rye histologic diagnoses for most cases. This is the first evaluation of contemporary and secular HD incidence by reliable histologic subtype and geographic region.

The distribution of HD was generally that expected in an affluent country. Some distinctive features of incidence in young persons--stable childhood rates, and high and increasing rates in young adults, particularly women--resulted from the elevated rates of the Nodular Sclerosis (NS) subtype. NS was the only histologic form with a rising incidence. Unexpectedly, among middle-aged and older persons rates of all subtypes declined during the 1970s.

HD incidence varied little across study regions and became more geographically homogeneous with time, notably among women. HD rates were highest in Connecticut and San Francisco-Oakland, lowest in Hawaii, Atlanta and New Orleans, and were positively correlated with regional socioeconomic levels. In areas with the highest young adult incidence, higher risk also affected a broader age range, including older children. Rates for young adults were posi-

tively associated with community socioeconomic status but did not covary with older adult rates. These patterns support the proposed infectious etiology of young adult HD.

Rates for the NS and Lymphocyte Predominance subtypes were inversely correlated across areas. NS incidence increased with community economic levels. Histology-specific rates otherwise showed little geographic variation.

These features suggest the incidence of HD in a well-developed country is not static but evolves, characterized by higher rates of NS in an increasingly broad age range of young, particularly female, adults, rising with small increments in socioeconomic status, and occurring over the relatively short study interval. Declines in rates at older ages may also result from socioeconomic changes, following depletion of susceptibles in young adulthood, or may reflect improvements in diagnostic accuracy. The findings support either the "two-disease" or the "host-susceptibility" theory of etiology.

Mary-Claire King

To Audrey and Natalie

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A dissertation is often presumed to be a solo endeavor. This one was something of a joint project with my teachers, colleagues, friends and family.

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GLOSSARY OF ABBREVIATIONS

EBV: Epstein-Barr virus

HD: Hodgkin's disease

HLA: Human lymphocyte antigen

ICD-O: International Classification of Diseases for Oncology

LBL: Lawrence Berkeley Laboratory

LD: Lymphocyte Depletion

LP: Lymphocyte Predominance

LPPR: Lymphoma Pathology Panel and Repository

MC: Mixed Cellularity

MOTNAC: Manual of Tumor Nomenclature and Coding

NCI: National Cancer Institute

NS: Nodular Sclerosis

SEEDIS: Socio-Economic-Environmental Demographic Information System

SEER: Surveillance, Epidemiology, and End Results

SMSA: Standard Metropolitan Statistical Area

SPSS: Statistical Package for the Social Sciences

TNCS: Third National Cancer Survey

Chapter 1

INTRODUCTION

Hodgkin's disease (HD) is an uncommon malignant disease of the lymphatic system whose enigmatic nature has long challenged students attempting to describe and treat it. The confusion arises from its complex clinical and pathologic appearance, which includes characteristics of malignancy, chronic infection or inflammation, and immunologic disorder (1). Although many questions about its nature and etiology are still unresolved, the classification of the disease, so central to its accurate epidemiology as well as clinical treatment, has gradually been refined. The presently accepted histopathologic nosology recognizes four subtypes whose morphologic, clinical and epidemiologic features underscore their distinctiveness and have been useful in clarifying some of the persistent ambiguity.

For 30 years, epidemiologists have been particularly intrigued by aspects of HD that are atypical of malignancy. The unusual age distribution, with its high incidence in children and young persons, and the age-specific differences in clinical symptoms and prognosis, early on prompted the theory that HD was two or three related diseases affecting particular age groups (2,3). Clinical and epidemiologic evidence of possible infectious etiology has inspired further epidemiologic interest. Consequently there has been

a wide range of investigations of this condition. For the most part, however, the studies have lacked data for considering disease behavior by histologic type, although the etiologic importance of this level of detail has been widely acknowledged (2,4-8).

In 1965, the current histologic classification was adopted, opening the way for contemporary histology-specific studies (9). However, simultaneous medical advances paradoxically hampered epidemiologic progress in this area. Tremendous successes in the treatment of HD began extending patient survival dramatically, so that by the early 1970s, mortality data, with the geographic scope for comprehensive study of HD, no longer adequately indicated the incidence of the disease (10). This change in the usefulness of mortality data seriously limited geographically based epidemiologic investigations, because the more appropriate cancer incidence data have not been routinely monitored across the United States.

Some geographically broad-based incidence data are available. The National Cancer Institute (NCI) has conducted periodic incidence surveys in several, mostly urban areas, but these have been of limited usefulness for histology-specific studies. The first survey, in 1937-1939, did not include HD. The second, in 1947-1948, included HD but did not present histologic data (11). The Third National Cancer Survey (TNCS), in 1969-1971, included epidemiologically useful histological detail but for only 31 percent of

the cases* (12). The consequences of these various circumstances have been a paucity of population-based studies of HD incidence by histologic category and a complete lack of such information at a systematic regional or nationwide level in the United States.

In 1973, when the present histologic classification was beginning to be widely used, the NCI instituted an ongoing survey--the Surveillance, Epidemiology and End Results (SEER) program--to ascertain cancer incidence in 10 study regions (13). In its first eight years, this ambitious project collected detailed data, including histologic diagnosis, on a substantial number of cases. The purpose of this dissertation is to take advantage of these newly available SEER data, with the unprecedented large case group, prevalent histologic diagnoses, and geographic coverage, together with 1980 census data for interpolating rate denominators, to describe contemporary HD incidence by histologic type across this country. Within this general goal, the project addresses specific issues:

1) the description of incidence by detailed age group, sex and histologic type for all areas combined, to estimate national incidence of the disease;

2) the description of incidence, as above, for each survey region, to document geographic variation of HD in the United States;

* See Chapter 3.

3) a preliminary evaluation of secular trends over most of the decade for all HD and for each histologic subtype, to monitor recent changes in incidence in all regions combined and by region;

4) the quantitative evaluation of covariation of age-specific rates, and of the effect of community economic conditions on disease behavior, a relationship often observed but not measured.

This study therefore will provide a detailed profile of overall and histology-specific distributions of HD across the United States. In doing so, it represents the first comprehensive evaluation of the incidence of this disease in this country. The regional analyses will help define the extent of geographic variability, particularly in relation to community economic status, and may provide evidence of regional causes of disease. Similarly, analysis of temporal trends may offer clues to changes of etiology. Furthermore, the findings may serve as the basis for present and future comparisons with data from other areas, as well as for subsequent analytic investigations of this population itself.

The following report presents this project. Chapter 2 describes HD clinically, reviews its histologic classification, and briefly discusses its epidemiology and associated etiologic hypotheses. Chapter 3 describes the selection and extraction of numerators and denominators, and the methods for calculating and evaluating rates. Chapter 4 presents

the detailed incidence of HD for all regions combined. Chapter 5 describes regional incidence and presents analyses of geographic variation in several incidence patterns. The final chapter discusses the findings, possible sources of bias in their derivation, their interpretation and implications, and additional descriptive issues to be investigated.

Chapter 2

BACKGROUND

Epidemiologic study, drawing hypotheses from the behavior of a disease and contributing evidence toward its clearer understanding, is necessarily tied to the level of knowledge about the nature and etiology of the illness. Therefore, an examination of the complex characteristics of HD will provide a useful context for exploring its incidence. This chapter briefly describes the clinical and pathologic appearance of the disease; discusses the evolution of histopathologic classification to clarify the significance of this perspective; and summarizes previous epidemiologic findings and their contribution to major etiologic theories.

CLINICAL CHARACTERISTICS

HD most commonly affects lymph nodes, occurring typically as a painless enlargement of cervical nodes. The swelling is usually gradual, developing over weeks or months, but it may appear quite suddenly, or wax and wane. A variety of constitutional symptoms, including cyclic fevers, night sweats and weight loss, may be present early in the illness, but usually indicates advanced disease. Without treatment, HD progresses to adjacent lymph nodes, often affects the spleen, liver and other organs, and is fatal (14). Persons with HD may have abnormal immune re-

sponses, with increased susceptibility to certain infections and a decreased reaction to antigens (1).

This range of symptoms, together with associated cytologic findings, illustrates the multifaceted clinical picture of HD. The metastatic spread and invariable fatality suggest malignancy; the fluctuating lymphadenopathy, fever and night sweats, and early involvement of the spleen are signs of chronic inflammation; and the functional impairment of cell-mediated immunity indicates a chronic immunologic disorder (15,16). Evidence of aneuploidy and clonal derivation in the affected cell of HD (the Reed-Sternberg cell) has established this disease as a malignancy albeit a distinctly unusual one (14).

The ambiguity about the nature of HD is documented historically in its classification as a cause of death. In 1939, it was listed in the Manual of the International List of Causes of Deaths under "other infectious and parasitic (communicable) diseases" (17). In 1948 it was reclassified as a neoplasm of lymphatic or hematopoetic tissue (18).

HISTOPATHOLOGIC CHARACTERISTICS

The complexity of the clinical appearance is mirrored in its pathology. The histology is quite varied, with characteristic bi- or multinucleated Reed-Sternberg cells (believed to derive from macrophages (16)), lymphocytes and other cellular components of lymph tissue present in varying forms and degrees. Once considered pathognomonic, Reed-Sternberg cells have subsequently been identified in infec-

tious mononucleosis and other diseases (19,20). Consequently, definitive diagnosis of HD is made on the basis of Reed-Sternberg cells and the surrounding stroma.

HISTOLOGIC CLASSIFICATION

Identification and classification of HD have been ongoing for 150 years. The process has been marked by the recognition of the disease as entity; by its naming; by the delineation of its histologic characteristics; and finally, by the classification of subtypes in clinically useful systems. A brief review of these landmarks reveals the persistent controversy about the nature of HD and the importance of histologic classification in clarifying some of the clinical and epidemiological confusion.

HD was first recognized as a distinct entity in 1832 by Sir Thomas Hodgkin, who described seven cases (21). That three of these were later felt to be tuberculosis, syphilis and lymphosarcoma (14) provides an early example of the difficulty in making the diagnosis. In 1865, Sir Samuel Wilks, presenting a further case series, named the illness Hodgkin's disease after its first reporter (22).

The next significant advance, made at the turn of the century, was a thorough histopathologic description, credited to Sternberg and Reed (23,24). Independently they described the giant cells later given their names. As Reed determined, this development was "of great assistance in diagnosis" (24, p.152). Her paper also recorded a few

epidemiologic observations still recognizable today as characteristic of that period:

> The disease occurs in more than half the instances in early life; probably the majority of cases are in children. Males are more frequently affected than females. (14, p.143)

The delineation of prognostically relevant histologic subtypes began in 1928 when Ewing labeled a virulent form of the disease Hodgkin's sarcoma (25). In 1937, Jackson noted the importance of classifying HD by recognizable histologic changes into categories correlated with "age incidence, prognosis and symptomatology" (26). Using these guidelines, he created the first systematic histologic scheme. In 1944, with its categories renamed paragranuloma, granuloma and sarcoma, it became known as the Jackson-Parker classification (27-29). Paragranuloma described a mild, slowly evolving form of the disease; granuloma included a large, heterogeneous group of cases with typical presentations; and sarcoma was a malignant, rapidly fatal variant. Jackson and Parker emphasized the importance of histologic subcategorization to a better understanding of HD, stating that "any description that includes all three [subtypes] as a single form of the disease must, of necessity, be inaccurate and of little value" (27, p.1).

The Jackson-Parker classification was used for the next 20 years and was still employed in 24 percent of the TNCS cases in 1969*. However, in 1963, Lukes pointed out the

* See Chapter 3.

serious limitation on its utility of including a large majority of cases in its granuloma category. Reviewing histologic diagnoses of 377 men with HD from the Armed Forces Institute of Pathology, he documented the grossly uneven distribution, showing that granuloma incorporated 91 percent of these cases (30). He further demonstrated the histopathologic heterogeneity of the granuloma subtype, showing two prognostically distinct variants it subsumed. In this and other work, he and his colleagues created a new classification with six categories based on identifiable histologic features and correlated with clinical stage and survival (31,32). In 1965, this system was condensed to four, more readily usable groups--lymphocyte predominance (LP), mixed cellularity (MC), lymphocyte depletion (LD) and nodular sclerosis (NS). This modification of the Lukes-Butler scheme has subsequently been dubbed the Rye classification, after the New York location where it was proposed (9).

Table 1 lists and describes the Rye histologic subtypes and their relation to the Jackson-Parker categories. Paragranuloma and sarcoma were directly incorporated into the Rye LP and LD subtypes respectively, but the large granuloma category was subdivided into NS and MC. The skewed distribution of the Jackson-Parker scheme and its lack of interchangeability with the Rye classification seriously diminish its usefulness in epidemiologic studies of HD by histologic type. Such investigations therefore are

Table 1. HISTOPATHOLOGIC CLASSIFICATION OF HODGKIN'S DISEASE*

Jackson-Parker	Rye	Distinctive Features	Prognosis**
Paragranuloma →	Lymphocyte Predominance	Reed-Sternberg cells may be sparse; abundant stroma of mature lymphocytes and/or histiocytes; no necrosis	+
Granuloma ↗	Nodular Sclerosis	Atypical "lacunar" Hodgkin's cells*** in clear spaces within nodules of lymphoid tissue; nodules separated by bands of doubly refractile collagen	+
Granuloma ↘	Mixed Cellularity	Unusually numerous Reed-Sternberg cells and mononuclear Hodgkin's cells in pleomorphic stroma of eosinophils, plasma cells, fibroblasts, and necrotic foci	-
Sarcoma →	Lymphocyte Depletion	Reed-Sternberg cells usually abundant; marked paucity of lymphocytes; diffuse nonrefractile fibrosis and necrosis may be present	-

* Adapted from (14), page 86

** Without treatment

*** Precursors of Reed-Sternberg cells

restricted to data from after the 1965 Rye conference. The suitability of the Rye categories for epidemiologic study, however, is demonstrated both by the correlation of these subtypes with clinical features and by their unique age- and sex-specific distributions (33).

Partitioning HD into histologic categories has been an important step in understanding its elusive nature. Whether the Rye classification will prove in the long run to be the ideal discriminator from a joint histopathologic, prognostic and etiologic point of view remains to be seen. At present it clearly provides a clinically and epidemiologically useful perspective on the disease. As such, this categorization offers the best readily available tool for epidemiologic examination of HD in histologic detail.

EPIDEMIOLOGIC CHARACTERISTICS

The epidemiology of HD has proven as complex as its clinical and pathologic behavior. Early epidemiologic evidence supporting both an infectious and malignant nature of the disease has inspired numerous subsequent studies (2,3). These have recently been reviewed quite thoroughly by several authors (8,34-36). The following discussion, therefore, will present first a brief epidemiologic profile, then a more detailed discussion of the modifying effects of age and histologic type, with a description of the major, still unresolved etiologic hypotheses.

PROFILE OF HD

Incidence

HD is a relatively rare disease. With an overall age-adjusted average annual incidence rate of approximately 3.0 per 100,000 in the United States in the 1970s, it is one-fifteenth as common as major cancers like those of the lung or breast (12,13). Like many neoplasms, its incidence increases with age. However, it is unusual in affecting children and particularly young adults: among persons aged 15-24 in this country, it is the most common malignant disease (13). The distinctive bimodality of the age-specific curve has been the primary source of the etiologic theories presented below.

Sex, Race and Ethnic Group

Disease incidence is approximately 50 percent higher in males, but the male excess varies considerably with age, as detailed below (3,12,13). There is an increase in risk of similar magnitude for whites compared to blacks. In this country, incidence among blacks is 2.0 per 100,000, lacks the prominent young adult excess but has higher childhood rates, and has a larger male-female ratio (13). HD is very uncommon among the Japanese, in whom there is no young adult disease (37-40). Rates among Jews in the United States have consistently been found to be elevated, particularly in older age groups (2,3,41-43).

Geographic Variation

The range in summary rates worldwide is relatively small considering international differences in diagnostic

practice, disease ascertainment, population enumeration and competing risks of illness. Table 2 lists recent incidence rates, adjusted to the world standard population, for a variety of international locations. With the exception of the unusually low rates in Asian countries, overall male incidence ranges primarily between 2.5 and 4.0 per 100,000, while female rates vary from 1.0 to 2.5 per 100,000 in most countries (40). In the United States, rates per 100,000 whites extend similarly from 2.8 in Hawaii to 4.0 in Connecticut for males, and 1.7 in Hawaii to 2.8 in Connecticut for females. However, this geographic uniformity does not persist at the age-specific level. There is considerable international variation in childhood and young adult incidence, to be presented in greater detail.

Time Trends

Secular behavior of HD, like its geographic distribution, has been remarkably stable. In both the United States and England, mortality increased slightly from 1920 onward (2,3, 44,45). However, internationally and in the United States, it varied little from the early 1950s (when the cause-of-death classification of HD became stable) until approximately 1970, when rates began to decline with the institution of effective medical treatment of the disease (10,46,47). Similarly, there has been only minimal change in incidence. Between the 1948 and 1969-1971 NCI surveys, incidence rates have increased only slightly (10). Figure 1

Table 2. AGE-ADJUSTED* INCIDENCE RATES OF HODGKIN'S DISEASE BY REGION AND SEX**

Region	Rates Males	Females
Czech., Slovakia	1.8	1.2
Denmark, 1968-72	3.3	2.2
1973-76	2.7	1.7
Germany, Hamburg	3.0	1.7
Saarland	2.3	1.7
Finland	2.7	1.7
France, Bas-rhin	3.1	1.8
German Dem. Rep.	2.7	1.9
Hungary, Szabolcs	1.7	1.2
Vas	1.6	1.6
Italy, Varese	4.0	2.1
Norway	2.6	1.6
Poland, Cracow City	2.8	2.2
Katowice	2.3	1.4
Warsaw City	2.8	1.7
Romania, County Cluj	2.0	1.0
Spain, Navarra	3.5	1.3
Zaragoza	3.8	2.0
Sweden	3.3	1.8
Switzerland, Geneva	3.5	1.3
Vaud	4.7	3.7
Yugoslavia, Slovenia	2.0	1.2
Israel, All Jews	2.6	2.3
U.K., Birmingham	2.7	1.9
North Western	3.4	1.8
Oxford	3.1	1.9
South Thames	2.7	1.6
Trent	3.1	2.1
Mersey	2.9	1.6
U.K. East Scotland	3.2	2.4
N.E. Scotland	3.0	2.5
S.E. Scotland	3.9	2.1
West Scotland	2.2	2.0
Brazil, Sao Paulo	3.5	2.2
Colombia, Cali	2.8	1.1
Cuba	2.5	1.1
Jamaica, Kingston	2.7	1.9
Netherlands Antilles	3.1	1.4
New Zealand, nonMaori	3.2	2.1
Australia, New S. Wales	2.6	1.7
Shanghai	1.1	1.0
Hong Kong	0.8	0.6
Japan, Fukuoka	0.6	0.5
Nagasaki	1.5	0.8
Osaka	0.6	0.3
Singapore (Chin)	0.6	0.4
India, Bombay	1.7	0.8
Poona	1.3	0.8
Canada, Alberta	3.4	2.2
British Colum.	3.0	1.7
Manitoba	2.8	1.7
Marine Provs.	3.2	1.6
Newfoundland	2.6	1.9
Ontario	3.5	2.5
Quebec	3.3	2.0
Saskatchewan	3.0	1.9
+Alameda, Calif.	3.3	2.4
+Bay Area, Calif.	3.6	2.8
+Los Angeles	3.3	2.2
Connecticut	4.0	2.8
+Atlanta	2.5	2.6
Iowa	3.4	2.3
+New Orleans	2.8	2.2
+Detroit	3.3	2.3
+New Mexico	3.9	2.3
New York State	3.9	2.8
Utah	3.5	2.1
Seattle	3.4	2.2
+Hawaii	2.8	1.7
Puerto Rico	2.1	1.4

* Adjusted to the world population
** Adapted from (40), pp. 766-767
\+ white population only

illustrates these recent trends in mortality and incidence. As with geographic variation, this consistency of rates in time has not been maintained at the age-specific level. In this country and in England, there have been significant, opposing secular trends in childhood and young adult HD, discussed below (2,3,44,45,47,48).

Socioeconomic Status

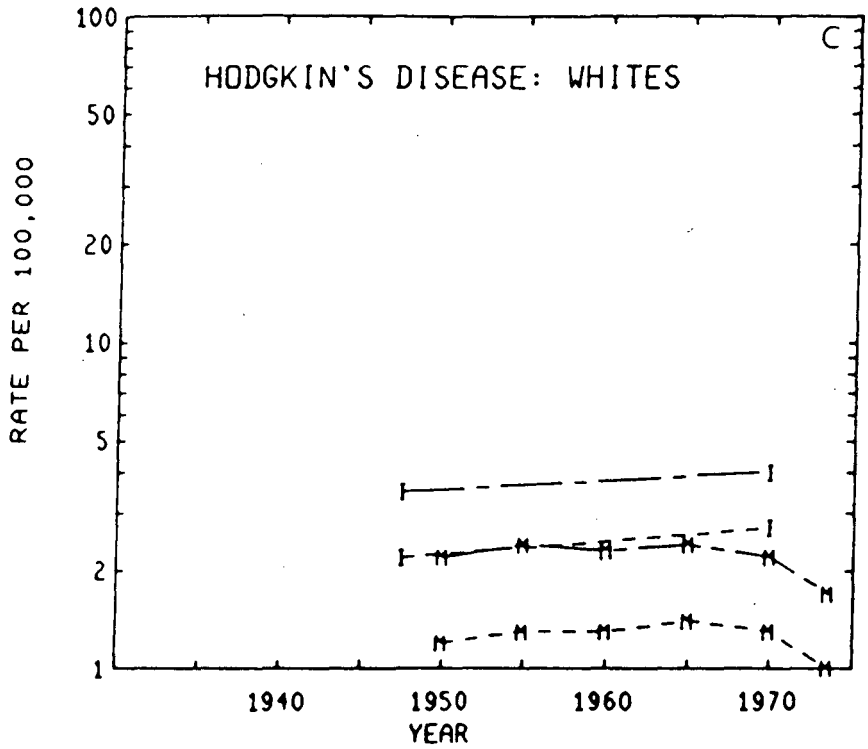
The risk of HD seems to rise with increasing socioeconomic status (SES). This relationship has been observed using different SES markers in many, although not all, study populations (3,48-54). Gutensohn and coworkers identified childhood socioeconomic conditions (family size, birth order, and neighborhood and housing characteristics) as more predictive of risk in young persons than SES at diagnosis (41,55,56). As with other descriptive variables, the positive association of HD with SES is modified by age, affecting predominantly young persons in the United States and England (3,42,43,48,54). For children and older persons, there may be an inverse relationship between disease and SES (42).

Other Risk Factors

Analytic epidemiologic studies of HD have identified a variety of other risk factors. Briefly summarized, they include:

HD in the family Conferring a threefold excess risk overall, familiality was associated with a sevenfold risk among siblings of young adult cases, particularly same sex

Figure 1. SECULAR TRENDS IN HODGKIN'S DISEASE INCIDENCE AND MORTALITY IN THE UNITED STATES AMONG WHITES, BY SEX*



I-- - --I = INCIDENCE, MALES
I- - - -I = INCIDENCE, FEMALES

M-- - --M = MORTALITY, MALES
M- - - -M = MORTALITY, FEMALES

* from (10)

siblings. No excess risk was found for siblings of older cases (8).

HL-A type Associations have been inconsistent, but seem to occur with loci A1, B5 and B18 (8). Berberich et al. have recently identified a consistent linkage between HLA locus and familial HD, indicating genetic susceptibility in such cases (57).

Parental consanguinity In Israel, a close blood relationship between parents tripled risk of HD and increased it fourfold in males (53). This finding has not been replicated.

Tonsillectomy This surgical procedure was first considered a possible risk factor after Miller pointed out that natural regression of lymphatic tissue occurs at the prepubertal ages at which HD incidence begins to increase sharply (58). In several studies controlled for SES, relative risks for tonsillectomy varied between 1.4 and 3.6 but were modified inconsistently by family size (35).

Infectious mononucleosis This disease came to attention because it is associated with Epstein-Barr virus (EBV), thought to cause Burkitt's lymphoma, and because it manifests Reed-Sternberg cells. In four studies, risks of HD were between 2.8- and 3.9-times greater in persons with a history of laboratory-confirmed infectious mononucleosis (8).

Primary EBV infection Persons with HD have repeatedly been

shown to have higher antibody titers to EBV than controls, although the proportions with positive titers have not differed (35). In one study, elevated EBV titers predated onset of HD and therefore could not be attributed to the immune deficiency of the disease itself (59). However, not all HD cases have shown serologic evidence of infection, and virus has never been recovered from tumor tissue.

Occupation Woodworking has been identified in several studies with a moderate increase in HD risk. Exposure to chemicals has been less consistently implicated. Grufferman points out that two specific compounds associated with HD--phenoxy acids and chlorophenols--are also used in wood-related industries (8).

Residence In rural Michigan, a cluster of persons with HD was identified living downwind from a navy-bean elevator (60). The possible significance of this finding was indicated when navy-bean dust, known to contain phytohemaglutinins, was shown to transform lymphocytes *in vitro* (61). A study of residence in Israel found that persons with HD had a significantly different residential distribution in districts of the country than their matched controls (62). The finding was unexplained in this population by any of the known personal or community-level risk factors.

Physical size In four studies, persons with HD were taller and heavier than controls (41,63-65). Young persons in a Danish investigation were larger at birth and throughout childhood than SES-matched controls (65).

Parity Low parity (fewer than three children) doubled the risk of HD in Israeli women, after SES was controlled (53).

Drug use Amphetamine use was associated with HD in two studies but unconfirmed in others (41,52,66-68). The mechanism for this association was suggested with the description of immunoblastic lymphadenopathy, a condition that clinically and pathologically resembles HD and may itself be a hyperimmune response to drug exposure (69).

Direct or indirect contact with HD Although research in New York State identified prior exposure to persons with HD as a risk factor for disease development, this finding has not been replicated in any of several subsequent studies. Furthermore, professionals (i.e., doctors, teachers) in contact with persons with HD were not systematically found to have increased HD risk (8).

THE MODIFYING EFFECT OF AGE AND HISTOLOGY

Age and histologic subtype both strongly modify the epidemiology of HD. The marked bimodality of the age-specific incidence curve, and the variations of other characteristics with age, have led to important hypotheses about the nature and cause of the disease. The role of histologic subcategorization on HD epidemiology, less thoroughly studied, has long been expected to yield valuable etiologic clues (2). The importance of these interactions justifies a detailed review of the effects of age and histologic type, and their impact on theories of etiology.

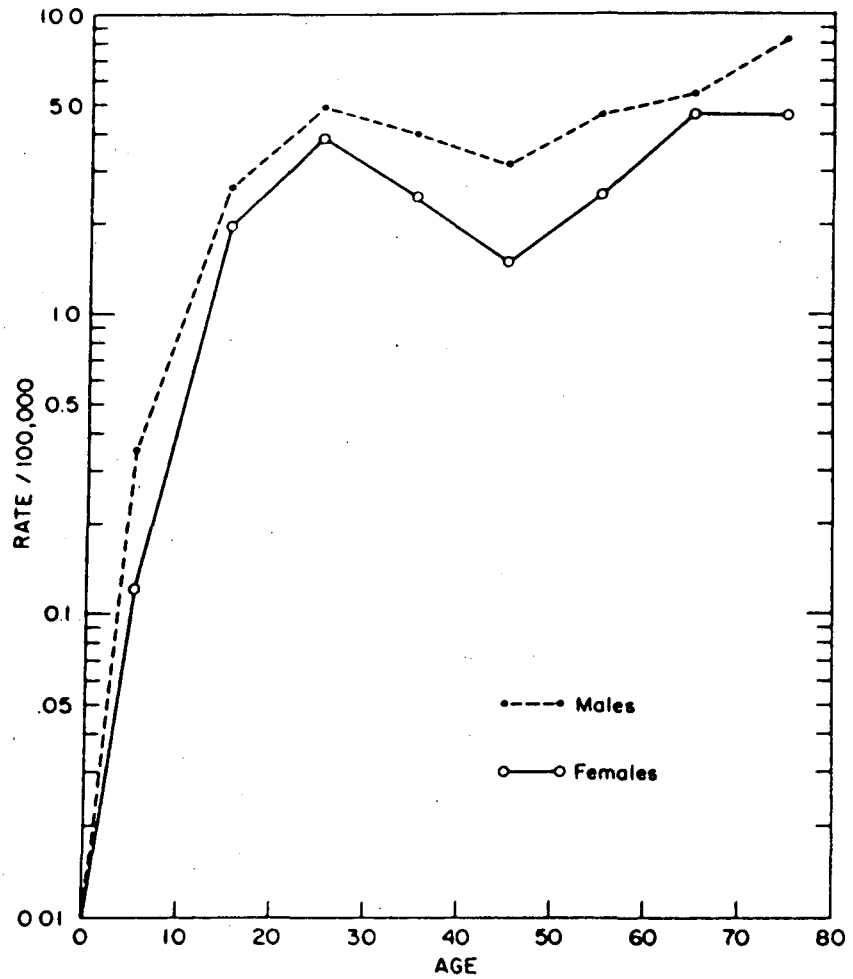
Age Modification of HD

Age In developed countries, HD age incidence takes a striking bimodal form. Figure 2 illustrates the age-specific curves for males and females in Connecticut in 1960-1968, showing clearly the prominent young adult and older adult incidence peaks (70). First describing this pattern in 1957, MacMahon thought it signified separate disease processes in young and older persons (2). This theory is elaborated in a later discussion.

Sex The male excess in HD varies significantly with age. In most data, it is greatest in childhood, lower in young adults, and evident in older persons (2,3,44,71). Some studies have reported a large male excess at intermodal ages (2,3,72), which is usually apparent in rates from well-developed countries. Grufferman proposed that the protective effect of parity in women, noted in Israel, may explain their relatively low incidence in middle adult years (8).

Geographic variation The substantial geographic variation in certain age-specific rates both internationally and nationally amply illustrates the differences in behavior of HD by age. MacMahon first noted that international variation in young adult rates seemed independent of variation in disease in older persons (2,3). Cole et al. showed that, while HD mortality rates in persons over age 45 varied little across the United States, rates for young adults were significantly lower in Southern states (73). Fraumeni and Li noted that childhood HD mortality also varied with loca-

Figure 2. AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE IN CONNECTICUT, 1960-1968, BY SEX*



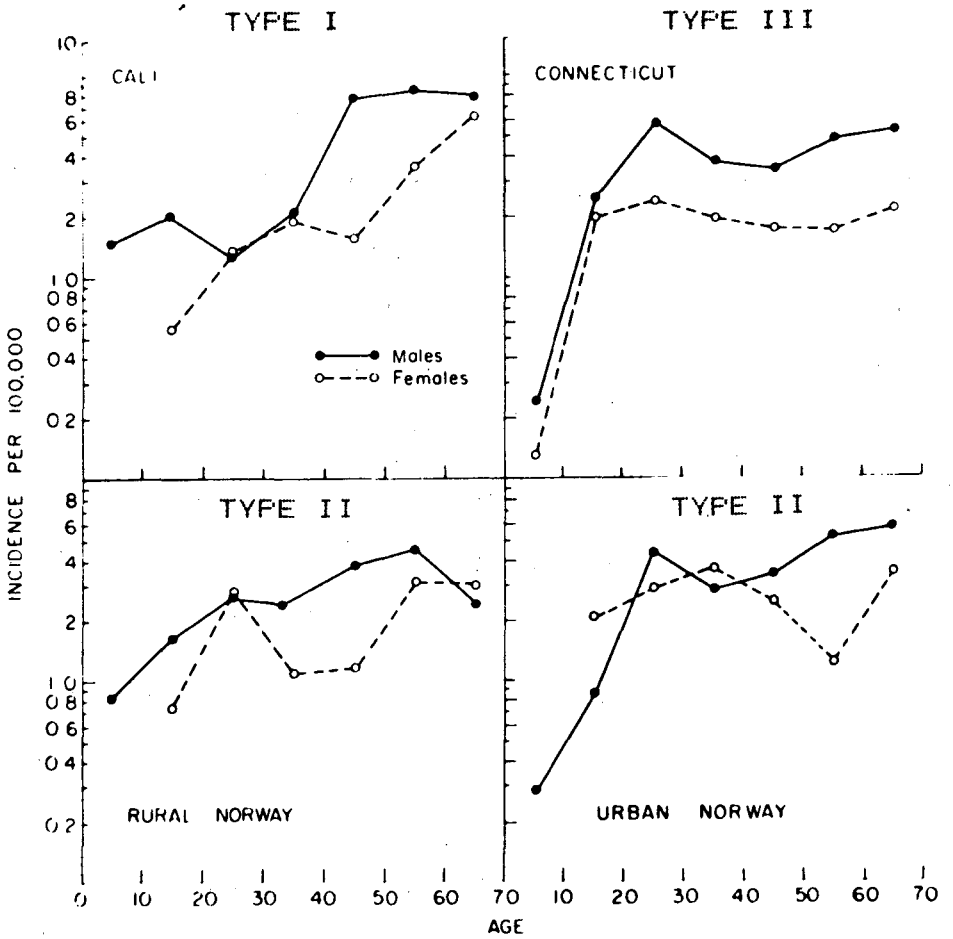
* from (70)

tion but was somewhat higher in the South (71).

Correa and O'Conor described a similar age-specific variability in international incidence data, showing a significant inverse relationship between childhood (ages 5-14) and young adult (ages 20-34) rates in males (4). They further associated the relative incidence of disease in these two age groups with the economic condition of the region and with the predominance of certain histologic subtypes (4,74). They summarized these interrelationships in three patterns of HD incidence, illustrated in Figure 3. Type I distribution occurs in underdeveloped countries, has high rates of childhood disease particularly in males, and low young adult rates, and shows a predominance of MC and LD, subtypes with poor prognosis. Type III pattern occurs in well-developed areas, features little childhood disease but a prominent young adult peak, and NS, a subtype with good prognosis. Type II disease has an intermediate pattern and occurs in intermediate economic environments, such as rural areas of Western countries. These patterns are apparent in both sexes but are more pronounced in males. For females, there is considerably less geographic variation. The shape of the female age-specific curve in all environments tends to assume a Type III form, and there is very little childhood HD in girls.

Abramson, and Vianna and Polan, independently evaluated disease variation among younger and older persons, finding negative associations between childhood and older

Figure 3. THREE PATTERNS OF AGE-SPECIFIC INCIDENCE OF HODGKIN'S DISEASE, ILLUSTRATED WITH DATA FROM CALI, COLOMBIA (1962-1966); CONNECTICUT (1960-1962); AND NORWAY (1964-1966), BY SEX*



* From (4)

age rates, and positive associations between young adult and older adult rates (75,76).

Although Correa and O'Conor's observations were made on international data, the three incidence patterns also exist within a single country. Cole et al. essentially described a Type II incidence curve for the southern United States and compared it with a Type III pattern for the rest of the country (73). Franssila et al. noted a similar Type II, Type III contrast for rural and urban Finland (77). Different patterns also appear in one region over time, as discussed below with other secular trends.

Latitude provides another explanation of geographic variation. In addition to economic standing, Correa had noted an association of incidence with latitude in South and Central America: he observed less childhood disease in more temperate climates (74). Recently DeLong et al. reported that the variation in young adult mortality described by Cole and coworkers was statistically explained by climate, a correlate of latitude, and to a lesser extent by SES (54). In their data, young adult rates increased with latitude, a pattern consistent with Correa's observations, given the inverse relationship between childhood and young adult disease.

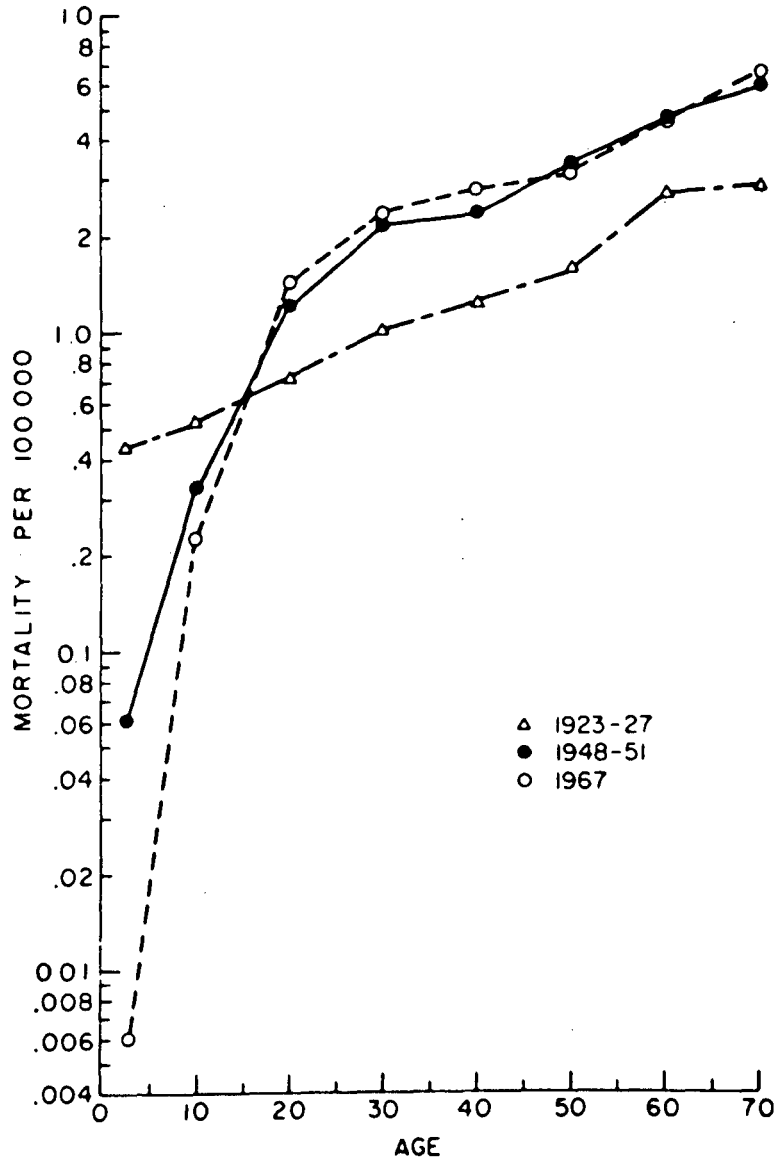
Correa and O'Conor interpreted the association of age-specific variability with economic level and prognostically differing histologic subtypes as evidence of "the interplay

of environmental and host factors influencing the natural history of a single disease" (4, p.199). They proposed that this pattern of variation reflected age-specific differences in host susceptibility and disease manifestation, both affected by the impact of socioeconomic conditions on host health and resistance. The three incidence patterns they described are well supported by the data from which they were derived, and have been widely accepted, but the associations with SES and histologic type have never been quantitatively established.

Secular variation While summary incidence and mortality rates have not changed dramatically in time, there have been definite age-specific secular trends. Several authors reported similar patterns in age-specific mortality in the United States and in England and Wales (2,3,44,45,48). They found that childhood rates declined in time, while mortality in older persons, especially young adults, increased. Figure 4 displays these changes for males in the United States (4). The secular age-specific patterns, in addition, are consistent with an evolution from Correa and O'Conor's Type II to Type III distributions, assuming a parallel improvement in economic conditions in the United States during those years (8). Gutensohn and Cole noted a similar Type II to Type III transition in Cali, Colombia over a single decade, which demonstrates how rapidly this evolution can can occur (35).

These characteristics--the bimodality of HD incidence,

Figure 4. AVERAGE ANNUAL AGE-SPECIFIC MORTALITY RATES OF HODGKIN'S DISEASE FOR MALES IN THE UNITED STATES, BY TIME PERIOD*



* from (4)

its differences in sex ratio, and the age-specific variation in regional incidence and secular trends--together illustrate the differences in HD behavior with age. In particular, incidence varies most notably in childhood and young adult years, in an inverse relationship correlated with economic status. In contrast, HD in older persons is relatively stable geographically and temporally.

Together with other identified risk factors, these age variations in HD incidence indicate that that the age-specific expression of this disease is sensitive to environmental factors. However, the stability of its overall incidence additionally suggests that its primary causes are ubiquitous, with regional conditions, presumably socioeconomic, controlling the balance of childhood and young adult disease.

Histology Subtype Modification

Like age, the histologic form of HD greatly modifies its behavior. Unlike age, the effect of histology has not been widely studied, due to the lack of adequately classified data. Most studies of histology-specific incidence have used hospital case series (70). In the last 10 years, there have been a few more broadly based surveys yielding relative frequencies of the Rye subtypes for international locations (40,77). These proportional data offer a general indication of histology incidence and geographic variability. In addition, six recent population-based studies gener-

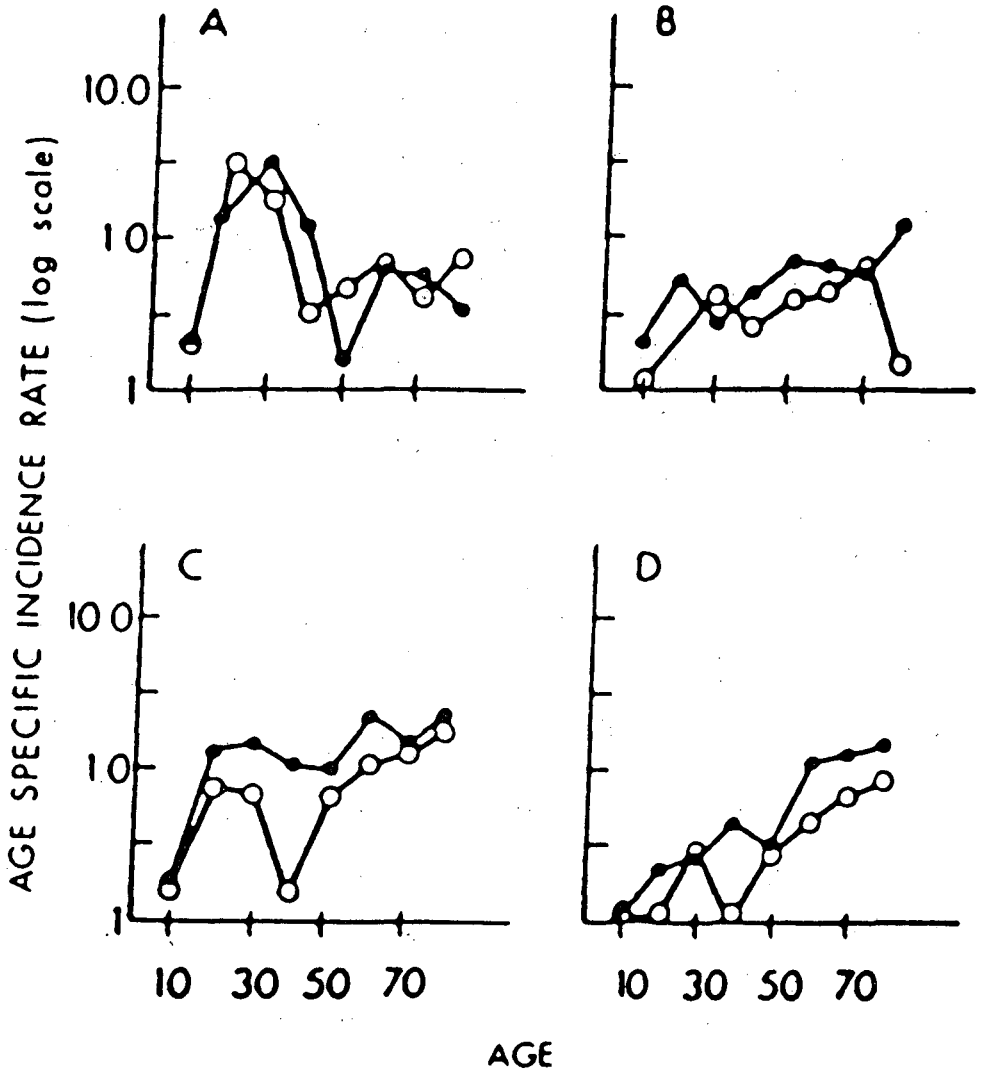
ated age-specific histology rates (7,52,70,77-79). In most of these reports, the rates were graphed but not reported. Therefore their actual values cannot be examined and compared.

Incidence HD is not evenly distributed in the four subtypes. In the United States, NS is the most common category, three to four times as frequent as LP or LD (40,77). In Los Angeles County, where histology-specific rates were available for 1972-1975, the incidence of NS was 1.0 per 100,000; MC was 0.9 per 100,000, and LP and LD were 0.4 and 0.3 per 100,000 respectively (52).

Age The differences in subtype incidences are greatly exaggerated at the age-specific level. Figure 5 depicts age incidence curves typical of the four Rye categories, with data from Los Angeles County. Both NS and MC have prominent young adult incidence. However, NS is primarily a disease of young persons, while the incidence of MC climbs with age. LD and LP have low rates, increasing with age in a manner typical of malignancies. Thus there is a partial but not complete correspondence of histologic type with broad age group.

Sex The male excess of HD also varies with histologic type. In Los Angeles County, there was an approximately twofold male excess in MC, LP and LD, while male and female risks were similar for NS. Recent relative frequencies from 13 international and 10 national locations indicate a female excess in NS in all areas (40).

Figure 5. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES* OF HODGKIN'S DISEASE IN WHITES, LOS ANGELES COUNTY (1972-1975), BY RYE HISTOLOGIC SUBTYPE AND SEX** +



A: Nodular Sclerosis; B: Lymphocyte Predominance;
C: Mixed Cellularity; D: Lymphocyte Depletion

* rates per 100,000 population
** pathology records not rereviewed for this study
\+ from (52)

Race Differences in histology-specific incidence by race have not been widely investigated. Blacks in Washington, D.C. and South Africa have lower proportions of NS and higher proportions of MC and LD, subtypes with poorer prognoses, than their white counterparts (80-82). Blacks in Los Angeles County showed relative frequencies similar to whites but had lower rates of every histologic type except MC (52). These observations, while suggestive of genetic differences in susceptibility, are also consistent with Correa and O'Conor's histology-SES association, and in fact were not controlled for the known effect of SES.

Geographic Variation There is considerable geographic variation in the relative frequencies of the four categories, in international data with rereviewed diagnoses (77). In the United States and Europe, NS is the prominent subtype, accounting for 30 to 50 percent of cases. Frequencies of LP and LD are low (approximately 15 percent and 10 percent respectively), and MC occurs in about 35 percent of persons with HD. In South and Central America, Africa and Asia, the relative distributions are different. NS is infrequent, affecting 4 to 25 percent of cases, while the other subtypes are more common than in the United States and Europe. In these and other international comparisons, NS seems to show the greatest variability, with frequency increasing roughly with level of economic development (40,77).

Unfortunately, evaluation of geographic variation in

histologic subtypes is limited to comparisons of relative frequencies. The few reliable histology rates available have been generated in studies from Connecticut; Alameda County, California; Los Angeles County, California; Norway; Finland; and Western Australia, but as mentioned above, the rates were not reported in most studies (7,52,70,77-79). The age-specific incidence in these areas will be examined with the regional SEER rates in Chapter 5.

Risk Factors There is also little information about the effect of histologic subtype on various risk factors. Henderson et al. and Holly reported an increased risk of SES primarily in NS (52,34), while in Israel, the SES association appeared in NS and MC (53). In Israel, the risk with woodworking was particularly elevated in persons with MC (53); in eastern Massachusetts, it appeared only in persons with LP (16).

Although there are few histology-specific rates, and the relative frequencies are only approximate measures of histology incidence, together they strongly illustrate the differences in the four subtypes in age-, sex-, race- and region-specific distributions. They make clear both the importance of evaluating HD by subtype, and the need for a thorough study of histology-specific incidence in this country, as first called for by O'Conor et al. in 1973 (70). Finally, they imply the potential impact of such new information on theories about the cause of HD.

ETIOLOGIC HYPOTHESES

The two major contemporary views on the nature and etiology of HD involve different interpretations of its bimodality and other epidemiologic features.

THE "TWO-DISEASE" THEORY

Expanding on his earlier theory, MacMahon proposed in 1966 that HD represented two or three separate diseases, one in children under 14, a second in young adults to age 35 and a third in persons over 50 (3). Citing differences between young and older patients in clinical presentation and prognosis, in sex ratios, in geographic variation and in secular trends, he further suggested that the disease in young persons was an inflammation of infectious origin and in older persons was a malignant neoplasm.

The proposal that HD was more than one disease has been subsequently supported with considerable evidence. Cole et al. and Fraumeni and Li demonstrated age-specific variation only in childhood and young adult HD in the United States (73,71). Newell et al. showed that younger and older patients had distinctly different histologic characteristics (83), and Gutensohn reviewed similar age-specific patterns in anatomic distributions of HD lesions (35).

The suggestion that HD in young persons was an infection has also been supported. Abramson interpreted the positive correlation between high young-adult-to-childhood rate ratios and disease in older persons as consistent with a viral infection. He proposed that primary infection in

childhood would protect against disease development later in life, while delayed infection would spare children but lead to higher HD incidence among young and older adults. He also noted that in older persons HD might result from a different, more complex combination of causal factors than in younger persons (75). The male excess in childhood HD has been considered consistent with an infectious etiology, as boys are known to be more susceptible to infections than girls in general (84).

Gutensohn and Cole expanded Abramson's theory, incorporating their own finding about the risks of childhood SES on young adult disease, and the epidemiologic similarities of HD to infectious mononucleosis and multiple sclerosis (48). They suggested that, like paralytic polio, HD in young adults

> is the rare sequel of infection with a common virus and the probability of its occurrence increases when infection is delayed until adolescence or young adulthood in some social settings (48, p.601)

such as those with small families, and more isolated residential environments in childhood.

The theory of differing etiologies for younger and older adults has recently been boosted by the observation of Gutensohn and Shapiro that older persons do not share the same childhood socioeconomic risk factors as young and middle-aged adults (43). Further, DeLong et al. found that climate and SES, factors related to infectious disease spread, explained variation in young adult but not older

adult HD mortality (54). Consequently, HD in older persons may not be explained by the same infectious etiology as the disease in children and young adults.

Considering histologic incidence, Franssila et al. concluded that several characteristics of the NS subtype--its young adult age specificity, equal sex ratio, unique pathologic appearance and lack of progression to other subtypes, anatomic distribution, and tendency to be the only histologic form of HD to vary geographically with SES in their analysis of international data--made it a likely candidate as a separate disease (77). They further postulated that the basic histologic type of the other HD entity was LP, with MC and LD heterogeneous categories describing more severe variants of LP and extreme, atypical versions of NS.

THE "HOST-SUSCEPTIBILITY" THEORY

The other interpretation of the bimodality of HD maintains that age-specific variation reflects age-modulated differences in host susceptibility and disease manifestion. Smithers first proposed this explanation, citing age-specific differences in disease duration and mortality, the apparent (if limited) bimodality of all subtypes, the occurrence of NS at all ages rather than solely young adulthood, and its female predominance (85). He believed NS represented not a separate disease but a favorable host response to HD, thus occurring more frequently in young (healthy) persons and in women, recognized for their lower incidence and longer survival. He explained the secular and geographic

variation in HD as "based on an uneven susceptibility in different node groups and an irregular impact of initiating stimuli" (85, p.1287).

Correa and O'Conor had a similar interpretation of their findings of age- and histology-specific variation with economic strata (4). They maintained that susceptibility to and histologic expression of HD were determined by host immunocompetence, which was itself controlled by environmental and socioeconomic factors, as occurred with tuberculosis and infectious mononucleosis. In poor countries, with crowding, inadequate sanitation and malnutrition causing early exposure to illness, children were more likely to develop HD, and, being physically compromised, were more apt to have a virulent form of the disease. In better economic situations, with less crowded and disease-conducive environments, persons were spared exposure to the etiologic agent until young adulthood and, being healthier, had a milder version of HD.

These SES effects on age-specific disease levels could explain the regional patterns of mortality in the United states described by Cole and coworkers as evidence of two diseases (73). In fact, DeLong et al. recently reported that this geographic variation could be attributed in part to regional differences in SES (54).

Silverman et al. thought that the minor differences in histology-specific incidence between Alameda County, Cali-

fornia and Connecticut (higher NS, lower LP in California) were consistent with regionally determined susceptibilities (7). However, they offered no evidence of environmental differences between the two areas.

While these two theories--one implicating separate disease causes and the other varying host reactions to a single cause--are substantively different, the epidemiologic findings to date do not discriminate well between them. In fact they seem to support either. There is strong although indirect evidence that HD in young adults is the consequence of infection. The conclusions about a separate etiology in those over 50 are based primarily an absence of such evidence at older ages. However, the differences between young and older adult disease behavior do not definitively disprove an infectious etiology, modified by age and other factors, in older persons. Thus the lack of discrimination between the two theories stems primarily from the focus on the infectious etiology in the young and a concomitant lack of attention to specific etiologies at older ages.

Whether infectious at all ages or not, the cause of HD can be said to be partly environmental, that is, requiring an external factor or factors as well as a host reaction. How the observed risk factors and other epidemiologic characteristics might all fit in this process can be suggested by arranging them, as in Table 3, according to 1) their effect on physiologic susceptibility, 2) their regulation of exposure to etiologic factors, and 3) their role as poten-

Table 3. HODGKIN'S DISEASE RISK FACTORS BY POTENTIAL ETIOLOGIC ROLES

SUSCEPTIBILITY	LIKELIHOOD OF EXPOSURE	ETIOLOGIC AGENT(S)
GENETIC	*community-level SES	*Epstein-Barr virus
*familial disease	*personal (childhood) SES	*other viruses
*HL-A linked inherited susceptibility	*race, ethnic origin (through SES association)	*wood dust
*parental consanguinity	*familial disease (if it reflects shared exposure)	*navy bean dust
*tonsillectomy (if it represents an increased tendency to develop infections)	*occupation	*chemicals
*race, ethnic origin	*residential location	*drug use
*hormones or other factors controlling: *male-female differences in age-incidence and prognosis *physical size *parity	*latitude	*???
	*drug habits	
*age (or specific factors controlling type and severity of disease response)		
INDUCED		
*SES (by controlling general level of health and resistance to disease)		
*tonsillectomy (if it reduces immunocompetence by removing lymphatic tissue)		
*infectious mononucleosis (characteristically causes immunosuppression)		

tial causal agents. The first category includes factors reflecting genetically determined susceptibility and factors inducing susceptibility by altering immunocompetence. The second includes variables controlling both community-level and personal contact with causal agents. The third category lists substances, biologic and nonbiologic, associated with HD and potentially functioning as initiators of the disease process.

Gutensohn has recently proposed a related model of pathogenesis, based on the premise that HD results from chronic low-grade antigenic stimulation, and integrating the malignant, infectious and immunologic features of the disease (16). She postulates that in young adults, infection (more severe than in children due to age) or long-term chemical exposure creates a chronic antigenicity. In older persons, the antigenic stimulation may result from natural age-related reduction in immune capacity. In both situations, expression of those genes mediating immmune response is altered so that the immune system becomes permanently "turned on". The resulting disease state is HD.

This hypothesis allows an explanation of the contradictory features of the disease. The malignant characteristics of HD tissue would result from the primary oncogenic change. The histologic features of inflammation would be caused by the overly stimulated immune system, and the

functional result of its imbalance would be the observed deficiency of cell-mediated immunity.

The proposed mechanism--unsuppressed immune response following chronic antigenicity--fits the present understanding of Reed-Sternberg cell derivation: i.e., from a macrophage whose function is to process antigens. It is also supported by the recent identification in familial HD cases of a susceptibility gene in or near the HLA system (57). If familial HD is influenced by an inherited genetic alteration of a gene in the immune system, as this finding indicates, then by extension, changes of such genes due to exogenous (viral or chemical) factors could also cause the disease.

In sum, the epidemiologic patterns and risk factors of HD suggest it is a rare, age-dependent host reaction, possibly an alteration of mediators of immune response, in persons genetically predisposed or artifically immunologically compromised. This host reaction follows a timely exposure to some possibly common infectious agent and/or other agent functioning as chronic antigenic stimulant(s). Because of the responsiveness of HD to the environment, information about geographic variation in its incidence, particularly at the histologic level, may provide further clues to its etiology.

Chapter 3

MATERIALS AND METHODS

This study uses cancer incidence and census data that were previously collected and are available in the public sector. This chapter describes these data, the selection of cases and populations, the interpolation of denominators, and the calculation of rates. For histology-specific incidence, it presents an analysis of data quality and decisions on histology rate inclusion. Finally, it discusses statistical tests used for comparing rates, examining time trends and evaluating associations between rates and economic variables.

CASE DATA: NUMERATORS

The most thorough study of geographic behavior of a disease requires data from the entire area under investigation. In the United States, geographically comprehensive mortality data no longer adequately indicate HD incidence, with the great success in the treatment of the disease in the last 15 to 20 years (10).

Fortunately, recent incidence data exist from the TNCS and subsequent SEER programs of the NCI. The usefulness of these surveys for geographic analyses is limited by their scope. Each covered only a few metropolitan areas and states (comprising approximately 10 percent of the population), selected not as representative samples but rather

for comparability to previous survey sites. However, as the only cancer incidence data in this country collected under uniform standards for more than a single metropolitan or state-wide region, they are logical sources of numerators for the study of the incidence and geographic patterns of HD rates.

DATA SOURCES: TNCS AND SEER PROGRAMS

The TNCS was established to ascertain all incident cases of malignant disease in the pericensal years 1969 through 1971, in seven metropolitan areas and two states. These areas were selected to be comparable to areas in a prior project, the Ten Cities Survey of 1947 (12). The subsequent SEER program, an ongoing incidence survey begun in 1973, included four of the TNCS regions as well as seven new ones, chosen for their reliable cancer registries and for particular demographic and environmental features (13). Table 4 lists the TNCS and SEER program regions and their dates of survey participation. These periods vary: Atlanta, New Orleans and Seattle-Puget Sound entered the program after 1973, and New Orleans and Puerto Rico ceased participating in 1977.

In both surveys data were collected for each cancer case on a number of variables including age, sex, race, county and census tract of residence at time of diagnosis, method of diagnosis, anatomic site and histologic type of cancer. During the study period, histologic diagnoses were classified first according to the Manual of Tumor Nomencla-

Table 4. REGIONS INCLUDED IN THE TNCS AND SEER PROGRAMS BY COUNTY AND DATES OF PARTICIPATION

Survey Region	Component Counties	Dates of Participation	Survey(s)
Atlanta	Clayton, Cobb, DeKalb, Fulton, Gwinett	1969-71, 1975-80	TNCS, SEER*
Birmingham	Jefferson, Shelby, Walker	1969-71	TNCS
Colorado	All	1969-71	TNCS
Connecticut	All	1973-1980	SEER
Dallas-Ft. Worth	Collin, Dallas, Denton, Ellis, Johnson, Kaufman, Rockwall, Tarrant	1969-71	TNCS
Detroit	Macomb, Oakland, Wayne	1969-71, 1973-80	TNCS, SEER
Hawaii	All	1973-1980	SEER
Iowa	All	1969-71, 1973-80	TNCS, SEER
Minn.-St. Paul	Anoka, Dakota, Hennepin, Ramsey, Washington	1969-71	TNCS
New Mexico	All	1973-1980	SEER
New Orleans	Jefferson, Orleans, St. Bernard	1974-77	SEER*
Pittsburgh	Allegheny, Beaver, Washington, Westmoreland	1969-71	TNCS
San Fran.-Oakland	Alameda, Contra Costa, Marin, San Francisco, San Mateo	1969-71, 1973-80	TNCS, SEER
Seattle-Puget Sound	Clallam, Grays Harbor, Island, Jefferson, King, Kitsap, Mason, Pierce, San Juan, Skagit, Snohomish, Thurston, Whatcom	1974-1980	SEER*
Utah	All	1973-1980	SEER
Puerto Rico	All	1969-71, 1973-77	TNCS, SEER*

* Part of 1973-80 SEER interval

ture and Coding, 1968 Edition (MOTNAC), and then by the International Classification of Diseases for Oncology (ICD-O) (86,87). However, there was no problem in code conversion for the histologic types of HD.

Incidence data from the TNCS, and from the SEER program for 1973 to 1977, reside at the Lawrence Berkeley Laboratory (LBL), University of California, Berkeley, on tapes obtained from the NCI. In addition, John Horm of the NCI kindly provided on tape a preliminary version of 1978-1980 SEER incidence data, which lacked only a few variables and information from Alaska, Arizona and rural Georgia. These LBL tape files were the sources of case data for rate numerators.

CRITERIA FOR SELECTION OF CASES

Microscopic Confirmation

Because HD cannot be diagnosed uniquely by anatomic site, and because of the epidemiologic importance of histologic type for this malignancy, I selected only microscopically confirmed cases from the TNCS, SEER 1973-1977, and 1978-1980 tapes at LBL, using MOTNAC codes 965.3-968.3 and ICD-O codes 9650-9662. Overall, this sample contained 98 percent of all ascertained HD cases. There was little geographic variation in the percent of cases with microscopic confirmation, which ranged from 95.7 to 99.1 in the TNCS data (12), and 97.9 to 100.0 in the SEER data for 1973-1977 (13)* (Table 5). The percent of cases classified by death

* These figures were obtained from the published sources.

Table 5. PERCENT OF SEER HODGKIN'S DISEASE CASES MICROSCOPICALLY CONFIRMED AND REPORTED ON DEATH CERTIFICATE ONLY, BY SURVEY REGION, 1973-1977
ALL RACES

Survey Region	No. of Cases	% Micro. Confirmed	% Death Cert. Only
San Fran.-Oak.	535	98.5	1.1
Connecticut	575	98.8	0.5
Atlanta	110	100.0	-
Hawaii	74	100.0	-
Iowa	457	97.6	0.7
New Orleans	95	98.1	-
Detroit	592	97.9	0.7
New Mexico	146	98.3	2.1
Utah	173	98.3	-
Seattle-P.S.	290	99.0	0.3
ALL AREAS	3047	98.4	0.7

certificate only, a measure of the thoroughness of identifying incident cases, was under 1.1 for data from every area except New Mexico. Together these figures indicate that the quality and completeness of case ascertainment across regions were high and sufficiently uniform to permit bias-free grouping of cases for combined-area rate calculations.

Race

Because of the small number of nonwhite cases and the differences in the epidemiology of HD by race, I selected only white cases for analysis.* Data from Puerto Rico were not available by race and therefore were excluded. All subsequent tables and figures will refer to this white case sample unless otherwise specified.

The total number of microscopically confirmed cases of HD in whites in this study is 6196. Table 6 organizes the cases by region and time period. The size of the total is noteworthy. It represents an extremely large sample of cases of this relatively rare disease and allows a detailed examination of its distribution by age, sex, histologic type, region and time. This level of detail has not been previously possible in descriptive studies HD.

POPULATION DATA: DENOMINATORS

The intercensal denominator estimates required for SEER rates were derived from population counts in the 1970 and 1980 United States Bureau of the Census censuses of

* This group included "Caucasians of Spanish Surname or Spanish origin".

Table 6. NUMBER OF MICROSCOPICALLY CONFIRMED CASES OF HODGKIN'S DISEASE FROM THE TNCS AND SEER PROGRAMS BY SURVEY REGION AND TIME PERIOD

Survey Region	1969-1971	1973-1976	1977-1980	1969-1980
Birmingham	33	-	-	33
San Fran.-Oak.	328	377	316	1021
Colorado	158	-	-	158
Connecticut	-	425	442	867
Atlanta	89	93	85	267
Hawaii	-	26	28	54
Iowa	282	356	375	1013
New Orleans	-	78	-	78
Detroit	314	392	407	1113
Minn.-St.Paul	182	-	-	182
New Mexico	-	104	113	217
Pittsburg	253	-	-	253
Dallas-Ft.Worth	188	-	-	188
Utah	-	139	131	270
Seattle-Puget S.	-	204	278	482
ALL AREAS	1827	2194	2175	6196

population. These data were available at LBL as a part of SEEDIS,** a computerized interactive data storage and manipulation system. To avoid discrepancies among certain of the census releases, I used the most updated versions available at LBL: for 1970, SEEDIS file R and for 1980, SEEDIS file CJ. To obtain denominators for each of the variously sized TNCS and SEER survey regions, I first extracted five-year age- and sex-specific 1970 and 1980 counts for whites for each component county, then aggregated them across counties to the appropriate SMSA, SMSA-plus-surrounding-counties, or state levels (see Table 4). A single exception to this approach occurred in the extraction of 1980 counts for Colorado and Hawaii. For these states I obtained 1980 data directly at the state level to avoid intercensal changes in county borders.

FORMULATING DENOMINATORS BY REGION

TNCS data

The 1970 census directly provided the age- and sex-specific white population counts that, multiplied by three, became denominators for average annual age-specific incidence rates for the TNCS cases.

SEER data

Intercensal population estimates were needed for SEER cases for three periods--1973-1980, and two subdivisions useful for time trend evaluations, 1973-1976 and 1977-1980.

** Socio-Economic Environmental Demographic Information System

These three sets of estimates were determined by straight-line interpolation, assuming census dates of April 1, 1970 and 1980. For each of the seven SEER areas participating for the entire study period (1973-1980), the estimated population counts for the i^{th} age group for both sexes combined, for males, and for females were derived as follows:

For 1973-1980:

$$\text{est. count}_i = 8\left[1980\ \text{count}_i - 3.25\left(\frac{1980\_\text{count} - 1970\_\text{count}}{(10)}\right)\right]$$

For 1973-1976:

$$\text{est. count}_i = 4\left[1980\ \text{count}_i - 5.25\left(\frac{1980\_\text{count} - 1970\_\text{count}}{(10)}\right)\right]$$

For 1977-1980:

$$\text{est. count}_i = 4\left[1980\ \text{count}_i - 1.25\ \frac{1980\_\text{count} - 1970\_\text{count}}{(10)}\right]$$

To include in these period subdivisions the three SEER registries with fewer years' participation, I altered the interpolation formulae as follows:

For Atlanta:

For 1975-1980:

$$\text{est. count}_i = 6\left[1980\ \text{count}_i - 2.25\left(\frac{1980\_\text{count} - 1970\_\text{count}}{(10)}\right)\right]$$

For 1975-1977:

$$\text{est. count}_i = 3\left[1980\ \text{count}_i - 3.75\left(\frac{1980\_\text{count} - 1970\_\text{count}}{(10)}\right)\right]$$

For 1978-1980:

$$\text{est. count}_i = 3\left[1980\ \text{count}_i - 0.75\left(\frac{1980\_\text{count} - 1970\_\text{count}}{(10)}\right)\right]$$

For New Orleans:

For 1974-1977:

$$\text{est. count}_i = 4\left[1980\ \text{count}_i - 4.25\left(\frac{1980\_\text{count} - 1970\_\text{count}}{(10)}\right)\right]$$

For Seattle-Puget Sound:

For 1974-1980:

$$\text{est. count}_i = 7\left[1980\ \text{count}_i - 2.75\left(\frac{1980\ \text{count} - 1970\ \text{count}}{(10)}\right)\right]$$

For 1974-1976:

$$\text{est. count}_i = 3\left[1980\ \text{count}_i - 4.75\left(\frac{1980\ \text{count} - 1970\ \text{count}}{(10)}\right)\right]$$

For 1977-1980:

$$\text{est. count}_i = 4\left[1980\ \text{count}_i - 1.25\left(\frac{1980\ \text{count} - 1970\ \text{count}}{(10)}\right)\right]$$

DENOMINATORS FOR ALL REGIONS COMBINED

Denominator estimates for all study areas combined were derived by summing the interpolated counts described above across all areas. The combined-area rates for 1973-1980, 1973-1976 and 1977-1980 therefore are based on slightly different time-period contributions from Atlanta, New Orleans and Seattle-Puget Sound.

COMPARABILITY OF THE INTERPOLATED DENOMINATORS TO OTHER ESTIMATES

Before the 1980 census data were available, the NCI published 1973-1977 SEER rates based for seven regions on extrapolated denominator estimates made by the United States Bureau of the Census, and on estimates provided by the states themselves for Hawaii, New Mexico and Connecticut (13). To compare these five-year population estimates with the interpolated 1973-1976 denominators from this study, I recalculated NCI-SEER denominators for the comparable four-year period by deriving the average annual population counts, and then quadrupling these to yield estimated four-year population counts.

Table 7 lists these recalculated NCI-SEER counts, the

Table 7. SEER REGION POPULATIONS BY METHOD OF ESTIMATION, AND MEASURES OF DIFFERENCE BETWEEN THE TWO 1973-1976

Survey Region	Extra-polation*	Inter-polation	Differences Absolute	Differences Percent
San Fran.-Oak.	10,121,693	9,868,748	252,945	-2.5
Connecticut	11,736,730	11,282,650	454,080	-3.9
Atlanta**	3,497,385	3,469,418	27,967	-0.8
Hawaii	1,061,558	1,237,497	-175,939	16.6
Iowa	11,258,902	11,243,971	14,931	-0.1
New Orleans***	2,700,106	2,695,209	4,897	-0.2
Detroit	13,285,772	13,041,032	244,740	-1.8
New Mexico	4,112,730	3,790,465	322,265	-7.8
Utah	4,690,198	4,797,410	-107,212	2.3
Seattle-P.S. +	6659,552	7,034,397	-374,845	5.6
ALL AREAS	69,124,626	68,460,797	663,829	-1.0

* $\left(\frac{1973\text{-}1977\_NCI\_counts}{5}\right)^4$

** 1975-1977

*** 1974-1977

\+ 1974-1976

interpolated 1973-1976 denominators for this study, and measures of the differences between the two by region. For all areas combined the interpolated population estimates are only 1 percent less than the NCI estimates, and for most individual regions the two are quite close. The areas with the largest discrepancies, Hawaii and New Mexico, have large ethnic populations whose racial identification in the census is problematic and may be partly responsible for the observed differences. It was not feasible to make corrections for these suspected inaccuracies. Thus disagreement between the published rates and those generated in the project should be slight but could reflect these methodologically based denominator discrepancies.

RATES

HD OVERALL--By Region

To document HD incidence over the entire SEER period, and to make a preliminary check of secular trends, I derived average annual age-specific and age-adjusted rates for each region, by sex and for both sexes combined, for three time periods: 1973-1980, and its halves, 1973-1976 and 1977-1980. I calculated the age-specific rates by dividing the total number of cases in each time period by the estimated denominator for that time period, for each age-sex group in each area. Most of these regional rates use a mix of 10- and 15-year age groups*.

* The exact age groups are 0-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, and 75 and over.

For some analyses of childhood HD, I used rates for the age group 0-9, as a recent analytic study suggested that the behavior of HD in the prepubertal years 10-14 may share more characteristics with adolescent patterns than those seen in childhood (43). Unless so specified, however, childhood rates were calculated for the age group 0-14.

HD OVERALL--All Regions Combined

Although the concept of a SEER region-wide rate makes little intuitive geographic sense, it offers the closest approximation of national incidence available at present. Therefore, I calculated rates for all SEER regions combined for various time periods. For the most part, the component areas were constant over these periods. In addition, Pollack and Horm interpreted the similarity in all-cancer rates for the seven areas surveyed from 1973 to 1976 to rates for all ten SEER regions over that period as adequate justification for calculating combined-area rates (88). The large number of cases from all regions together allowed a detailed examination of age-specific incidence using five-year age groups.

The evaluation of secular trends among the years 1969, 1969-71 and 1977-80 involves comparing differently composed combinations of regions. However, Pollack and Horm showed that trends formed by the sequential use of TNCS and SEER data (all respective areas combined) were very close to trends in data from only the four areas common to both surveys (88).

DeVesa et al. also concluded that, while data for 1947 were probably less reliable than the TNCS and SEER data, "no consistent strong patterns indicating noncomparability of the data are apparent" (89, p.278).

I did not calculate TNCS rates, except for a secular analysis for the four areas surveyed since 1969, as this had recently been done (34). The 1947 and 1969-1971 data for trend analyses were from published sources (11,12).

HD BY SUBTYPE

The potential for elucidating the important histologic behavior of HD is a particular attraction of the SEER data. However, secular and regional variation in the prevalence of Rye histologic diagnoses necessitates careful examination of data completeness prior to calculating histology-specific rates.

Prevalence of Rye Histologic Diagnoses in Time

The gradual implementation of the Rye version of the Lukes-Butler classification left a decade-long period following its 1965 adaptation when the number of cases categorized by these histologic subtypes was small but increasing. Figure 6 shows the yearly percent of TNCS and SEER cases classified by the Rye, Jackson-Parker, and no specified schemes for all survey areas combined. Table 8 summarizes use of the Rye system by region and time period. Although the proportion of cases with Rye diagnoses has increased substantially since 1969, during the TNCS years it was only at 34 percent, and for the next four-year period

Figure 6. PERCENT OF HODGKIN'S DISEASE CASES IN EACH HISTOLOGIC CLASSIFICATION, BY YEAR OF DIAGNOSIS

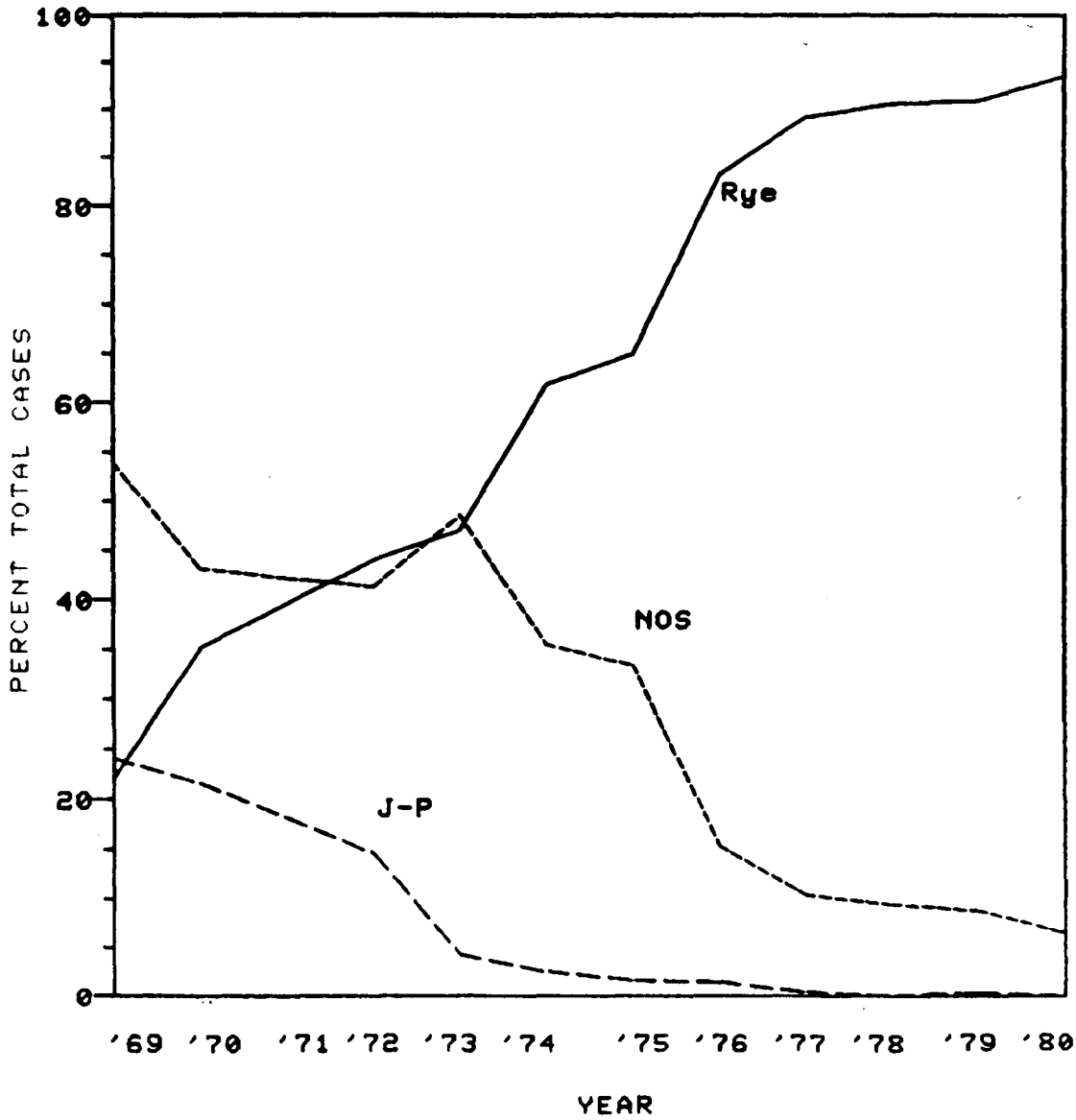


Table 8. NUMBER AND PERCENT OF HODGKIN'S DISEASE CASES IN EACH REGION AND TIME PERIOD CLASSIFIED BY THE RYE HISTOLOGIC SCHEME

Survey Region	1969-1971		1973-1976		1977-1980	
	n	%	n	%	n	%
Birmingham	10	33.3	-	-	-	-
San Fran.-Oak.	118	36.0	119	31.6	289	91.5
Colorado	53	33.5	-	-	-	-
Connecticut	-	-	300	70.6	399	90.3
Atlanta	40	44.9	83	89.2	81	95.3
Hawaii	-	-	22	84.6	28	100.0
Iowa	86	30.5	267	75.0	340	90.7
New Orleans	-	-	69	88.5	-	-
Detroit	115	36.6	205	52.3	365	89.7
Minn.-St.Paul	49	26.9	-	-	-	-
New Mexico	-	-	86	82.7	99	87.6
Pittsburgh	71	28.1	-	-	-	-
Dallas-Ft.Worth	73	38.8	-	-	-	-
Utah	-	-	107	77.0	117	89.3
Seattle-Puget S.	-	-	197	96.6	259	93.2
ALL AREAS	615	33.7	1455	66.3	1977	90.9

averaged 66 percent. Furthermore, it varied considerably from region to region until after 1976,* when its use was consistently high. The initially low and geographically varying prevalence of Rye diagnoses raises the issue of the comparablilty of cases with and without Rye histologic detail. Could histology-specific rates for the entire study period be calculated, or rates from the various periods be compared, without bias from these differences?

COMPARABILITY OF CASES WITH AND WITHOUT RYE HISTOLOGIC DIAGNOSES

To address these questions, I compared the 10- and 15-year age distributions and mean ages for persons with and without Rye diagnoses for the periods 1969-1971, 1973-1976, and 1977-1980. Tables 9 and 10 present the results of these χ^2 and t-tests. They show that, for all regions combined, cases with Rye subclassification had significantly different age distributions and were significantly younger in all three time periods than non-Rye cases. This greater likelihood of young persons to have been Rye-classified suggests especially detailed diagnostic attention to young persons with a suspected malignancy.

* For the period 1973-1976 only 31 percent of cases from San Francisco-Oakland were Rye-classified, in contrast to over 70 percent for most other areas. This relatively low proportion occurred because the local NCI contractor submitted to SEER a version of incidence data without consistent histologic detail. Following the 1977 conversion to ICD-O, this problem was eliminated (personal communication, Kay U. Bragg, California State Department of Health Services, Resource for Cancer Epidemiology).

Table 9. χ^2 VALUES FOR COMPARISONS OF AGE DISTRIBUTIONS OF CASES WITH AND WITHOUT RYE HISTOLOGIC CLASSIFICATION BY REGION AND TIME PERIOD

Survey Region	1969-1971		1973-1976		1977-1980	
	χ^2	p	χ^2	p	χ^2	p
Atlanta	14.59	.042*	12.33	.090	12.90	.075
Birmingham	14.30	.046*	-	-	-	-
Colorado	10.05	.186	-	-	-	-
Connecticut	-	-	12.37	.089	17.06	.017*
Dallas-Ft.W	10.82	.147	-	-	-	-
Detroit	3.95	.785	5.87	.555	14.07	.050*
Hawaii	-	-	19.78	.019*	(100% Rye)	
Iowa	15.07	.035*	23.17	.002*	19.65	.006*
Minn.-St. P	12.60	.083	-	-	-	-
New Mexico	-	-	4.04	.776	12.05	.098
New Orleans	-	-	9.52	.217	-	-
Pittsburgh	5.33	.619	-	-	-	-
San Fran.-O	14.15	.049*	4.72	.690	11.28	.127
Seattle-P.S	-	-	6.17	.521	17.70	.013*
Utah	-	-	7.73	.357	4.02	.778
ALL AREAS	41.92	<.001*	27.72	<.001*	69.09	<.001*

* statistically significant at $p \leq 0.05$

Table 10. MEAN AGES AND T-VALUES FOR COMPARISONS OF HODGKIN'S DISEASE CASES WITH AND WITHOUT RYE HISTOLOGIC CLASSIFICATION BY REGION AND TIME PERIOD

Survey Region	1969-1971 $\bar{X}$ AGE Rye	NonRye	t	p	1973-1976 $\bar{X}$ AGE Rye	NonRye	t	p	1977-1980 $\bar{X}$ AGE Rye	NonRye	t	p
Atlanta	37.7	46.1	-1.90	.06	37.1	48.6	-1.62	.108	33.8	61.5	-2.98	.004*
Birmingham	32.9	50.5	-2.22	.03*	-	-	-	-	-	-	-	-
Colorado	33.5	44.0	-3.11	.002*	-	-	-	-	-	-	-	-
Connect.	-	-	-	-	38.5	45.0	-3.11	.002*	38.7	50.6	-3.56	<.001*
Dallas-F.W.	40.9	44.9	-1.26	.207	-	-	-	-	-	-	-	-
Detroit	40.5	42.5	-0.82	.414	39.1	39.5	-0.21	.83	38.3	48.1	-2.88	.004*
Hawaii	-	-	-	-	31.3	61.8	-3.39	.002*	34.4	(100% Rye-typed)		
Iowa	42.0	49.5	-2.66	.008*	40.2	52.7	-4.66	<.001*	40.1	52.9	-3.29	.001*
Minn.-S.P.	39.6	46.3	-1.89	.061	-	-	-	-	-	-	-	-
New Mexico	-	-	-	-	36.2	46.1	-1.81	.07	36.9	48.3	-1.95	.054*
New Orleans	-	-	-	-	43.4	36.4	0.94	.35	-	-	-	-
Pittsburgh	42.3	46.8	-1.55	.121	-	-	-	-	-	-	-	-
San Fran-O.	35.7	45.0	-3.81	<.001*	38.8	43.1	-1.75	.08	36.6	45.3	-2.15	.03*
Seattle-PS.	-	-	-	-	39.5	27.1	1.57	.12	36.6	55.8	-3.92	<.001*
Utah	-	-	-	-	36.1	44.5	-2.02	.05*	33.7	43.6	-1.64	.104
ALL AREAS	39.1	45.8	-6.40	<.001*	38.7	43.7	-5.22	<.001*	37.6	49.8	-7.17	<.001*

* statistically significant at $p \leq 0.05$

The extent of age differences between Rye and non-Rye cases varied geographically. As seen in Table 9, the age distributions for Rye cases differed significantly from those of non-Rye cases in several regions. Table 10 shows that Rye cases were significantly younger than non-Rye cases in four of nine TNCS regions, four of ten regions in 1973-1976, and seven of eight* areas for 1977-1980. (For the last period, analyses were based on very small numbers of non-Rye cases in most areas). Together, these findings indicate that persons with Rye diagnoses were younger than those without in all time periods for most but not all study locations.

Because of these significant age differences and the well-established age-specific characteristics of HD, where possible I chose to limit histology-specific analyses to the later SEER years, when the effect of age-related bias was reduced by the high percentage of cases in the Rye group. The use of post-1976 data further skirted the earlier-mentioned serious underrepresenation of San Francisco-Oakland cases, one of the largest regional case groups.

CALCULATION OF HISTOLOGY-SPECIFIC RATES

To establish the epidemiologic patterns for HD by histologic type, I calculated age-specific and age-adjusted rates by sex for each Rye histologic type, by region and for all regions combined, for 1977-1980, using the methods described for HD overall. The small numbers in age-, sex-,

* By 1977, all cases in Hawaii were Rye-classified.

histology-, period-specific cells necessitated the use of the larger age groups. These small numerators and secularly varying proportions of cases with Rye detail made the analysis of regional time trends unfeasible.

To avoid the instability of regional age- and sex-specific rates for the rare histologic variants, LP and LD, I calculated rates for these two subtypes for the longer period 1973-1980. Because these 1973-1980 rates were based on lower and regionally variable proportions of all cases, I evaluated the effect of geographic differences in Rye proportions on the geographic variation in the rates of all four subtypes. There were no significant Spearman rank correlations between the percent of cases with Rye diagnoses in 1973-1980 and the age-adjusted rates of any of the subtypes for those years. Therefore completeness of numerators alone is not a strong enough factor to order the ranking of rates for this period and limit their usefulness in analysis.

The histology-specific rates calculated for this study represent the first reliable multi-region population-based rates available. All-area SEER rates describe the histopathologic behavior of HD in the largest group of incident cases ever collected.

AGE-ADJUSTMENT

All summary rates were age-adjusted according to the direct method, by applying the 10- and 15-year age-specific rates to the 1970 United States standard million population

(13, p.1082).

STATISTICAL ANALYSES

Three types of analyses required statistical testing. These were: 1) determination of differences in age-specific and age-adjusted rates between the sexes, and among regions and time periods; 2) establishment of secular trends in histology-specific incidence, given the problems with numerator completeness in the earlier rates; and 3) tests of hypotheses about correlations between various age-specific rates, and between rates and measures of community economic status, across all regions.

DIFFERENCES IN RATES

Differences between rates were considered significant if their respective 95 percent confidence intervals did not overlap. For age-adjusted rates confidence intervals based on a normal distribution were derived using standard errors calculated by the method of Chiang, as described in Lilienfeld and Lilienfeld (90). Standard errors of proportions were used for intervals around age-specific rates.

TIME TRENDS IN HISTOLOGY-SPECIFIC INCIDENCE FOR ALL REGIONS COMBINED

The limitations of the histology data prior to 1977 affect the reliability of the rates. Therefore, investigation of secular trends in histology-specific incidence required several different analyses used together to provide an accurate view of the behavior of the subtypes through the

1970s. The methods for three of these analyses are described below.

Tests for Trend in Age-Specific Relative Proportions

To evaluate histology incidence trends without the bias of rate incompleteness, I first examined the relative proportions of cases in each histologic subtype for evidence of steady change in time. For each age group I calculated a χ^2 statistic for testing the significance of the slope of a regression line formed by graphing the relative frequencies against time (91). A χ^2 value greater than 3.84 indicated that the slope differed from zero at $p \leq .05$, and therefore that the use of that histologic subtype in that age group was increasing or decreasing significantly in time.

Determining Differences in Secular Trends by Histologic Type

To test the hypothesis that the extent of secular change in rates differed from subtype to subtype, I calculated the 1977-1980 rates expected under the null hypothesis of no subtype-specific change, for comparison with observed 1977-1980 rates. The null hypothesis stated that, for each subtype, age-specific rates would change in time from their 1973-1976 level only by the age-specific changes for HD overall and by the age-specific increases in Rye use. The 1973-1976 rates used as the baselines for these calculations were first modified themselves to estimate "true" 1973-1976 histology-specific incidence, i.e., derived from 100 percent of HD cases, so as to remove the bias of incomplete numerators from these estimations. The expected 1977-1980 rates

were derived from actual 1977-1980 Rye proportions and consequently represent the rates expected under the null hypothesis given those partial numerators. As such they are directly comparable to the observed 1977-1980 rates.

The calculation of the expected rates involved three assumptions:

(1) For 1973-1976 "true" baseline rates: Each observed 1973-1976 age-, histology-specific rate was a proportion of the "true" 1973-1976 rate, equivalent to the percent of all HD cases in that age-group that were Rye-classified in 1973-1976. Thus, for each histologic subtype:

"true" 1973-1976 age-specific rate$_i$ = (observed 1973-1976 age-specific rate$_i$) X (1/1973-1976 proportion$_i$ of all HD cases Rye-classified)

(2) For determining secular change under the null hypothesis: Between 1973-1976 and 1977-1980, the percent changes in age-specific rates for HD overall would occur equally in each subtype. Therefore for each histologic subtype:

"true" 1977-1980 age-specific rate$_i$ = ("true" 1973-1976 age-specific rate$_i$) + (("true" 1973-1976 age-specific rate$_i$) X (((1/1973-1976 overall age-specific rate$_i$) X (1977-1980 overall age-specific rate$_i$ - 1973-1976 overall age-specific rate$_i$)) X 100))

(3) For making expected rates comparable to observed rates: Each expected 1977-1980 age-specific histology rate would be a proportion of the "true" 1977-1980 age-specific rate, equivalent to the percent of all HD cases in that age group that were Rye-classified in 1977-1980. Thus for each

histologic subtype:

expected 1977-1980 age-specific rate$_i$ = ("true" 1977-1980 age-specific rate$_i$) X (1977-1980 proportion$_i$ of cases Rye classified)

Differences between the observed and expected rates in any subtype would indicate that the secular change in that histologic category differed from trends for all HD, i.e., was histology-specific. The significance of such differences is determined, as above, by the overlapping of 95 percent confidence intervals, for sensitivity to age-specific differences.

Appendix Table A-1 contains the 1973-1976 and 1977-1980 overall age-specific proportions and the overall age-specific percent changes in rates between the periods, used in these calculations.

Approximation of Histology Rates for 100 Percent of HD Cases

To estimate time trends that would have occurred if histology rates were based on all possible cases, I approximated the "true" incidence of each histology type for 1973-1976 and 1977-1980. The projection of these "true" rates assumed that each observed age-specific rate was a proportion of the "true" rate, equivalent to the percent of all HD cases in that age group with a Rye diagnosis. Thus for each subtype:

"true" 1973-1976 age-specific rate$_i$ = (observed 1973-1976 age-specific rate$_i$) X (1/1973-1976 proportion$_i$ of all HD cases Rye-classified)

true" 1977-1980 age-specific rate$_i$ = (observed 1977-1980 age-specific rate$_i$) X (1/1977-1980 proportion$_i$ of all HD cases Rye-classified)

As above, secular trends were evaluated using confidence intervals around the rates.

ASSOCIATIONS BETWEEN AGE-SPECIFIC RATES, AND BETWEEN RATES AND COMMUNITY SES

Correa and O'Conor first reported in detail the geographic variation in age-specific rates, and the effect on this variation of community economic status (4). However, these relationships were not all quantified and have not been explored in United States incidence data. In this study, associations between various age-specific rates, and between rates and SES, were summarized by Spearman rank correlation coefficients calculated for all nine or ten SEER regions (depending on the period examined).

To analyze the relationships between rates and community-wide SES, it was necessary first to derive measures of economic standing for each study area. This involved selecting economic variables and then estimating their region-wide levels.

Determining Community-Level SES

I chose county-level measures of income and educational attainment available in the United States Bureau of the Census County and City Data Books, 1947-1977, installed as File F in SEEDIS. Where possible, I obtained the variables for two years, 1960 and 1970, under the hypothesis that earlier socioeconomic status might have more bearing on HD, a disease with a presumed long latent period, than concomi-

tant status. I identified measures of poverty (percent of families with income below $3000 (1960) or $5000 (1970)), wealth (percent of families with income above $10,000 (1960), $15,000, or $25,000 (1970)), average economic level (median family income), poor education (percent of persons over age 25 with fewer than five years schooling), good education (percent of persons with a high-school education or more (1970)), and average educational level (median years of education).

To estimate an overall economic level for each study area, I calculated population-weighted averages for each independent variable for each SEER region. The SES variable values were obtained for each county in the study region, multiplied by the proportion that county's population represented of the study region total, and then summed across all counties in the study region to yield the weighted average. For some metropolitan areas, e.g., San Francisco-Oakland, the averages were calculated for a small number of contiguous urban areas, while for the states, e.g., Utah, the averages were made across all counties, urban and rural, in the entire state.

Table 11 presents these average socioeconomic measures for 1960 and 1970 for each SEER area. The effect of statewide averaging is apparent in the lower median incomes of Iowa, New Mexico and Utah, presumably reflecting in part the contributions of poorer rural counties. Within some areas there are notable discrepancies between ranks of in-

Table 11. POPULATION-WEIGHTED AVERAGE SOCIOECONOMIC MEASURES FOR STUDY AREAS

1960

Survey Region	Total Pop	Pop Density Per Sq. Mile	Pct Fam Earning <$3000	Pct Fam Earning >$10000	Median Family Income	Pct Persons >25 Yrs <5 Yrs School	Median School Years
San Fran-Oak	2648762	5250.9	11.7	24.7	7138	5.4	12.2
Connecticut	2535234	850.0	9.8	22.0	6914	6.3	11.0
Atlanta	1017188	871.4	20.9	16.9	5717	10.0	10.9
Hawaii	632493	668.2	13.0	22.1	6418	14.8	11.3
Iowa	2757537	115.3	25.1	10.8	5064	3.0	11.1
New Orleans	868480	2362.9	24.3	13.4	5154	13.3	9.5
Detroit	3762360	3360.5	13.5	21.9	6830	6.6	10.8
New Mexico	951023	70.5	25.0	14.2	5290	12.5	10.9
Utah	890627	263.6	14.7	13.8	5912	2.8	12.1
Seattle-Puget S.	1822582	283.5	13.7	18.3	6488	3.1	11.9

1970

	Total Pop	Pop Density Per Sq. Mile	Pct Families Earning <$3000	<$5000	>$15000	>$25000	Median Family Income	Pct Persons >25 Yrs old <5 Yrs School	>High School	Median Yrs School
San Fran-Oak	3109519	4550.5	7.1	13.9	31.9	7.6	11775	4.0	16.8	12.5
Connecticut	3031790	990.2	5.4	11.0	31.0	8.0	11903	4.3	13.6	12.2
Atlanta	1390164	1098.6	8.2	16.3	26.1	6.0	10582	5.9	14.2	12.1
Hawaii	768561	871.6	6.7	13.3	32.6	7.8	11620	8.2	14.1	12.1
Iowa	2824376	133.2	10.1	20.8	16.3	3.5	9074	1.9	9.4	12.2
New Orleans	982225	2140.9	14.5	25.9	17.3	4.3	8515	8.0	10.5	11.3
Detroit	4199931	3223.0	6.4	12.4	33.0	6.9	12144	4.5	9.5	11.9
New Mexico	1016000	93.4	15.6	29.0	14.6	3.0	7856	9.1	12.7	11.8
Utah	1059273	327.8	8.8	18.6	16.9	3.2	9333	2.1	14.1	12.5
Seattle-Puget S.	230262	2352.0	6.9	14.2	25.7	5.2	10965	1.9	13.7	12.4

come and education. For example, in 1960, Seattle-Puget Sound, Iowa and Utah had the highest percents of persons earning less than $3000 a year, but the lowest percents of persons with less than five years of school; Detroit has the opposite pattern, with high median income and low median education. These opposing trends indicate that levels of income and education may not be correlated in certain areas in the United States. Consequently the directions of relationships between these two groups of measures and the dependent variables may differ.

Associations Between Age-Specific Rates and Community SES

All correlations involved rates for the entire study period (1973-1980). To test quantitatively for the frequently noted relationships between the young adult segment of the age-specific curve and community SES in these United States populations, I defined young adult incidence as occurring between ages 10-14 and 35-39, based on examination of the age-specific curve for these SEER data (Chapter 4, Figure 7). I then measured this young adult peak three ways: a) by its height (for each region the highest five-year rate in that age range), b) by the profile of its peak (the average percent change in subsequent five-year rates between ages 15 and 34), and c) by its area (estimated by counting the grid squares (grid = one five-year age group unit by one rate unit) in the space under the curve between the aforementioned ages). Each of these three variables was

used in correlation analyses. The older adult peak rate was similarly identified as the highest 10- or 15-year rate over age 55 for each region for use in additional correlations.

All data were extracted, stored, manipulated and graphed using SPSS (Statistical Package for the Social Sciences) and LBL software on a Digital Equipment Corporation VAX/VMS 11-780 computer.

Chapter 4

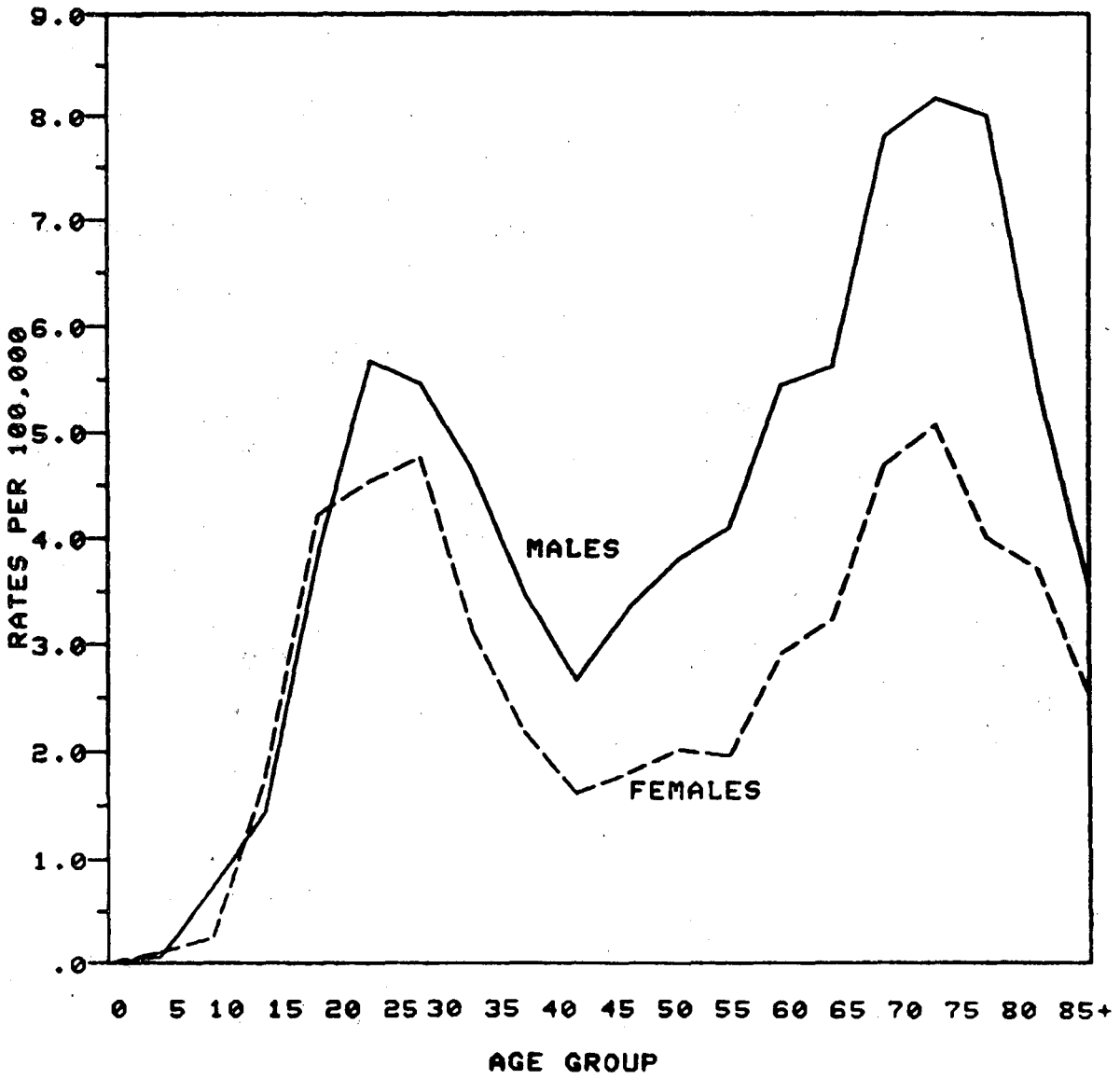
HODGKIN'S DISEASE INCIDENCE ACROSS ALL REGIONS COMBINED

This chapter describes HD among persons from all survey regions. It provides an approximate view of its nationwide incidence by age, sex and histologic subtype, variables well known to modify its behavior. It also examines changes in disease incidence since 1947, with particular attention to the SEER years. The distributions and time trends are presented first for HD overall and then for each of its four histologic categories using newly available, reliable data. Because of their number, many of the supporting tables for this chapter, including those listing 95 percent confidence intervals, are contained in Appendix B.

INCIDENCE BY AGE AND SEX FOR ALL HD

Across the ten SEER areas, HD is distributed as expected from previous studies. The average annual age-adjusted incidence rate in whites for 1973-1980 is 3.0 per 100,000, with the slight male excess evident in a male-female ratio of 1.4. Figure 7 and Appendix Table B-1 show for each sex the age-specific incidence patterns typical of HD in well-developed countries. The first, or young adult, mode peaks between ages 20 and 30, while the older age rates are highest between ages 75 and 80. The shapes of both male and female curves are bimodal, differing only in two respects: 1) female young adult incidence peaks at a slightly

Figure 7. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE FOR ALL SEER REGIONS COMBINED, BY SEX, 1973-1980



older age, as previously reported (6), and 2) among males, disease incidence is greatest in old age, while for females, old age and young adult rates are similar in magnitude.

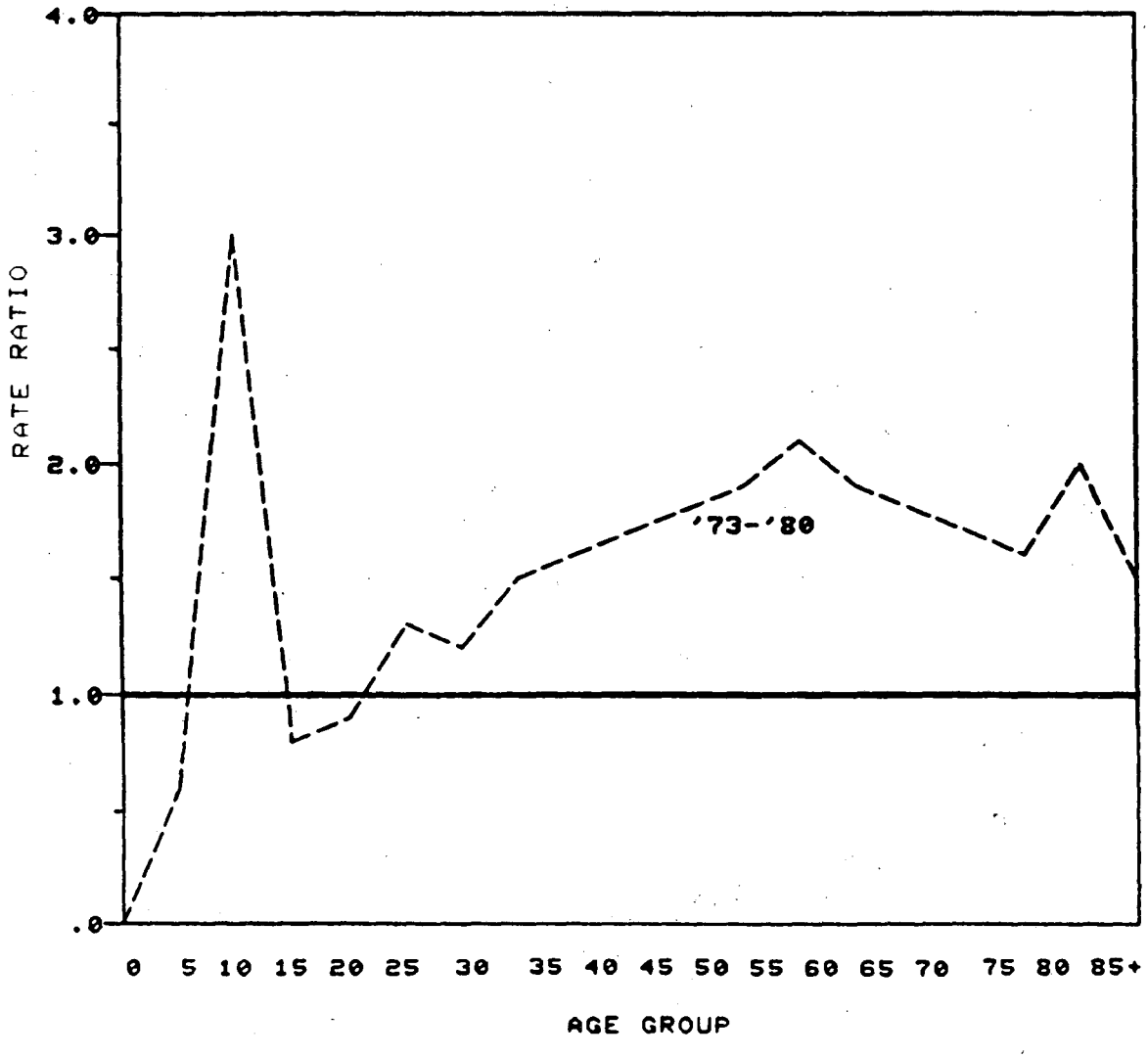
At all ages over 20, male incidence exceeds female incidence, but the sex ratios, seen in Figure 8, vary with age, as expected. Male predominance is greatest in childhood, disappears in early young adult years, then increases with age, peaking in the intermodal period and again around age 80. An intermodal male excess has been previously reported (2,3,8,72). The old-age male predominance reflects the relatively low levels of disease in older women in this population.

These data thus corroborate the characteristic patterns of HD: low incidence overall, bimodal age-specific curve, and the higher but age-varying risk in males. The features of these findings that are most distinctive (although not unique) are: 1) the slight female excess between ages 10 and 20, and 2) the low female incidence at older ages.

TIME TRENDS IN INCIDENCE: 1947-1980

In the 30 years over which the last three NCI incidence surveys have occurred, HD rates show two general secular trends. The first, between 1947 and 1969-1971, comprises previously noted incidence increases (10) and age-specific changes associated by Correa and O'Conor and others with improving economic status (4,48). The second trend,

Figure 8. MALE-FEMALE HODGKIN'S DISEASE RATE RATIOS FOR ALL SEER REGIONS COMBINED, BY AGE, 1973-1980



apparent during the 1970s, involves slight declines in incidence, particularly among older persons.

1947 to 1969-1971:

HD incidence underwent a significant increase, between the Ten Cities survey of 1947 and the TNCS, from 2.9 to 3.4 per 100,000. The age-adjusted rates and associated 95 percent confidence intervals are presented in Table 12. The increase was slightly greater in males (19.4 percent) than in females (11 percent) but not statistically significant at $p = 0.05$ for either sex.

As expected in this disease, changes in incidence were apparent only in certain age ranges. Figure 9 and Appendix Table B-2 document the secular development of pronounced bimodal curves in both sexes. In males, the change in the overall rate reflects a significant increase in young adult disease and a slight increase, as well as a transfer in location from age 65 to 85, of the second peak. In females the increase occurred at older ages and was not statistically significant. Although several investigators have reported a secular decline in childhood HD, presumed to occur with economic improvement (2,3,4,44,48), these SEER data do not follow that pattern. Table 13 presents rates for three time periods for children of two age groups. In boys and girls of both age ranges, the rates were stable between 1947 and 1969-1971. With this exception, the age- and sex-specific patterns of change in this period typify the evolution from Correa and O'Conor's Type II to Type III age incidence

Table 12. AVERAGE ANNUAL AGE-ADJUSTED HODGKIN'S DISEASE INCIDENCE RATES AND 95 PERCENT UPPER AND LOWER CONFIDENCE INTERVALS FOR FOUR TIME PERIODS, BY SEX

	BOTH SEXES			MALES			FEMALES		
		C.I.			C.I.			C.I.	
Year	Rate	Lower	Upper	Rate	Lower	Upper	Rate	Lower	Upper
1947	2.9	2.6	3.2	3.4	2.9	3.9	2.5	2.1	2.8
1969-71	3.4	3.2	3.5	4.1	3.8	4.3	2.7	2.5	2.9
1973-76	3.1	2.9	3.2	3.6	3.4	3.8	2.6	2.4	2.7
1977-80	2.9	2.8	3.1	3.5	3.3	3.7	2.5	2.3	2.6
1973-80	3.0	2.9	3.1	3.6	3.4	3.7	2.5	2.4	2.6

* All rates adjusted to the 1970 standard U.S. million population (13)

Figure 9. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE BY TIME PERIOD FOR ALL SURVEY REGIONS COMBINED, FOR MALES AND FOR FEMALES

1947, 1969-1971

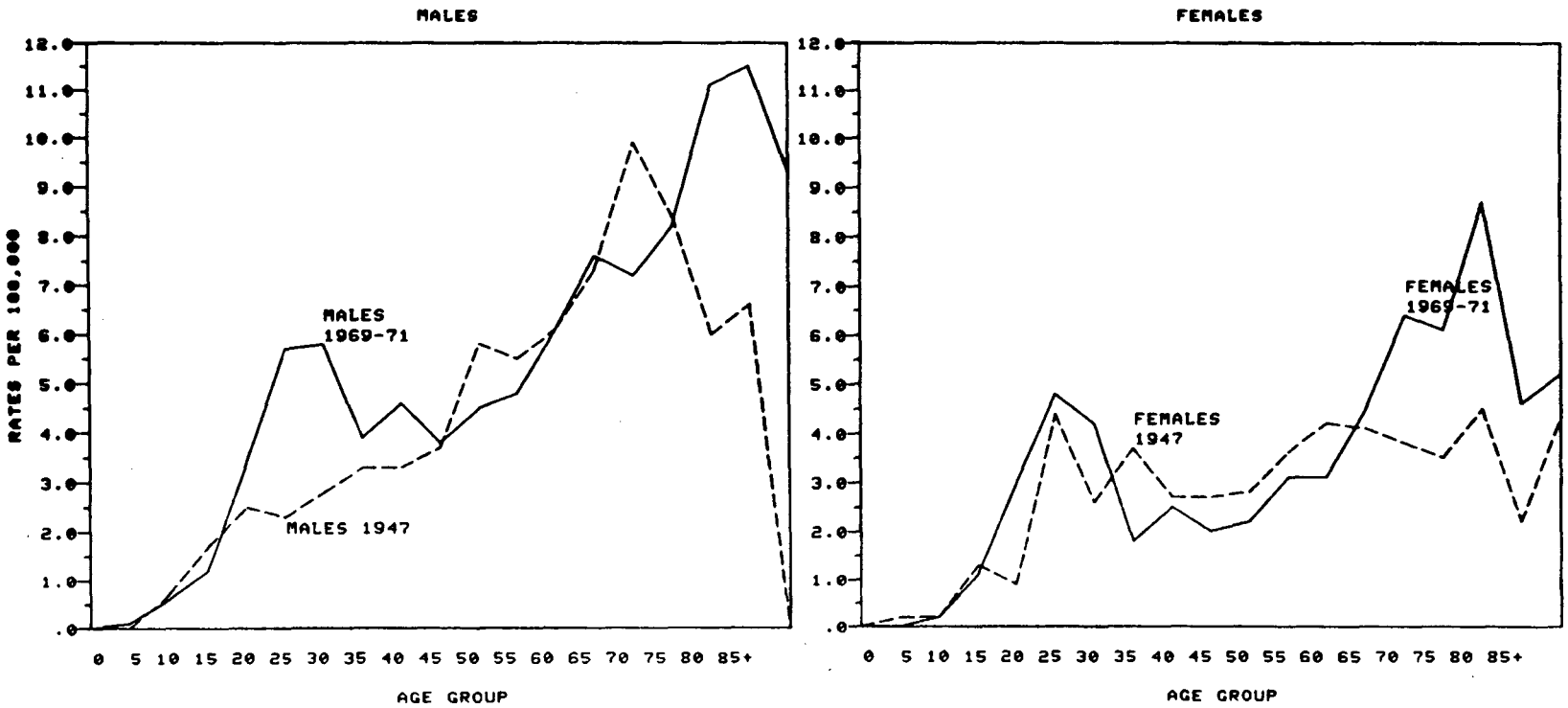


Table 13. AVERAGE ANNUAL INCIDENCE RATES OF HODGKIN'S DISEASE IN CHILDREN OF TWO AGE RANGES, BY SEX AND TIME PERIOD

	AGES 0-9				AGES 0-14			
	Males		Females		Males		Females	
Year	Rate	n	Rate	n	Rate	n	Rate	n
1947	.29	3	.20	2	.70	10	.50	7
1969-71	.4	-	.1	-	.68	54	.46	35
1977-80	.46	23	.17	8	.83	65	.73	54

curves, with the development of a young adult peak, and changes generally more pronounced in males.

1969-1971 to 1977-1980

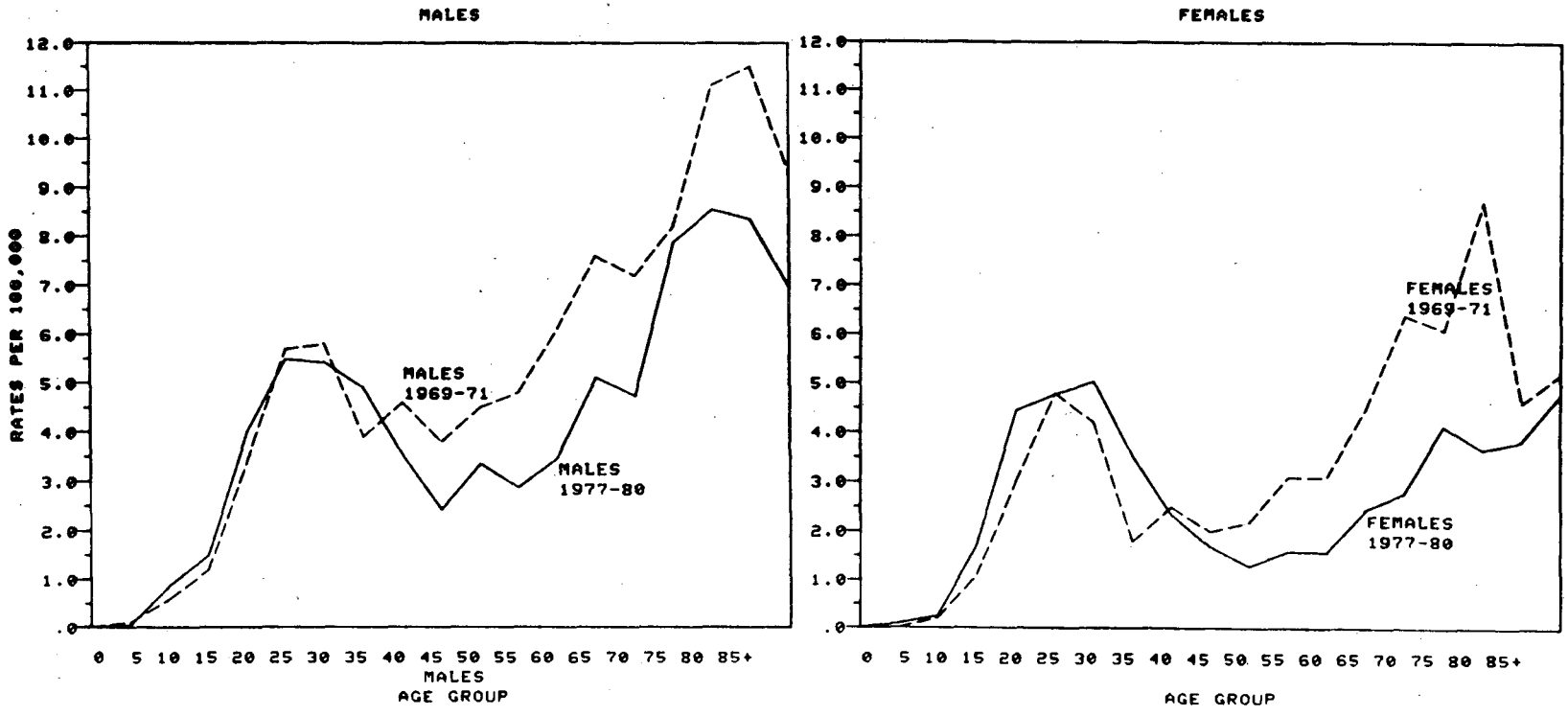
Between 1971 and 1980, the trend of increase in overall incidence stopped. Age-adjusted rates (Table 12) decreased steadily, with the 1977-1980 rate of 2.9 per 100,000 significantly lower than the 1969-1971 rate of 3.4 per 100,000. Again the percent change over the decade was greater for males (-15.0 ver-sus -8.8 for females), and only in males was the difference significant at p = 0.05. However, the direction and gradient of the change were the same for both sexes.

These secular trends also varied with age and sex, as illustrated in Figure 10. The decline in incidence clearly occurred only among persons over age 35. Rates in young adults showed small increases, apparent for males only at ages under 20 and between 30 and 35. For children under ten (Table 13), disease levels continued to be stable, but for those under 14, rates rose a little, reflecting increases seen in persons over age 10.

Two of these trends were more distinct in females. 1) Among older women, the incidence decrease was statistically significant at ages 65-69 and 75-79 (Appendix Table B-2) and sufficiently pronounced to lower the peak old age rates below the peak young adult rates. 2) At most ages under 35, female rates increased slightly (statistically significant at ages 30-34) but consistently enough to suggest that HD

Figure 19. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE BY TIME PERIOD FOR ALL SURVEY REGIONS COMBINED, FOR MALES AND FOR FEMALES

1969-1971, 1977-1980

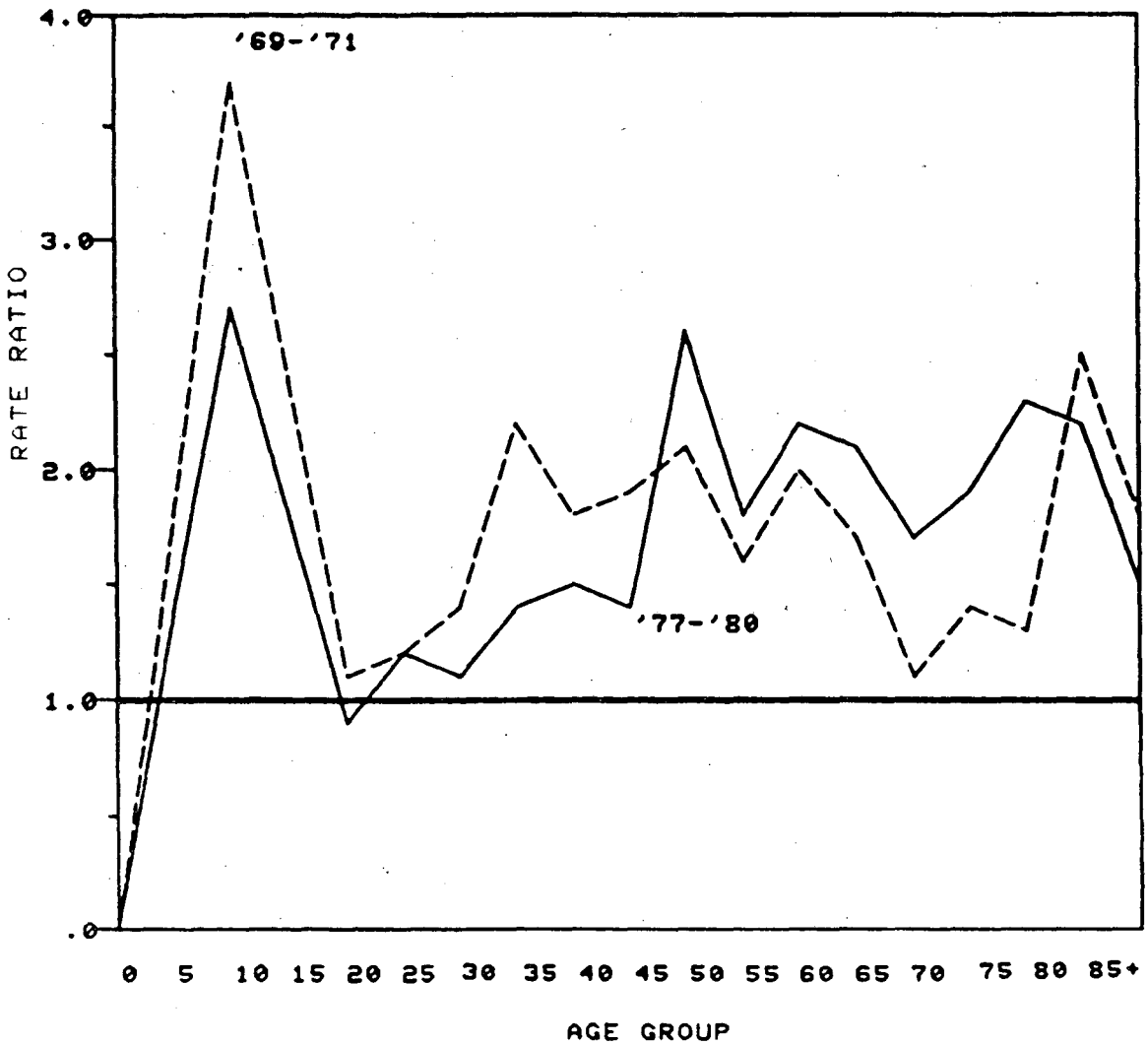


was continuing to increase in young women in time.

Figure 11 and Appendix Table B-3 summarize the way secular trends in the 1970s were modified by age and differed between males and females. The figure illustrates age-specific sex ratios for 1969-1971 and 1977-1980. Between these two periods, the male excess became less pronounced in young adulthood and more apparent over age 45, reflecting the increasing risk of HD in younger women and the decreasing risk among older women. The large male excess in childhood has also diminished with time.

While the secular trends in HD incidence in the 1970s were not dramatic, four of them were unanticipated and therefore noteworthy. 1) The decreases in age-adjusted rates contrast with increases occurring until 1971, suggesting a changing overall incidence of this disease. 2) These changes involved trends that were characteristically age-specific but operated in unexpected, contradictory directions. There was a substantial drop in incidence in older persons, while simultaneously, rates in young adults continued to increase. Opposing trends in these age groups have not been previously described. Furthermore, at the oldest ages, the preliminary rate rise, with the shift in location of its peak to an older age, followed by the subsequent rate decreases, suggests a cohort phenomenon affecting persons middle-aged by 1947. 3) Both the young adult increase and the older-age decrease were more distinct in female rates, although age-specific variation, at least geographically,

Figure 11. MALE-FEMALE HODGKIN'S DISEASE RATE RATIOS FOR ALL REGIONS COMBINED, FOR 1969-1971 AND 1977-1980, BY AGE



has been noted to be much less pronounced in women (4,75). The rates for older females were quite low by 1977-1980. 4) The expected decreases in childhood rates did not occur. In addition, there was a decline in the male excess at ages under 14.

Thus the distribution of HD across the surveyed regions of this country is mostly consistent with previous reports of its epidemiologic characteristics in economically affluent environments. However, the distribution differs from established pattern in certain time trends, specifically the drop in incidence in persons over 35, the rate stability in children, and the pronounced secular variation in women. The role of histologic subtype in these findings will be explored in the next section.

INCIDENCE BY AGE AND SEX FOR THE FOUR RYE HISTOLOGIC SUBTYPES, 1977-1980

The SEER data support the frequent observation that the epidemiology of HD varies among the histologic subtypes (7,52,53,70,77-79). For 1977-1980, the period in which numerators for histology-specific rates were based on 91 percent of all cases, rates by histologic type had markedly different age- and sex-specific distributions. The behavior of the NS form was particularly distinctive.

Table 14 and Appendix Table B-4 present 1977-1980 incidence rates with 95 percent confidence intervals by histologic type, age, and sex. At 1.5 per 100,000, NS was the most common form, with an age-adjusted rate double that

Table 14. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE BY RYE HISTOLOGIC SUBTYPE AND SEX, 1977-1980 FOR ALL REGIONS COMBINED

	AGE GROUPS								
SUBTYPE	00-14	15-24	25-34	35-44	35-44	45-54	55-64	65-74	AAR
NS Males	.45	3.12	3.03	1.35	1.19	1.18	1.48	1.78	**1.60**
NS Females	.52	3.63	3.32	1.20	.79	.62	.47	.41	**1.52**
LP Males	.10	.37	.46	.38	.34	.28	.56	.28	**.30**
LP Females	.00	.10	.12	.08	.08	.26	.20	.35	**.10**
MC Males	.17	.95	1.22	.80	1.07	1.55	2.10	2.72	**.95**
MC Females	.12	.62	.66	.45	.33	.71	1.42	1.82	**.53**
LD Males	.08	.08	.14	.15	.28	.62	1.07	1.41	**.28**
LD Females	.01	.00	.04	.10	.08	.26	.59	.66	**.11**

for MC (0.7 per 100,000) and significantly higher than for the three other subtypes. LP and LD were both rare, with similar summary incidence (0.2 per 100,000). Male rates were two to three times female rates in all subtypes except NS.

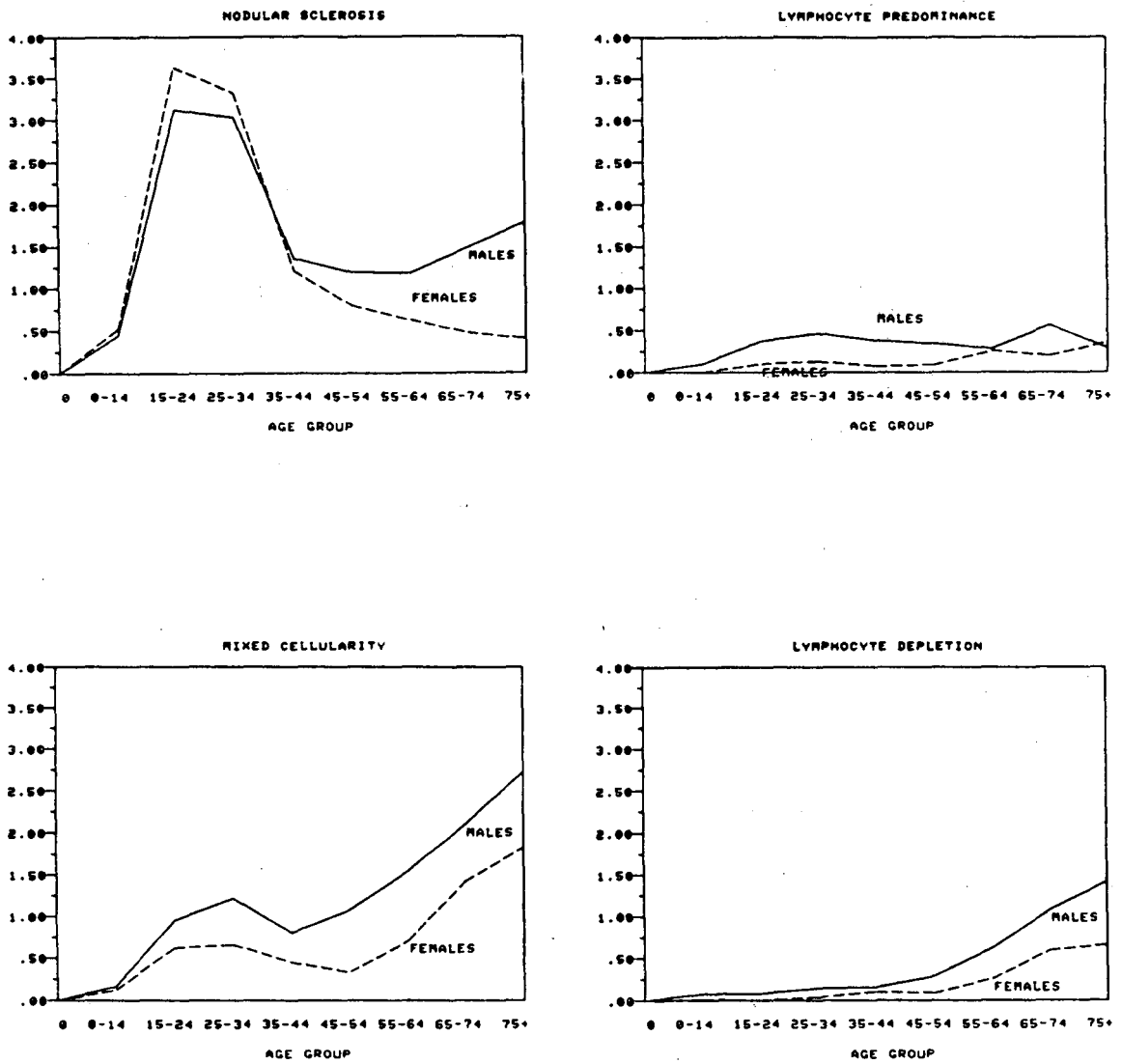
AGE

The age-specific curves, illustrated in Figure 12, are also unique to each of the four categories. The distribution for NS had the high young adult incidence seen in the first mode for HD overall, although peaking at a young age, but low rates over age 44. The highest childhood rates occurred in this subtype, as Correa and O'Conor first reported for well-developed countries (4). MC had a bimodal curve with low young adult peaks, occurring later than in NS, and the highest rates of all the subtypes for persons over 55. LP had very low rates at all ages but, like NS and MC, did occur in young adults. Only LD showed an age-specific pattern typical of malignant disease. Thus, as observed in other data, each subtype was predominantly associated with a certain age range, but none had incidence limited entirely to a single age bracket (7,52,70,77-79).

SEX

The characteristic male predominance of HD occurred consistently with age in three of the subtypes, MC, LP, and LD, and each of these had similarly shaped male and female curves. NS was distributed differently. It had a lower sex ratio, at 1.1, a clear female excess in the young adult

Figure 12. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES* OF HODGKIN'S DISEASE, BY RYE HISTOLOGIC SUBTYPE AND SEX ALL SEER REGIONS COMBINED, 1977-1980



* rates per 100,000 population

years, and higher female than male childhood rates. Furthermore, after age 35-44, its male and female curves diverged with age, with female rates significantly lower than male rates over age 65. This progressive decrease in female NS incidence with age produced a unimodal age-specific curve for women. Thus NS stands apart from the other subtypes in both age-specific and particularly sex-specific behavior, being primarily a disease of young adults with a female excess below age 44. This difference led investigators to postulate that NS is etiologically distinct from the other subtypes, perhaps constituting the first disease of the two-disease hypothesis (52,77). Its interpretation in this study will be taken up in Chapter 6.

TIME TRENDS IN HISTOLOGY-SPECIFIC RATES: 1969-1971 to 1977-1980

Incomplete histologic detail in these data hinders the investigation of time trends in histology rates. However, the SEER cases provide the first opportunity to monitor secular patterns at this important level. Considering several forms of the data--relative frequencies, observed and estimated rates--aids evaluation of the trends in the face of biases in the existing data.

The following six analyses indicate that the secular behavior of HD has differed among the subtypes, and within certain subtypes, by age.

(1) Time Trends in Relative Frequencies

The use of relative frequencies of cases in each

subtype circumvents part of the problem of small and changing proportions of persons with histologic diagnoses: in their magnitude, these percentages do not reflect the size of the case population Rye-classified, while histology-specific rates do. Table 15 presents relative frequencies of HD by histologic type for 1969-1971, 1973-1976 and 1977-1980, detailing the age-specific differences in time trends for each histologic category. Over this decade, the proportions of cases classified as NS showed a gradient of increase at most ages under 65, statistically significant in young adults and persons aged 45-54. In contrast, the proportions called LP showed significant, steady declines in almost every age group. The summary relative frequencies of MC and LD have not changed. However, young adult relative frequencies MC have decreased, while the proportions of older persons with both MC and LD have increased. The frequencies in each of the three time periods are based on different totals (percentages of all cases with Rye diagnoses). However, they clearly delineate the differences among subtypes in their age-specific frequencies across the decade, particularly the increases in NS and the decreases in LP.

(2) Time Trends in Age-Adjusted Rates: 1969-71, 1973-76, 1977-80

Table 16 presents the age-adjusted rates for these three periods. Based only on histologically classified

Table 15. PERCENT OF HODGKIN'S DISEASE CASES IN EACH AGE GROUP CLASSIFIED IN EACH HISTOLOGIC SUBTYPE WITH VALUE OF χ^2 TEST FOR TREND, BY TIME

Nodular Sclerosis	Year			
Age Group	'69-71	'73-76	'77-80	χ^2
0-14	52.9	59.2	66.7	0.025
15-24	63.3	69.8	76.1	10.556*
25-34	47.5	56.9	70.7	29.372*
35-44	47.0	44.0	56.7	3.217
45-54	24.7	32.7	47.7	13.117*
55-64	27.9	30.9	33.0	0.618
65-74	25.5	24.1	24.1	0.029
75+	23.7	22.6	20.8	0.183
TOTAL	43.3	48.6	58.2	

Lymphocyte Predominance	Year			
Age Group	'69-71	'73-76	'77-80	χ^2
0-14	17.6	14.3	7.2	3.760
15-24	13.3	7.9	5.3	10.455*
25-34	20.3	8.6	6.5	18.314*
35-44	18.2	14.2	10.0	3.188
45-54	27.2	12.7	10.1	10.943
55-64	36.8	17.0	9.9	23.231*
65-74	29.4	12.8	9.4	11.210
75+	28.9	5.4	7.7	9.059
TOTAL	22.1	10.9	7.4	

* statistically significant at $p \leq 0.05$

Table 15. continued

Mixed Cellularity	Year			
Age Group	'69-71	'73-76	'77-80	χ^2
0-14	26.5	19.4	19.8	0.452
15-24	21.5	19.6	17.7	1.230
25-34	28.8	31.6	20.9	7.816
35-44	28.8	35.1	27.8	0.268
45-54	37.0	37.3	33.6	0.341
55-64	25.0	37.6	41.2	4.955
65-74	31.4	44.4	45.3	2.312
75+	36.8	53.8	50.0	1.005
TOTAL	28.2	31.8	27.4	

Lymphocyte Depletion	Year			
Age Group	'69-71	'73-76	'77-80	χ^2
0-14	2.9	7.1	6.3	0.261
15-24	1.9	2.6	0.9	1.936
25-34	3.4	3.0	2.0	1.140
35-44	6.1	6.7	5.6	0.057
45-54	11.1	17.3	8.7	0.739
55-64	10.3	14.5	15.9	1.145
65-74	13.7	18.8	21.2	1.384
75+	10.5	18.3	21.5	2.203
TOTAL	6.4	8.7	7.0	

* statistically significant at $p \leq 0.05$

Table 16. AVERAGE ANNUAL AGE-ADJUSTED INCIDENCE RATES OF HODGKIN'S DISEASE AND SELECTED 95 PERCENT CONFIDENCE INTERVALS BY RYE HISTOLOGIC SUBTYPE, SEX AND TIME PERIOD

BOTH SEXES

	1969-1971			1973-1976			1977-1980		
Subtype	Rate	C.I. Lower	C.I. Upper	Rate	C.I. Lower	C.I. Upper	Rate	C.I. Lower	C.I. Upper
NS	-	-	-	.99	.91	1.07	1.54	1.44	1.64
LP	-	-	-	.22	.18	.26	.20	.16	.24
MC	-	-	-	.64	.58	.70	.73	.67	.79
LD	-	-	-	.18	.14	.22	.19	.15	.23
ALL	3.4			3.1			2.9		

MALES

Subtype	Rate	C.I. Lower	C.I. Upper	Rate	C.I. Lower	C.I. Upper	Rate	C.I. Lower	C.I. Upper
NS	.50 *	-	-	1.00	.90	1.10	1.60	1.46	1.74
LP	.38 *	-	-	.31	.25	.37	.30	.24	.36
MC	.40 *	-	-	.85	.75	.95	.95	.85	1.05
LD	.08 *	-	-	.24	.18	.30	.28	.22	.34
ALL	4.1			3.6			3.5		

FEMALES

Subtype	Rate	C.I. Lower	C.I. Upper	Rate	C.I. Lower	C.I. Upper	Rate	C.I. Lower	C.I. Upper
NS	.45 *	-	-	.98	.88	1.08	1.52	1.38	1.66
LP	.12 *	-	-	.15	.11	.19	.10	.06	.14
MC	.23 *	-	-	.46	.38	.54	.53	.45	.61
LD	.06 *	-	-	.13	.09	.17	.11	.07	.15
ALL	2.7			2.6			2.5		

* from (34)

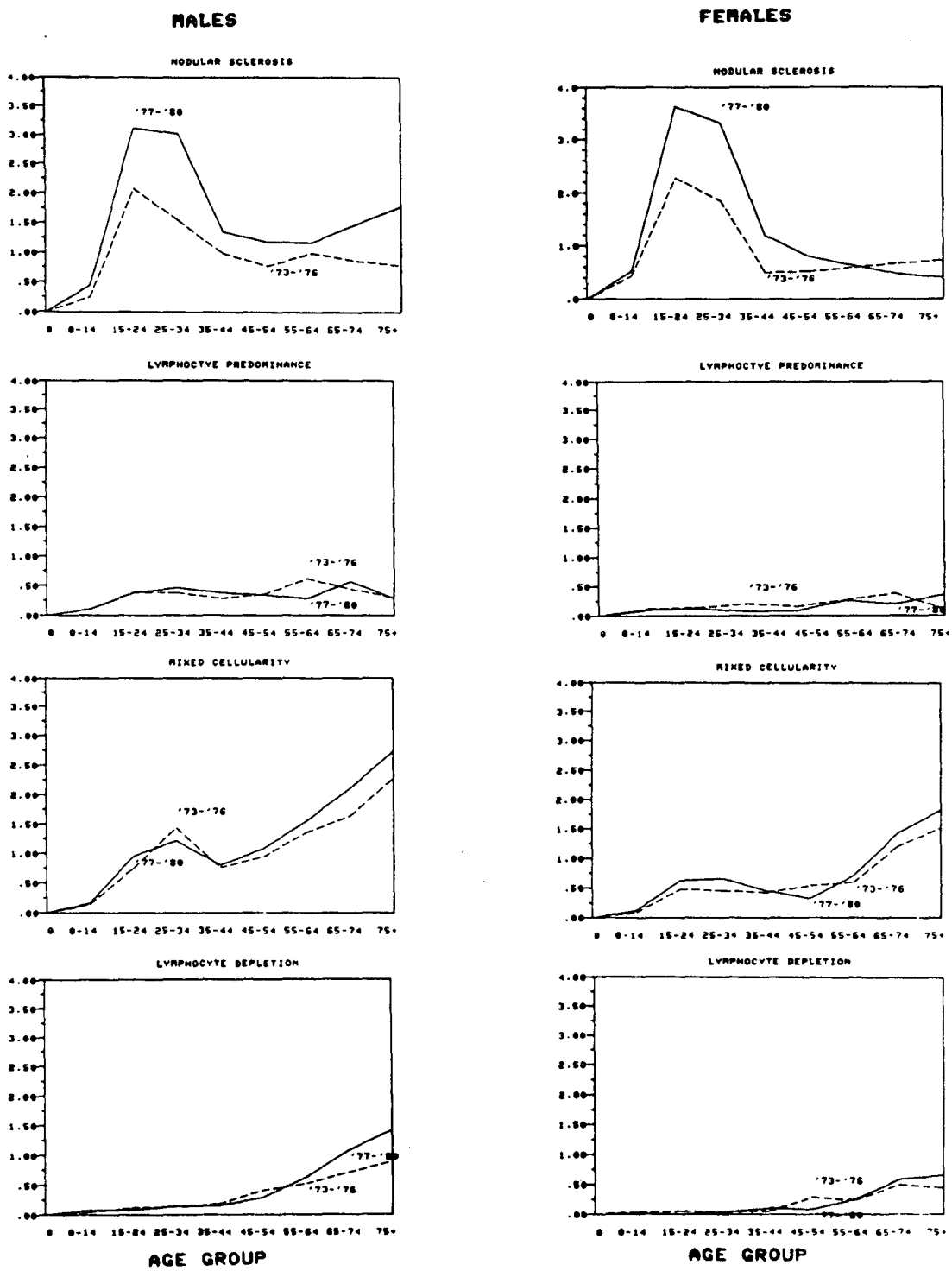
cases, these rates reflect increases (especially large between 1969-1971 and 1973-1976) in the proportions of cases with Rye detail, as well as any real secular trends. As expected under such circumstances, incidence did rise between the first two periods for NS, MC and LD. However, rates of LP did not increase, as incidence decreases (documented in Table 15) probably were averaged with secular increases in histologically classified numerators. Between 1973-1976 and 1977-1980, MC, LP and LD rates were unchanged, in spite of numerator increases. Only NS showed persistent significant increases across the decade.

(3) Time Trends in Age-Specific Rates: 1973-1976, 1977-1980

In the SEER years, numerators for histology-specific rates included a sufficiently large proportion of all cases to allow examination of temporal changes at the age-specific level. Figure 13 and Appendix Tables B-4, B-5 and B-6 show that such trends differed not only among subtypes but also, to a limited extent, with age. There were two notable secular patterns. 1) The above-noted increases in NS occurred in the young and mid-adult years for both sexes. 2) MC and LD had clear rate increases in older persons. However, given the decrease in HD overall in this age range, it is likely these rate rises partly represent increases in the proportions of Rye-subtyped cases over the period.

Together, the histology-specific rates and relative frequencies suggest certain pronounced differences in incidence time trends of the four subtypes, although it is

Figure 13. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES* OF HODGKIN'S DISEASE FOR MALES AND FEMALES, BY TWO TIME PERIODS: 1973-1976 AND 1977-1980, AND RYE HISTOLOGIC SUBTYPE, ALL SEER REGIONS COMBINED



* rates per 100,000 population

difficult to estimate the confounding influence of changes in classification prevalence. The incidence of NS increased, predominantly in young persons, while LP incidence declined at all ages. The minor secular trends in MC and LD depended on age. The increases in these two subtypes at older ages are apparent in both relative frequencies and rates. However, as they contradict the trends in HD overall, they may reflect the progressive inclusion of an older segment of the population into the Rye-classified group as this group incorporated a larger proportion of all HD cases over time.*

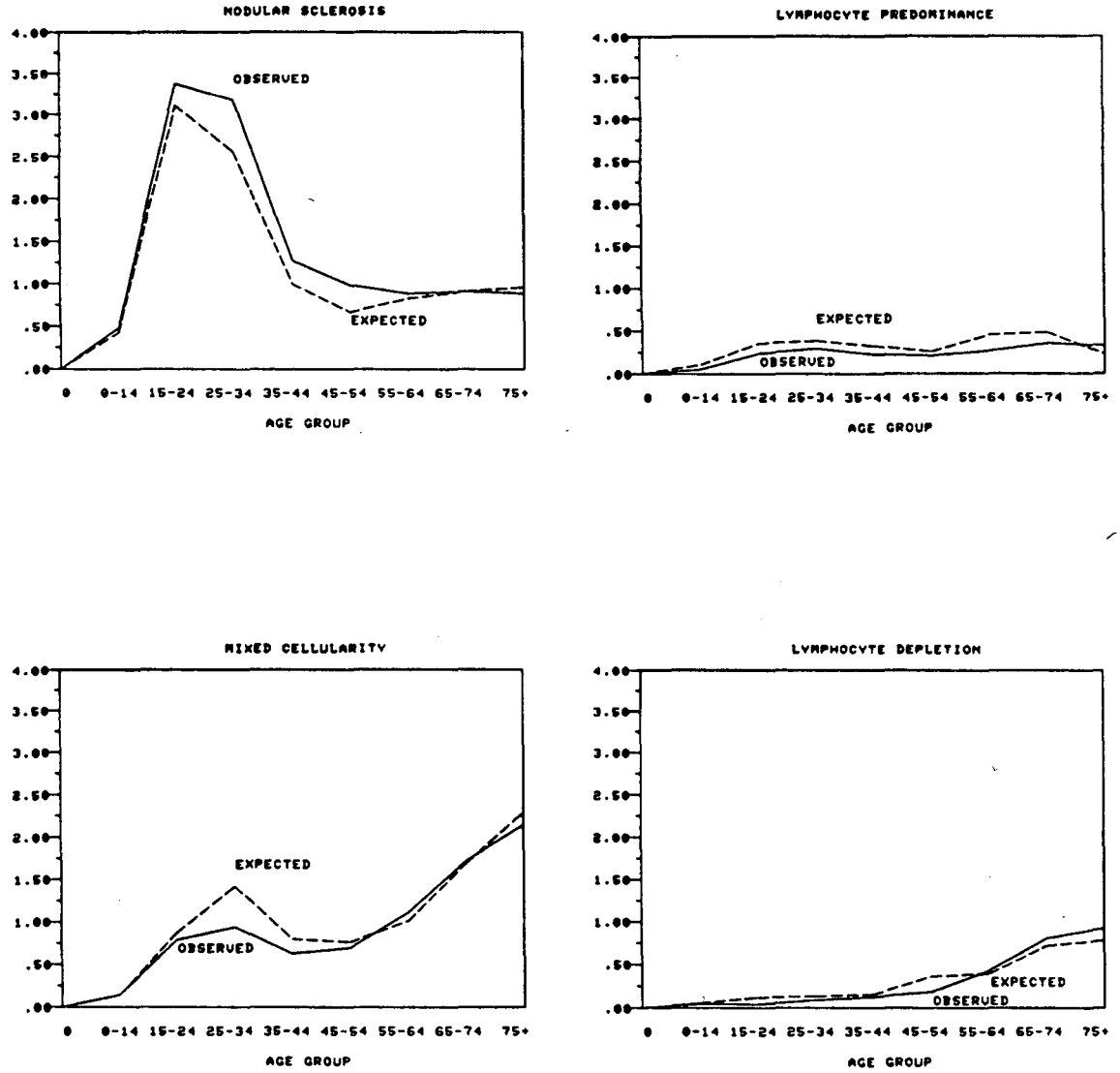
Does this variation in time trends by subtype reflect any true histology-specific differences, any change beyond that seen for HD overall? This question is explored with rates estimated for 1977-1980 for each histologic type under the null hypothesis of no histology-specific change, utilizing the 1977-1980 proportions of Rye-classified cases and the age-specific secular changes for all HD.

(4) Estimated 1977-1980 Rates Given No Histology-Specific Trends

Figure 14 and Appendix Tables B-7 and B-8 present both the actual 1977-1980 rates and those expected for this period under this null hypothesis. The graphs clearly illustrate that the observed time trends in each histologic variant are not identical to the trend recorded for HD

* See Chapter 3 for a discussion of the age differences between Rye and non-Rye cases, and the change in proportions of Rye- classified cases with time.

Figure 14. OBSERVED AND EXPECTED AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES* OF HODGKIN'S DISEASE FOR BOTH SEXES, BY RYE HISTOLOGIC SUBTYPE ALL SEER REGIONS COMBINED, 1977-1980



* rates per 100,000 population

overall. Rates of NS in young and middle-aged adults were higher than expected (differences significant at ages 25-34). In contrast, rates of young adult MC, LP and LD did not increase as projected. Secular changes thus were not uniform across histologic type, especially in the young adult ages.

(5) Time Trends in Estimated Complete Rates for 1973-76, 1977-80

It is not possible to evaluate true time trends for each histologic type because incomplete numerators bias histology-specific rates and, consequently, secular patterns. As a result, trends in incidence cannot be distinguished from trends in diagnostic completeness. Therefore to complete this investigation of time trends, it is useful to approximate the secular behavior the HD subtypes would be expected to show if all cases had been histologically categorized. This was done by estimating 1973-1976 and 1977-1980 rates, assuming Rye diagnoses for 100 percent of the cases. While the values of these extrapolated rates are strongly influenced by the actual rates on which they are based, their absolute magnitudes are not restricted by the proportion of all cases they include, as are the magnitudes of the actual rates. Consequently, for evaluating secular trends, the comparison of estimated rates from the two periods is more reliable than the comparison of actual rates, made in Figure 13.

The estimated numerator-complete rates, graphed in

Figure 15 and listed in Appendix Tables B-10 and B-11, do not differ dramatically from the actual rates. They reinforce the impression that at the histologic level, the only secular increase has been in young adult NS. However, unlike the actual rates, these estimated rates decreased slightly in most other age-histology groups between 1973-1976 and 1977-1980. The fact that these decreases in older age ranges are consistent with the trend for all HD, and contradict increases in the actual rates (Figure 13 and section 3 above) is further evidence that the observed rate increases were most likely trends in diagnostic completeness rather than incidence.

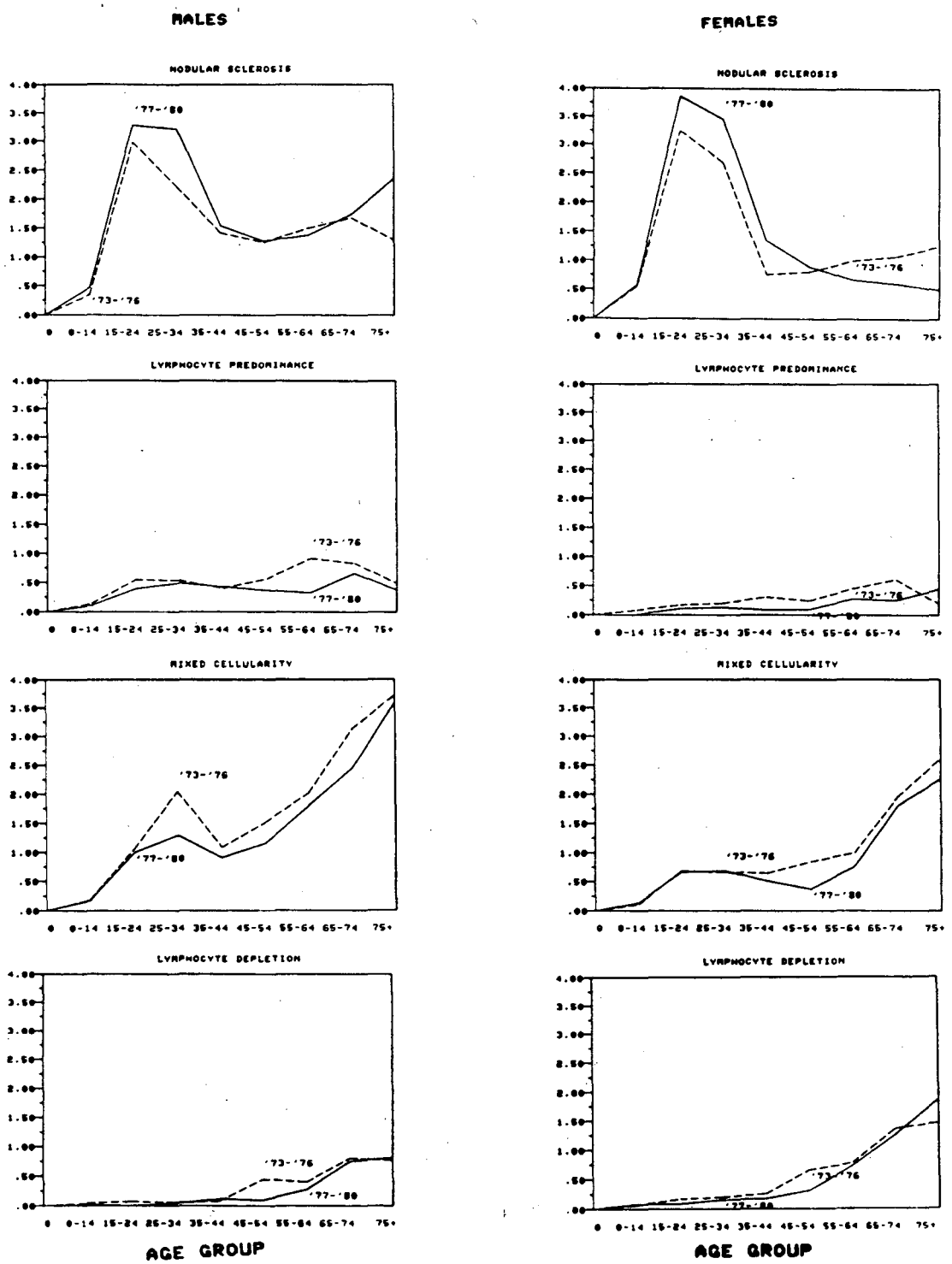
The projected secular trends are quite similar for males and females with two exceptions, both in young adults: 1) in NS, male increases exceeded female increases at ages 25-34, and 2) the incidence of MC has dropped significantly in males while remaining unchanged in females.

Thus these extrapolated rates show essential differences in the incidence of the histologic subtypes in time. The NS form of HD has increased in its highest risk age group, while the rates of the other subtypes have actually decreased slightly over the decade.

(6) Systematic Mis- or Reclassification as an Explanation of Time Trends, 1973-1976 to 1977-1980

Could the secular patterns in the estimated histology rates result from systematic reassignment of cases from one

Figure 15. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES* OF HODGKIN'S DISEASE, ESTIMATED FOR 100 PERCENT OF THE CASES, BY TIME PERIOD AND RYE HISTOLOGIC SUBTYPE FOR MALES AND FEMALES, ALL SEER REGIONS COMBINED



* rates per 100,000 population

subtype to another? Are they trends in classification rather than incidence? Only reexamination of original pathologic material could answer this question definitively. However, the SEER rates do permit a crude evaluation of the possibility of diagnostic changes creating trends.

Table 17 displays numerical differences in the estimated rates of each subtype between 1973-1976 and 1977-1980. In the age-adjusted rates, the combined decreases in LP, MC and LD are larger than the projected secular increases in NS. Therefore these decreases could not be explained entirely by an increase in the use of the NS diagnosis. In certain age- and sex-specific groups, particularly among males, increases in NS rates could have resulted numerically from systematic reclassification of the other subtypes. However, the greater presence of such transfers in males than in females, as well as their nonsystematic restriction to a few age groups, make reclassification an unlikely single explanation of the projected secular trends.

Taken together, these six analyses show differences in the incidence trends of the four subtypes in the 1970s. The only incidence (as opposed to classification) increases occurred in NS at all ages under 55, with the largest (and significant) increases in young adults between 25 and 45. Rates of MC, LD and LP remained stable or declined at almost all ages, especially in middle age. During the SEER years, these changes were greater than predicted from secular patterns of HD overall, and they are not simply explained by

Table 17. DIFFERENCES BETWEEN 1973-76 AND 1977-80 ESTIMATED AGE-SPECIFIC RATES OF HODGKIN'S DISEASE FOR MALES AND FEMALES, BY RYE HISTOLOGIC SUBTYPE

MALES

	Age Group								
Subtype	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	AAR
NS	.13	.31	1.01	.13	.02	-.12	.06	1.06	.26
LP	-.03	-.15	-.05	.03	-.20	-.59	-.18	-.11	-.13
MC	-.01	-.06	-.75	-.18	-.36	-.22	-.69	-.13	-.24
LD	.02	-.08	-.05	-.08	-.34	-.05	-.11	.40	-.06
		*		*	*		*		

FEMALES

	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	AAR
NS	.03	.61	.78	.59	.09	-.33	-.47	-.75	.20
LP	-.08	-.06	-.07	-.22	-.15	-.18	-.35	.24	-.11
MC	.03	-.02	.03	-.14	-.48	-.24	-.15	-.35	-.11
LD	-.03	-.07	-.02	.04	-.35	-.13	-.06	.04	-.07
	*				*				

* combined differences of LP, MC and LD could explain increases in NS

systematic mis- or reclassification among subtypes.

From these histology-specific secular patterns, particularly those in the extrapolated estimates, it is possible to attribute three notable time trends for all HD to their histologic sources. 1) The slight enlargement of young adult, particularly female, risk (Figure 10) must have been caused by the significant young adult increases in NS, in these data a dominantly female disease in youth. This impact of the NS increase on all-HD rates was tempered somewhat by the young adult rate decreases in the other subtypes, particularly male MC. 2) The stability of rates in children under age 14 results from slight increases in NS counterbalancing decreases in LP and little change in MC and LD (Appendix Table B-10). Furthermore, the high and increasing rates of female childhood NS probably account for the female excess between ages 10 and 20 (Figure 7) and the drop in the childhood male excess noted in Figure 11. Thus the lack of the expected childhood decline in HD and its lessening male predominance reflect the broadening of NS risk into younger as well as older young adult age groups. 3) The decline in rates of middle-aged and older persons is not a histology-specific phenomenon but is present to some degree in each subtype except in NS in males.

Thus the secular behavior of childhood and young adult HD reflects the increases in the NS form of the disease, while the declines in HD among older persons seem to be occurring in all its histologic forms in the United States.

COMPARISONS WITH OTHER HISTOLOGY DATA

Comparisons of SEER histology data to rates from other areas is hindered by the lack of geographically comparable population-generated sources. Of the six population-based studies listed in Chapter 2, three described incidence in single United States counties or states, two of which are SEER participants (7,52,70). Only three of the six reports listed summary rates (52,77,79), and in two cases, they were age-adjusted to different standard populations than used in this project (77,79). Consequently, the only valid comparisons for the SEER data must utilize relative frequencies of cases in each subtype from locations around the world (77). The proportions, from histologic material rereviewed in all areas except the United States, are presented in Table 18.

Compared with the other regions, the United States had very high proportions of NS, increasing with time, and very low proportions of LD over the three survey periods. The U.S. incidence of LP progressed from an intermediate to lowest rank. Levels of MC were also low. The relative proportions of the four subtypes are similar to those from Europe and Israel. However, they contrast strikingly with the patterns in other continents, which had low frequencies of NS with much higher proportions of LD and MC. Examining these data without the TNCS and SEER frequencies, Franssila et al. concluded that NS was the only subtype to show sub-

Table 18. PERCENT DISTRIBUTION OF HODGKIN'S DISEASE CASES IN EACH RYE HISTOLOGIC CATEGORY BY REGION (ALL RACES)*

Region	n	NS	LP	MC	LD
NORTH AMERICA					
TNCS** +	614	43	22	28	6
SEER 1973-1976**	1455	47	11	33	10
SEER 1977-1980**	1977	58	8	28	7
SOUTH AMERICA					
Buenos Aires, Ar.	497	21	20	47	12
Brazil: Recife	118	26	34	25	15
Sao Paulo	141	25	15	50	10
Columbia: Cali	102	11	17	50	22
Bogota	200	15	21	51	13
Medellin	390	16	27	36	21
El Salvador	138	17	8	63	21
Lima, Peru	220	6	20	45	29
AFRICA					
Egypt	86	13	29	44	14
Nigeria	227	4	13	46	37
ASIA					
Japan	47	19	11	51	19
Singapore	74	24	38	34	4
Israel++	418	46	10	29	9
EUROPE					
Finland	186	64	13	16	7
Norway	111	30	15	35	20
AUSTRALIA					
Western Aust.+++	158	27	10	46	17

* Adapted from (77)
** Histologic diagnoses not rereviewed
\+ (34)
++ (53)
+++ (79)

stantial geographic variation (77). However, in the contemporary United States data high levels of NS occur in conjunction with low levels of the other subtypes. Furthermore, during the SEER years, the frequency of NS increased with time as the proportions of LP, MC and LD declined.

Even in the absence of specific information about the economic status of each region, it seems clear from these international data that higher frequencies of NS and lower proportions of the other subtypes, particularly LD, occur in well-developed countries. This apparent association is partly consistent with the original observations by Correa and O'Conor that both the NS and LP subtypes were more predominant in economically affluent environments (4). In the TNCS and SEER data, however, the proportions of cases with the LP subtype are much lower than those authors predicted. Given the differences among these international sites in study sample sizes, racial composition, population structure, time period and data quality, it is not reasonable to draw further conclusions about geographic variation in histology-specific incidence. The findings of the six population-based studies will be reviewed with regional United States data in the following chapter.

SUMMARY

The epidemiology of HD in these samples of the United States population for the most part shows the characteristics expected of the disease in an affluent area. Most of its distinctive features--prominent and increasing young

adult incidence, particularly in women, close male-female risks between ages 10 and 20, and secularly stable childhood rates--can be attributed to NS, which has a high and growing incidence in this country. The other notable feature of HD in this study--its declining incidence in middle and older-aged persons--has not been previously reported and cannot be attributed to any histology-specific change. The significance and possible explanation of these findings will be discussed in Chapter 6.

Chapter 5

HODGKIN'S DISEASE INCIDENCE BY SURVEY REGION

Are the patterns of HD incidence for all survey sites combined apparent in each of the component areas? How much regional variability exists in age-, sex-, time-, and histology-specific distributions? In United States populations, is there the geographic variation at young ages and with changes in economic environments noted in international data (4,74-76)? This chapter addresses these questions, describing HD incidence by region and examining relationships between age-specific rates and community economic conditions. Like Chapter 4, it considers HD patterns first overall and then by histologic subtype. At both levels it presents age, sex and secular distributions, and the results of correlation analyses. Supporting data and 95 percent confidence intervals are included in Appendix C.

INCIDENCE BY SEX AND AGE FOR ALL HD

Like the international data, the SEER regional summary rates, listed in Table 19 and Appendix Table C-1 for 1973-1980, do not vary dramatically across the ten study areas. The age-adjusted rates extend from 2.0 per 100,000 in Hawaii to 3.6 per 100,000 in Connecticut. Within this uniformity, three sets of statistically significant differences identify the range of incidence rather than any outstanding geographic deviations. 1) The high rate in Connecticut signifi-

Table 19. AVERAGE ANNUAL AGE-ADJUSTED RATES OF HODGKIN'S DISEASE BY SEX, AND MALE-FEMALE RATIOS, BY REGION, 1973-1980

	RATES			
Survey Region	Both Sexes	Males	Females	M:F RATIO
San Fran.-Oak.	3.24	3.76	2.76	1.36
Connecticut	3.59	4.20	3.07	1.37
Atlanta	2.45*+	2.53*+#!	2.40	1.05
Hawaii	2.03*+#!	2.56	1.66*+	1.54
Iowa	3.02+	3.59	2.53	1.42
New Orleans	2.73+	2.87+	2.44	1.18
Detroit	3.00+	3.60	2.49+	1.45
New Mexico	2.77+	3.51	2.08+	1.69
Utah	2.72+	3.41	2.12+	1.61
Seattle-Puget S.	2.61*+	3.14+	2.14+	1.47
ALL AREAS	3.0	3.5	2.5	1.4

* Rate significantly lower ($p \leq 0.05$) than San Fran.-Oak. rate
\+ Rate significantly lower ($p \leq 0.05$) than Connecticut rate
\# Rate significantly lower ($p \leq 0.05$) than Detroit rate
! Rate significantly lower ($p \leq 0.05$) than Iowa rate

cantly exceeds rates in every other region except San Francisco-Oakland. 2) Incidence in San Francisco-Oakland, also high, is significantly elevated over incidence in Atlanta, Hawaii and Seattle-Puget Sound. 3) The rate in Hawaii is significantly lower than in the four areas of highest incidence. With these exceptions, however, rates do not differ among regions.

SEX

There is no striking variation in sex-specific incidence. Rate ranges are similar for men (2.5-4.2 per 100,000) and women (1.7-3.1 per 100,000). The male-female ratio varies narrowly between 1.4 and 1.7, except in Atlanta and New Orleans, where low male incidence brings ratios nearer one. Connecticut has the highest rates for both sexes. The lowest male incidence occurs in Atlanta, where rates are significantly lower than in Connecticut, San Francisco-Oakland, Detroit and Iowa. Hawaii has the lowest incidence of female HD.

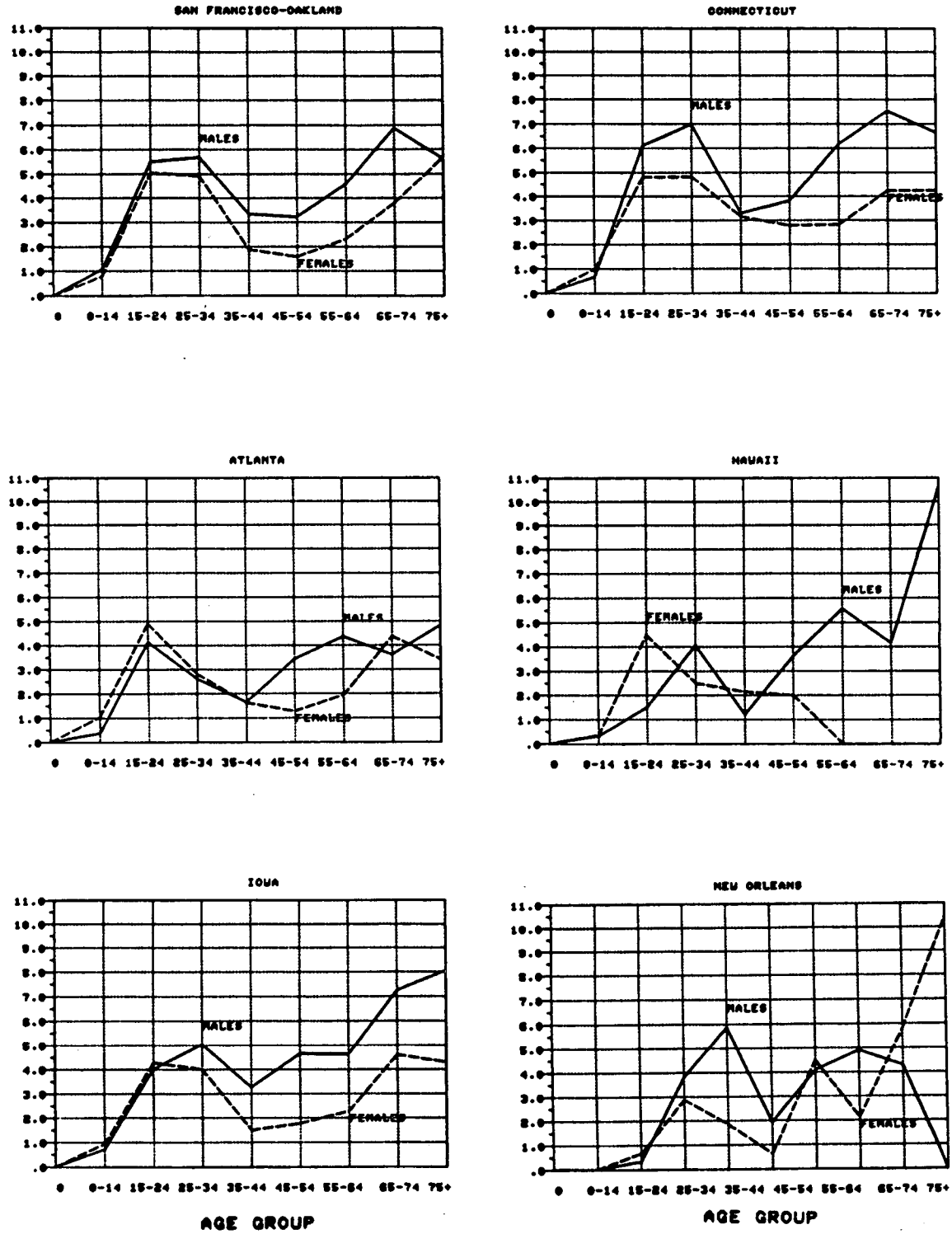
AGE

At the age-specific level, rates continue to be consistent geographically, as documented in Figure 16 and Appendix Table C-2. For most of the ten locations, the age incidence curves display the following patterns observed in combined-region data.

(1) All the curves are clearly bimodal with typical Type III shapes.

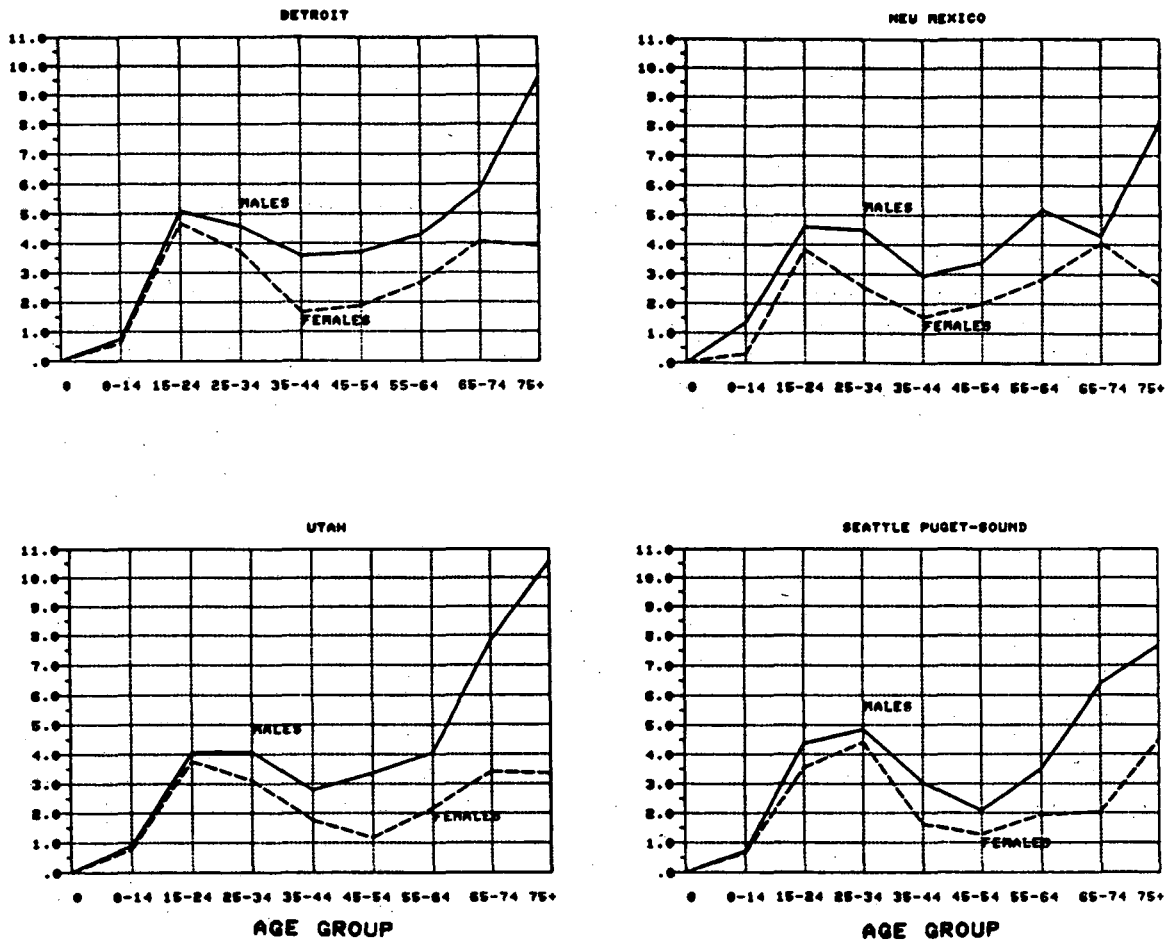
(2) Female curves are lower than but parallel to male

Figure 16. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES*
OF HODGKIN'S DISEASE FOR EACH SEER REGION, BY SEX, 1973-1980



* rates per 100,000

Figure 16., continued



curves in every location except Hawaii, where small numbers of cases affect rate stability.

(3) The sex difference in relative magnitude of younger and older age rates is maintained. For women over age 65, rates are at a level similar to rates in young adulthood. For men, the highest rates occur in old age in all areas except New Orleans, another region with a very small case group.

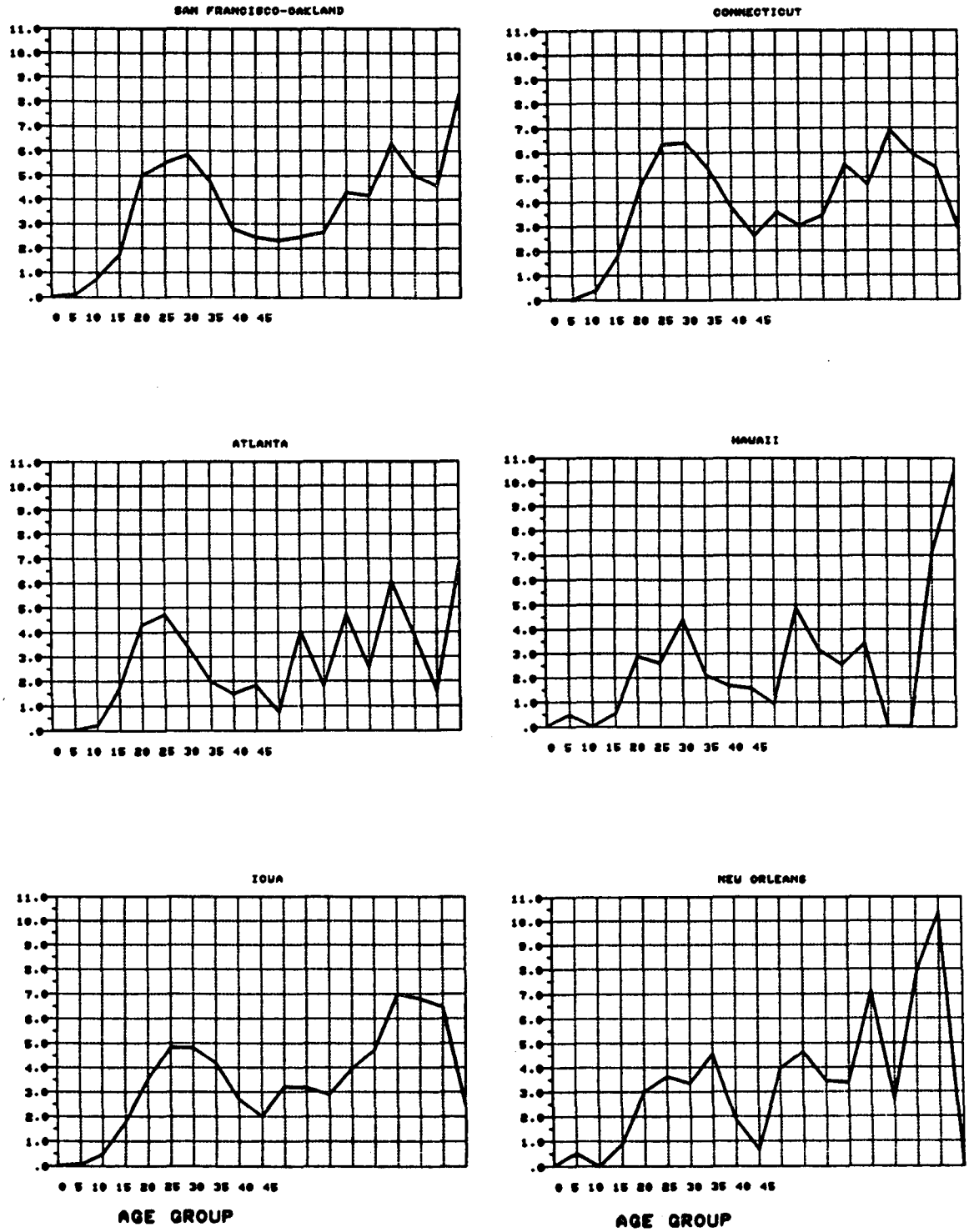
(4) The incidence of HD in children is low is all locations. Rates for children under ten, presented in Table 20 and Appendix Table C-3, fluctuate more than rates based on larger numbers of cases but show no significant interregional differences. In most areas with adequate data, childhood male incidence is two to three times female incidence.

(5) A fifth observation of combined-area rates--the location of the first incidence peak between ages 20 and 30--also applies to every region. However, there is subtle variation in the location and the size of the young adult portion of the curve, illustrated in Figure 17 with five-year age-specific rates. From these more detailed graphs, it appears that in areas with the highest rates of young adult HD, incidence is high across a wide range of young persons from ages 10-14 and 35-39. Young adult curves in these regions have tall, broad shapes, as seen in Connecticut. In contrast, areas with lower peak young adult rates, like Utah or Seattle-Puget Sound, have lower rates at all young adult

Table 20. AVERAGE ANNUAL RATES OF HODGKIN'S DISEASE IN CHILDREN AGED 0-9, BY SEX; AND MALE-FEMALE RATIOS, BY REGION, 1973-1980

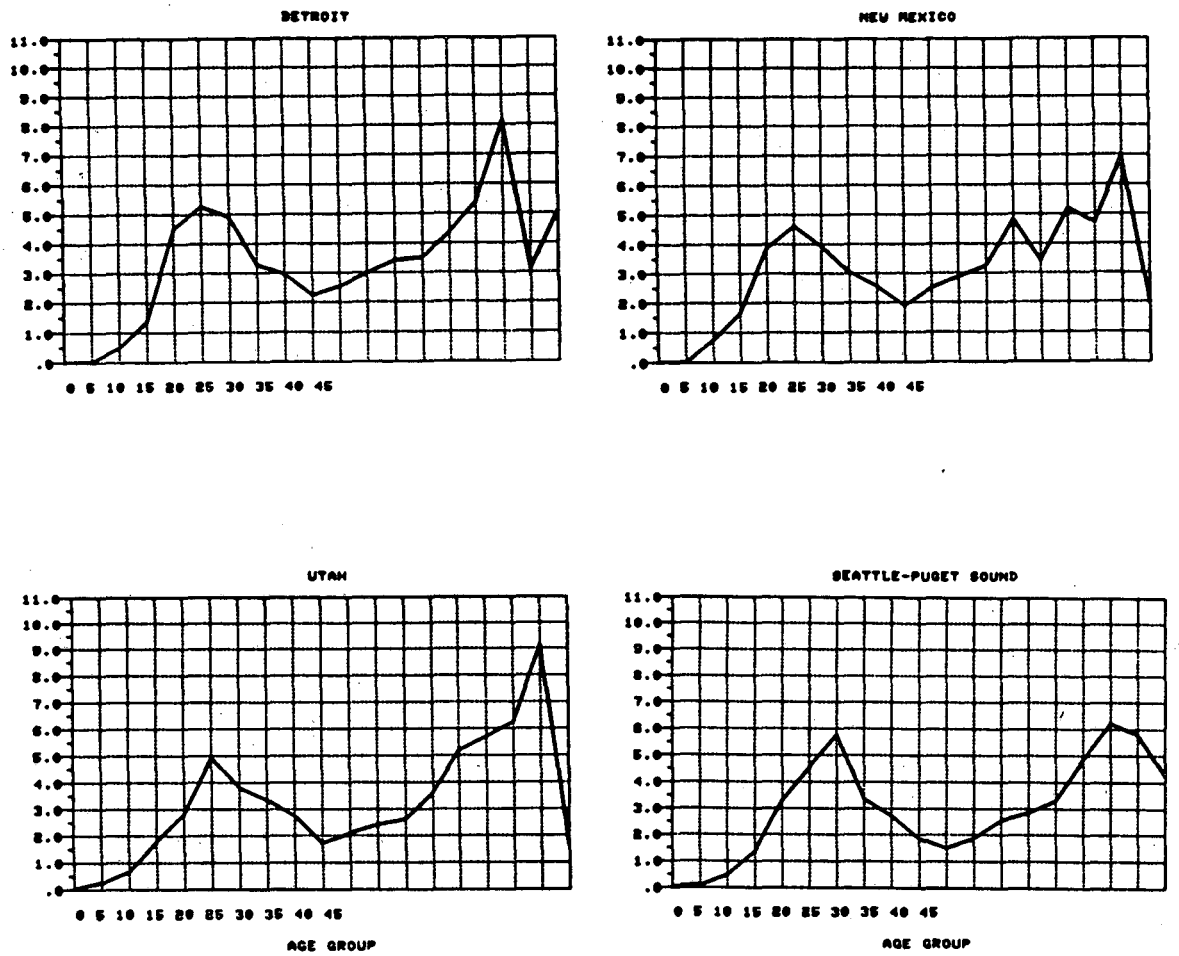
	BOTH SEXES		MALES		FEMALES		
Survey Region	Rate	n	Rate	n	Rate	n	M:F Ratio
San Fran.-Oak.	.43	10	.76	9	.09	1	8.61
Connecticut	.20	6	.19	3	.20	3	.95
Atlanta	.10	1	.19	1	-	-	-
Hawaii	.24	1	.47	1	-	-	-
Iowa	.28	10	.39	7	.17	3	2.23
New Orleans	.25	1	-	-	.51	1	-
Detroit	.26	10	.40	8	.11	2	3.79
New Mexico	.38	5	.60	4	.16	1	3.83
Utah	.44	10	.43	5	.45	5	.95
Seattle-Puget S.	.29	7	.40	5	.17	2	2.38

Figure 17. AVERAGE ANNUAL FIVE-YEAR AGE-SPECIFIC INCIDENCE RATES* OF HODGKIN'S DISEASE FOR EACH SEER REGION, 1973-1980



* rates per 100,000

Figure 17., continued



ages. Their age-specific curves are shorter and narrower, although they still retain a prominent peak between ages 20 and 30. Thus while all SEER regions have substantial levels of young adult HD, the peak risk of the disease in this age range seems to be related to the level of disease for the overall young adult group. (This observation is tested below). At older ages, the five-year incidence curves also vary across regions but are not stable enough to reveal any patterns.

REGIONAL ANOMALIES IN AGE-SPECIFIC INCIDENCE, 1973-1980

Within the general geographic stability of these age- and sex-specific rates, certain unusual regional patterns deserve mention (although they will be more thoroughly discussed in Chapter 6):

(1) In Connecticut, an area with numerically stable rates, male young adult incidence is very high, but the rates for boys are relatively low. The male-female ratio for children under age 15 is 0.68, contradicting a previously reported ratio for this age range of 1.8 (70).

(2) San Francisco-Oakland, similar to Connecticut in the number of cases and general incidence of HD, paradoxically has the highest rates for boys under 15. Here the male-female ratio is 1.68, although a prior study of this area found a ratio of less than one (7).

(3) In Atlanta, rates for older males are quite low.

(4) Rates in Hawaii are also depressed, especially among older women.

Even with these extremes, the age- and sex-specific distributions of HD in the 1970s are remarkably stable across regions. There is uniformity in total rates, male-female ratios, and, most notably, in the age-specific curves, where the observed differences are slight in contrast to the substantial geographic variation found in international data. There are a few significant differences in the levels of incidence from place to place. Rates in Connecticut and San Francisco-Oakland are high, particularly for young adults, while rates in Atlanta, New Orleans, Seattle-Puget Sound and Hawaii, especially among older women, are lower. However, with few exceptions, these differences are ones of degree. There are no sharp departures from the typical Type III HD incidence pattern in any of the locations surveyed. Thus the age- and sex-specific distributions of HD for all areas combined reflect a reasonably similar contribution from each geographic component.

TIME TRENDS IN INCIDENCE

The short duration of the SEER program curtails the analysis of time trends. Nevertheless the comparison of rates from the first and second halves (1973-1976, 1977-1980) of the eight-year study interval provides a preliminary check of recent regional secular changes in HD incidence. Data from the four locations included in both TNCS and SEER programs allow examination of trends over a slightly longer period.

1973-1976 to 1977-1980: SEER AREAS

Between 1973-1976 and 1977-1980,* rate changes were minimal in most of the ten areas, mirroring the minor change reported for all regions combined. Table 21 and Appendix Table C-4 indicate that age-adjusted rates of HD for both sexes together decreased slightly in San Francisco-Oakland, Atlanta and Utah but were unchanged in other areas. These regional differences result from the variation in the direction of secular rate changes by sex. Rate decreases were more geographically pervasive among males, occurring in six of nine areas.** Among females, rates dropped in three areas but increased in three others. Although these patterns were distinctively sex-specific, none of the interregional rate differences was statistically significant.

Trends by Age and Sex

Similarly, there were almost no significant time trends in age-specific rates (Appendix Tables C-5 and C-6), graphed by sex in Figures 18 and 19. However, two secular patterns seen in the nation-wide data occurred with regularity at the regional level. These were:

(1) slight rate increases in young adult incidence. For females the increases occurred in almost every location, and for males, only in Connecticut, New Mexico and Atlanta.

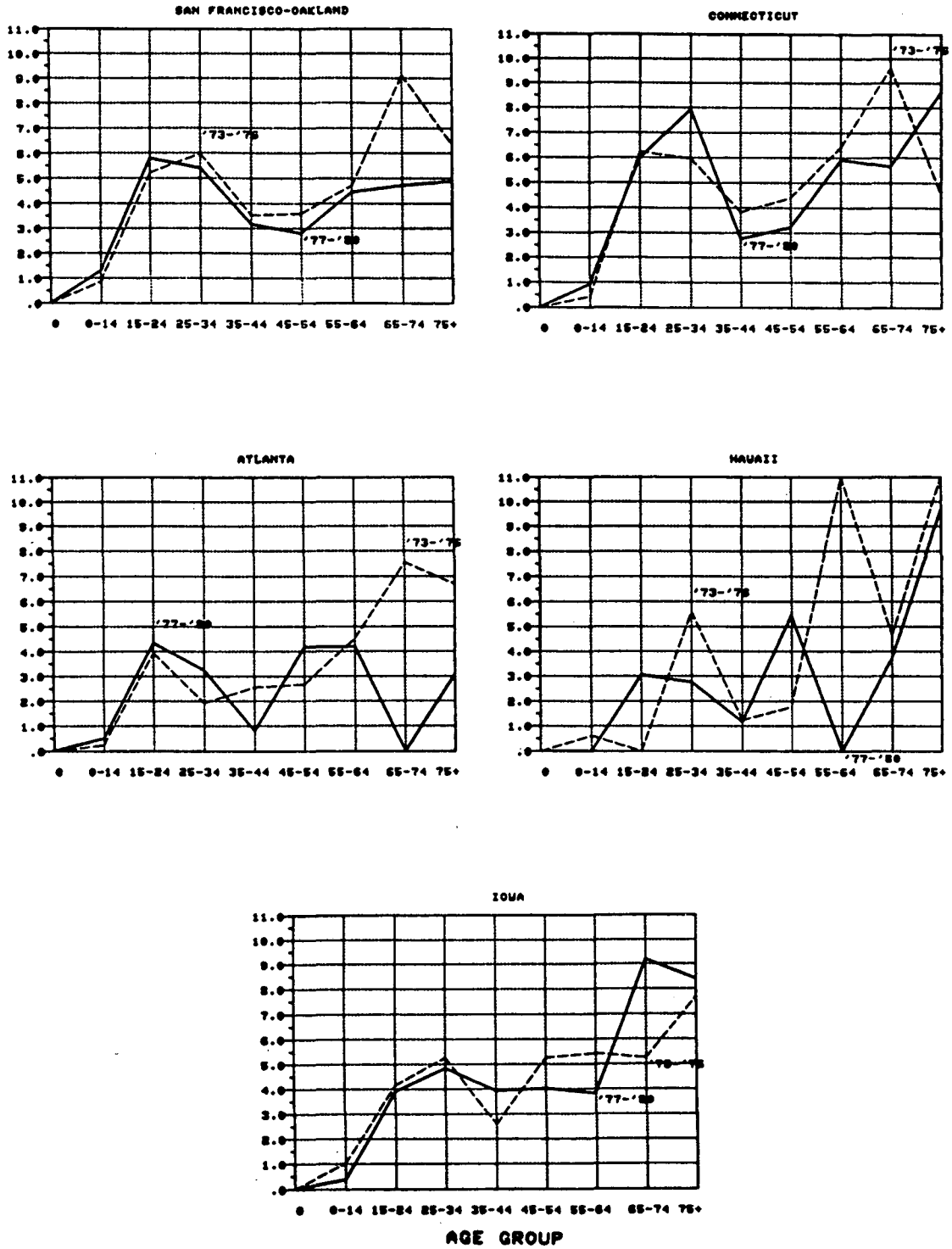
(2) decreases in some age group over 45 for both sexes in almost all areas. This drop was particularly

* This period is shorter for Atlanta and Seattle-Puget Sound. See Chapter 3.
** For New Orleans, data exist for four years only.

Table 21. AVERAGE ANNUAL AGE-ADJUSTED RATES OF HODGKIN'S DISEASE BY SEX, TIME AND REGION

	BOTH SEXES		MALES		FEMALES	
Survey Region	'73-76	'77-80	'73-76	'77-80	'73-76	'77-80
San Fran.-Oak.	3.5	3.0	3.9	3.6	3.1	2.4
Connecticut	3.6	3.6	4.2	4.2	3.0	3.1
Atlanta	2.7	2.2	2.7	2.4	2.8	2.0
Hawaii	2.1	2.1	3.0	2.2	1.3	2.1
Iowa	3.0	3.0	3.7	3.5	2.4	2.7
New Orleans	2.7	-	2.9	-	2.4	-
Detroit	2.9	3.1	3.6	3.6	2.4	2.6
New Mexico	2.8	2.7	3.6	3.4	2.1	2.1
Utah	3.0	2.5	4.0	2.9	2.2	2.1
Seattle-P.S.	2.7	2.6	3.2	3.1	2.3	2.1
ALL AREAS	3.1	2.9	3.6	3.5	2.6	2.5

Figure 18. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES* OF HODGKIN'S DISEASE IN MALES FOR EACH SEER REGION, BY TIME PERIOD (1973-1976, 1977-1980)



* rates per 100,000

Figure 18., continued

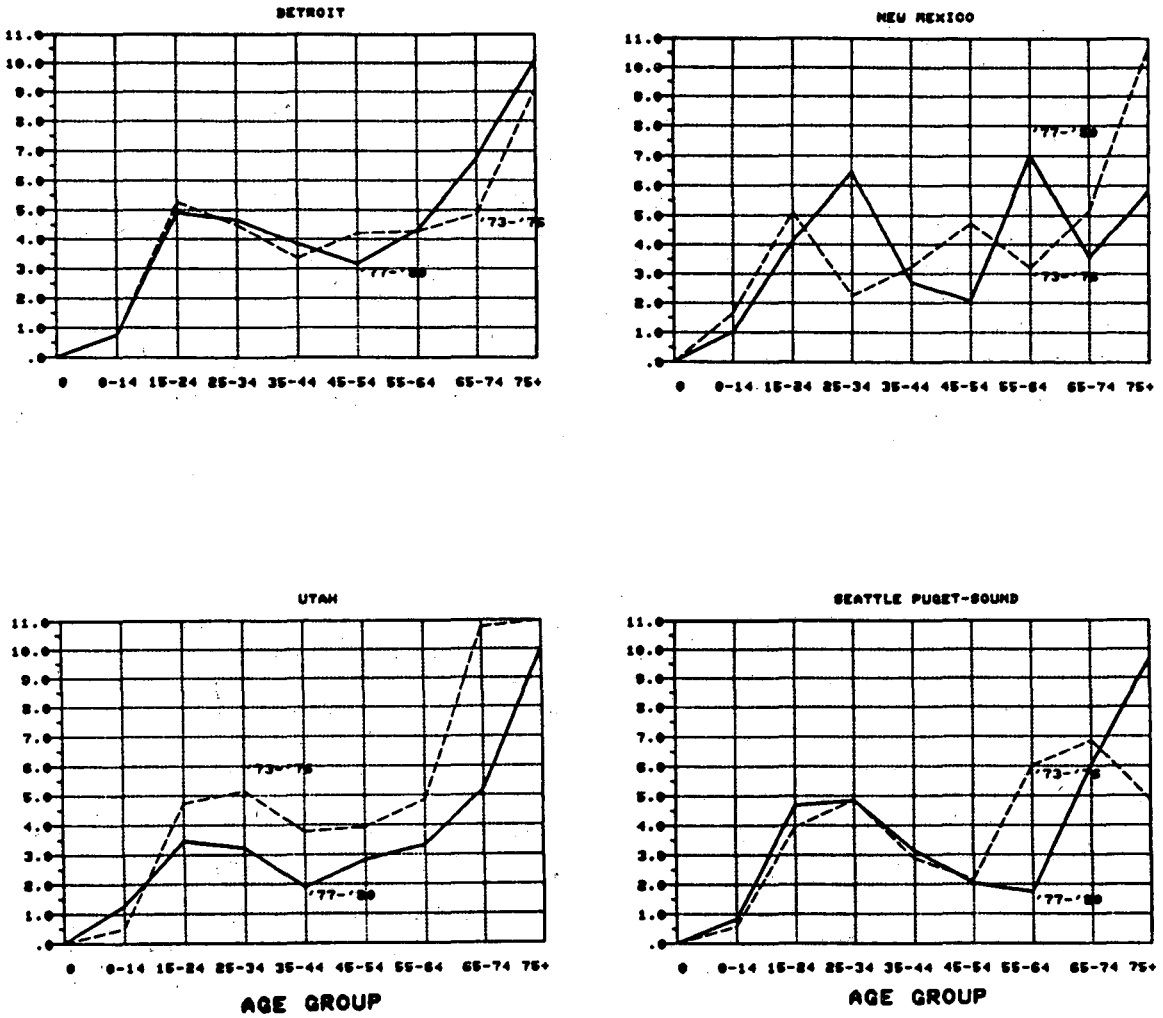
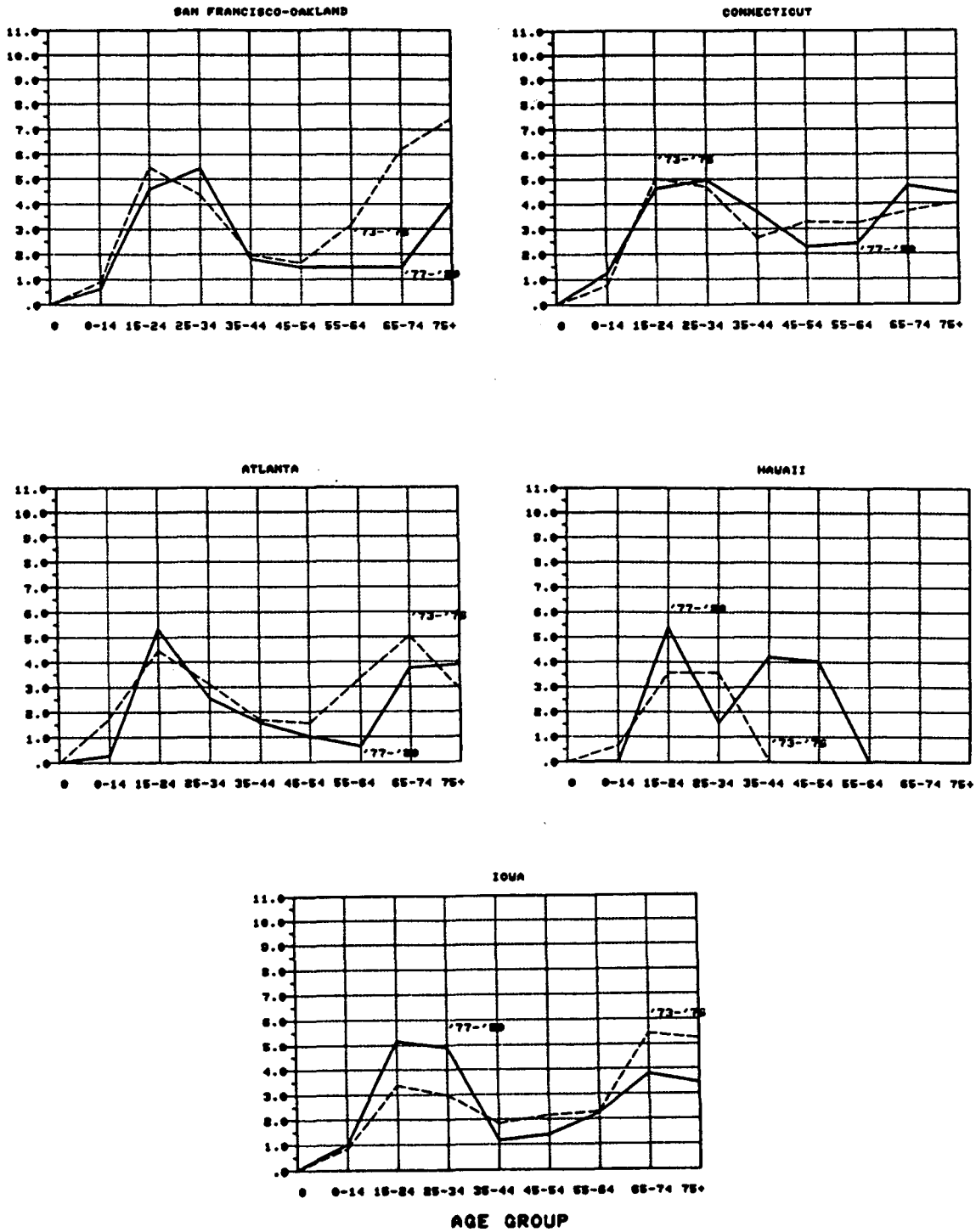
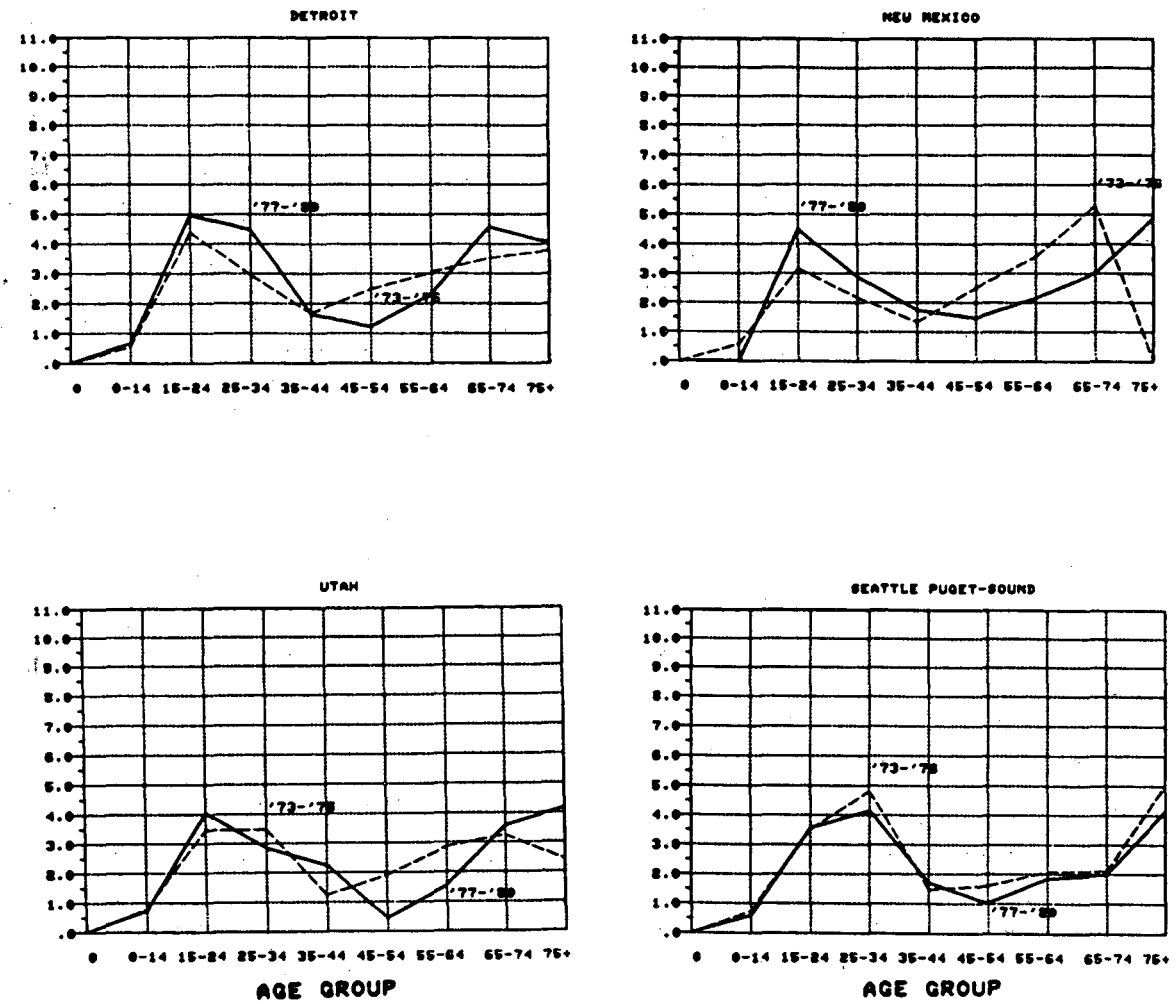


Figure 19. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES* OF HODGKIN'S DISEASE IN FEMALES FOR EACH SEER REGION, BY TIME PERIOD (1973-1976, 1977-1980)



* rates per 100,000

Figure 19., continued



marked for persons over age 65 in San Francisco-Oakland.

Both these changes were a little more distinct and more geographically uniform in women. The balancing of female old-age rate declines with persistent increases in young adult incidence led to the greater secular stability and fewer decreases noted above in the female age-adjusted rates. Furthermore these consistent regional changes in incidence in women produced the stronger time trend in female than male data for all regions combined (Figure 10). The similarity of regional 1977-80 age-specific curves across regions suggests in addition that geographic differences are disappearing from female HD.

With two exceptions--a notable decline in male young adult rates in Utah, and the significant drop in San Francisco-Oakland in rates of older persons described above--the secular trends in the 1970s, like other features of HD incidence, demonstrated limited geographic variation. The extent of changes varied slightly by sex. Among women there was a more geographically consistent increase in young adult rates, and a secularly progressive homogeneity in age-incidence curves across areas. Among men, the young adult increase was less prevalent, and there was more apparent regional variation in 1977-1980 age-specific rates. These differences in sex-specific patterns are not as noteworthy, however, as the overall geographic uniformity in time trends.

1969-1971 to 1977-1980: SAN FRANCISCO-OAKLAND, ATLANTA, IOWA AND DETROIT

In the four locations surveyed nearly continuously since 1969, secular changes were more diverse. However, again variation was mostly in the degree rather than the direction of trend. Age-adjusted rates, seen in Table 22, declined in three of the areas, with larger percent decreases in males than in females. These changes were greatest and statistically significant only in San Francisco-Oakland, which experienced a steady, 25 percent decrease in HD over the decade (Appendix Table C-7). In contrast, rates in Detroit were unchanged.

Trends by Age and Sex

Secular trends in age-specific incidence from 1969-1971 to 1977-1980, are illustrated in Figure 20. Like the age-adjusted rates, they also exaggerated the trends of the SEER years. Young adult rates increased slightly in all areas except San Francisco-Oakland, while rates among older persons dropped significantly in San Francisco-Oakland, Atlanta, and Iowa (Appendix Table C-8). The age-specific trends in San Francisco-Oakland were unusual and pronounced, showing an uncharacteristic decrease in HD in young adult ages, particularly in males, and large drops in incidence in older persons. The decline in rates in both age ranges produced the significant decrease in summary incidence in this area.

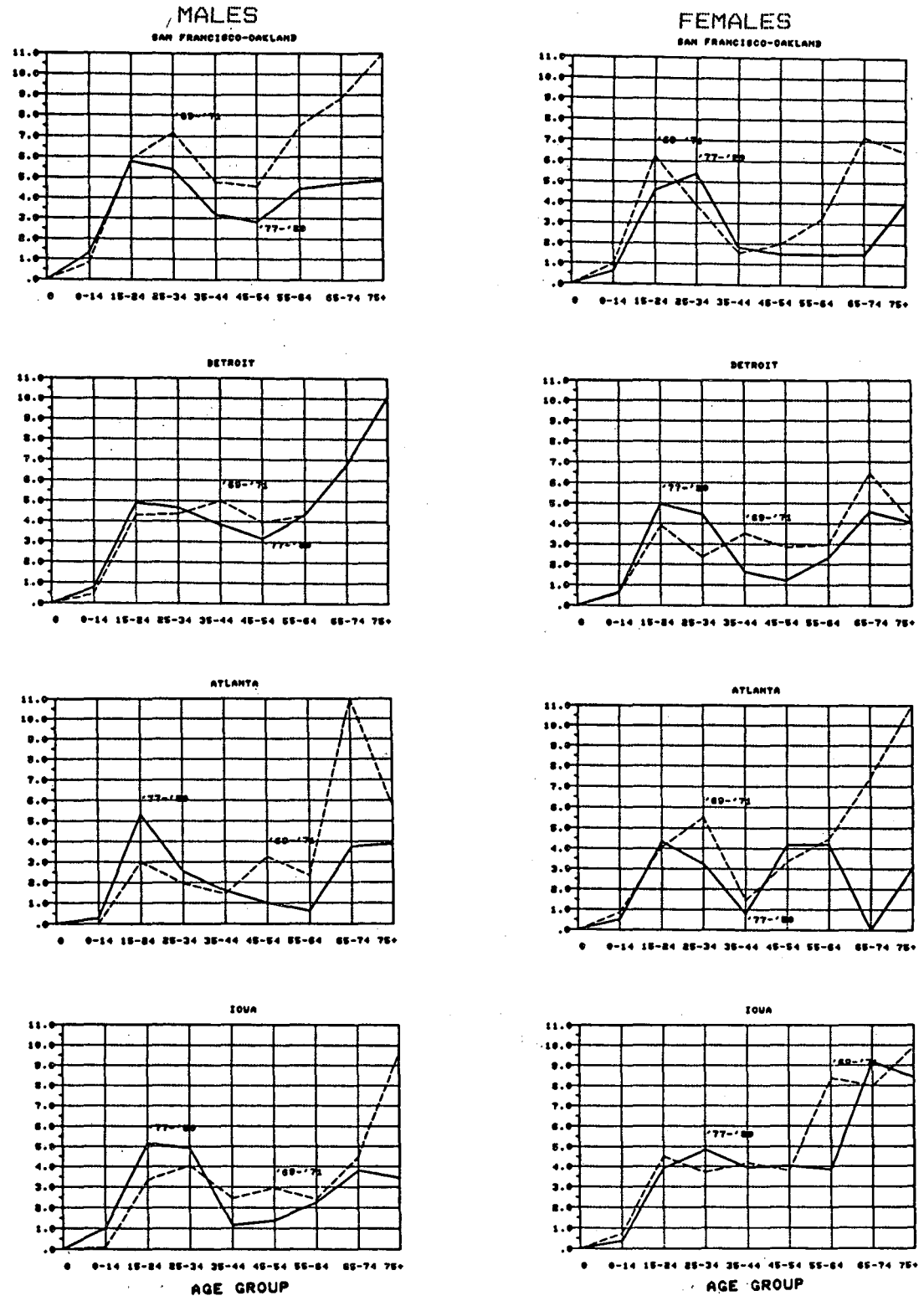
Overall, for both periods, there were few regional

Table 22. AVERAGE ANNUAL AGE-ADJUSTED RATES OF HODGKIN'S DISEASE AND PERCENT CHANGE IN RATES, BY SEX AND TIME FOR FOUR REGIONS

Survey Region	'69-71	'73-76	'77-80		% Change '69-'71 to '77-80
BOTH SEXES					
San Fran.-Oak.	4.04	3.51	2.98	*	-26
Atlanta	2.96	2.68	2.22		-25
Iowa	3.25	3.00	3.02		-7
Detroit	3.13	2.94	3.05		-3
MALES					
San Fran.-Oak.	4.97	3.93	3.61	*	-27
Atlanta	3.50	2.71	2.37		-32
Iowa	3.98	3.66	3.52		-12
Detroit	3.62	3.57	3.63		0
FEMALES					
San Fran.-Oak.	3.22	3.11	2.40		-25
Atlanta	2.47	2.75	2.04		-17
Iowa	2.57	2.39	2.65		+3
Detroit	2.69	2.39	2.58		-4

* 1977-80 rate significantly different than 1969-71 rate at $p \leq 0.05$

Figure 20. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES* OF HODGKIN'S DISEASE FOR MALES AND FEMALES, BY REGION AND TIME PERIOD (1969-1971, 1977-1980)



* rates per 100,000

variations from the combined-area time trends of slight increases in young adult incidence and slight decreases among older adult rates, both more prominent in females. Two deviations were notable. 1) In San Francisco-Oakland, HD declined markedly in both younger and older persons from 1969 through the decade. 2) Among males in Utah, the disease decreased substantially at all ages over 25. In most areas, however, the limited regional variations are diminishing with time. There seems to be a tendency for increasing geographic uniformity in age-specific incidence, particularly for women. The significance of both the geographic consistency in rates and secular trends and the specific regional deviations will be discussed in Chapter 6.

PATTERNS IN RATES ACROSS THE SEER REGIONS

With their regional scope, the SEER data provide an opportunity to evaluate quantitatively systematic patterns of geographic variation in incidence. Among the populations just described, there were in fact few geographic rate differences at any age. Nevertheless both the SEER data and earlier studies have suggested several patterns of regional variation testable under these conservative conditions of geographic homogeneity. These patterns include: 1) the apparent relationship between height and breadth of young adult incidence curves, and 2) the previously reported age-specific variations in incidence, and 3) their association with community economic environment.

RELATIONSHIPS BETWEEN THE HEIGHT AND BREADTH OF THE YOUNG ADULT PORTION OF THE AGE-SPECIFIC CURVE

In the five-year age-specific rates of Figure 17, high young adult peak rates seemed to be associated with elevated incidence between ages 10-14 and 35-39, and lower peak rates seemed to occur where incidence at these ages was lower overall. This pattern suggested a connection between peak young adult risk and the risk of the larger age group. To evaluate the relationship between the height and breadth of the young adult curve, the association was measured two ways and tested with rank correlation coefficients.

The first correlation, between the highest young adult five-year age-specific rate and the area under the curve between ages 10-14 and 35-39, was significantly positive ($r_s = 0.8788$, $p \leq 0.001$). This finding indicates that, as observed, higher peak young adult incidence of HD did occur where incidence was elevated at all ages between 10 and 40. A second coefficient measured the association beween the highest young adult rate and the profile (percent change in rates) of the peak of the young adult curve. In this test, the hypothesis was that tall curves would have a wide profile, with a small percent change in rates, the variables were independent. As expected, rho was negative although not significant ($r_s = -0.4182$, $p = 0.115$), indicating that high peak rates in young adults tend to be inversely associated with the narrow curves that reflect an overall lower incidence at these ages.

The strengths of these associations were different for males and for females. The correlation between the height and area of the young adult curve was strong for each sex, but it was significant at $p \leq 0.05$ only for women (males: $r_s = 0.4909$, $p = 0.075$; females: $r_s = 0.5877$, $p = 0.037$). There was no association between young adult curve height and profile for either sex.

These statistics jointly suggest that as risk of HD increases in young adults in the United States, it does so in a wide age range of young persons, especially in women. Persons between ages 20 and 30 are most susceptible to developing HD, but their risk does not operate independently of the risk for the broader group of persons aged 10-40.

RELATIONSHIPS BETWEEN CHILDHOOD AND YOUNG ADULT RATES

As described in Chapter 2, Correa and O'Conor, and Vianna and Polan observed a striking inverse relationship between childhood and young adult disease rates in international data (4,76). Abramson proposed that this pattern fit a viral etiology of HD, with early childhood exposure providing subsequent immunity to infection and malignancy, and, conversely, early protection from exposure causing disease to develop at a later age (75). In these United States data, rates of HD in children are all very low (Table 20), so that variation may be insufficient to produce the inverse childhood-young adult rate pattern.

In fact, for the ten SEER areas, the association

between rates in persons aged 5-14 and 20-34 was positive, not negative, for both sexes combined (r_s = 0.5152, p = 0.064). It was not significant for either sex separately (males: r_s = 0.1841, p = 0.635; females: r_s = 0.5394, p = 0.108), although the correlation was stronger for females. With childhood redefined to ages under 10, the associations no longer approached significance. Thus the findings in international rates were not duplicated in data from this country.

What produces this contradictory association? Gutensohn and Shapiro recently reported that socioeconomic risk factors for older children (aged 10-14) were intermediate between those of younger children and young adults in eastern Massachusetts (43). This finding suggests that in a well-developed country, persons of all ages under 15 may not share HD risk factors and host responses. In the SEER populations, rates for ages 10-14 were strongly positively correlated with rates for ages 20-34 (r_s = 0.6606, p = 0.02). This association is consistent the Gutensohn-Shapiro finding and most likely contributes to the positive correlations above between rates in children ages 5-14 and young adults.

These direct childhood-young adult associations in the SEER data support the preliminary impression of geographic homogeneity in incidence at these ages. In addition the positive age-specific covariation reflects the Type III pattern of these data, with high disease levels across a broad range of young persons, including older children.

RELATIONSHIPS BETWEEN THE YOUNG ADULT AND OLDER ADULT MODES

Are levels of incidence related in the two highest-risk age groups (young and older adults)? Many researchers observed differences in geographic variation between these age ranges, considering this evidence that HD represented two diseases or disease responses (2-4,54,73). However, two quantitative analyses contradicted this finding. Evaluating international data, Abramson, and Vianna and Polan independently reported positive associations between rates in young adults and in persons over 50 (75,76). Such correlations tend to favor a common etiology for both age groups. In the SEER data, peak young adult incidence was not significantly correlated with the peak older age rate for both sexes combined (r_s = .0424, p = .454) or separately (males: r_s = -.1152, p = .376; females: r_s = -.0837, p = .415). The lack of covariation in these age groups agrees with many of the earlier reports, including one using United States mortality data (73).

In males, the highest old-age rate was negatively although not significantly correlated with young adult rates but was positively associated with rates for children ages 5-14 (r_s = 0.6667, p = 0.05). This observation supports a further finding by Gutensohn and Shapiro that male children and older adults have common childhood socioeconomic risk factors not shared by young adults (43). Together these associations suggest that in the United States, HD behaves

independently in younger and older persons, as several investigators observed, but in contrast to the interdependence noted by Abramson and by Vianna and Polan in international data. The discrepancies in these findings may reflect methodologic differences, which are discussed in Chapter 6.

RELATIONSHIPS BETWEEN AGE-SPECIFIC RATES AND COMMUNITY-WIDE ECONOMIC STATUS

Correa and O'Conor associated economic stratification with age-specific patterns of variation in worldwide rates (4,74). They noted that in poor countries, childhood rates were high and young adult rates were low, while in affluent areas, childhood disease was negligible, and young adult incidence was prominent. Clearly, the community-wide average economic conditions in the contemporary United States vary less than those between the developing and well-developed countries Correa and O'Conor considered. Nevertheless, because the effects of gross community-level status on HD in young persons have never been quantified in any data, these particular relationships were tested with the SEER rates.

YOUNG ADULT RATES AND COMMUNITY SES

The correlations between young adult incidence and community SES, presented in Table 23, corroborate the prior reports, in spite of the limited socioeconomic variation across the SEER locations (Table 11). The peak young adult rate was significantly positively correlated with measures of well-being (average median family income, average median

Table 23. SPEARMAN RANK CORRELATION COEFFICIENTS AND ASSOCIATED P VALUES FOR CORRELATIONS* BETWEEN PEAK YOUNG ADULT HODGKIN'S DISEASE RATES AND COMMUNITY-LEVEL SES VARIABLES, BY SEX

	Correlation Coefficients					
	BOTH SEXES		MALES		FEMALES	
SES Variables	r_s	p	r_s	p	r_s	p
1960						
Pop Density	.2364	.511	-.0545	.881	.1879	.603
% Fam Inc <$3000	-.6242	.054 **	-.3576	.310	-.4788	.162
% Fam Inc >$10000	.4788	.162	.4182	.229	.5394	.108
Med Fam Inc	.7697	.009 **	.3091	.385	.5879	.074
% Persons <5 yrs schooling	-.6485	.043 **	.4545	.187	-.0788	.829
Med Yrs Ed	.4788	.162	-.1879	.603	.1515	.676
1970						
Pop Density	.2364	.511	-.0545	.881	.1879	.603
% Fam Inc <$3000	-.6121	.060	-.2606	.467	-.3939	.260
% Fam Inc <$5000	-.6242	.054 **	-.2242	.533	-.4182	.229
% Fam Inc >$15000	.3212	.365	.1030	.777	.2364	.511
% Fam Inc >$25000	.4181	.229	.3333	.347	.3939	.260
Med Fam Inc	.6727	.033 **	.1273	.726	.4182	.229
% Persons <5 yrs schooling	-.6242	.054 **	.4182	.229	.0424	.907
% Persons > high school	.2121	.556	-.0788	.829	.4909	.150
Med Yrs Ed	.6606	.038 **	-.2727	.446	.2000	.580

* $n = 10$

** statistically significant at $p \leq 0.05$

years of education) and inversely associated with measures of poverty (average percent of families earning less than $3000 in 1960 and $5000 in 1970, average percent of persons over age 25 with fewer than five years schooling). Thus, as predicted, incidence of young adult HD increases with the affluence of the community, even where the variation in rates is low, and the overall standard of living is high. These associations were not significant for male and female rates separately. However, the correlations were stronger for women than men.

CHILDHOOD RATES AND COMMUNITY SES

The lack of range in childhood incidence and in economic strata in the contemporary United States noted above suggests that an association between childhood incidence and poverty might not be found here. In fact, rates in children (0-9 or 5-14) were not significantly associated with any of the economic variables (Table 24). However, the directions of these associations tended to reverse those for young adults, as in previous studies.

OTHER AGE GROUPS AND COMMUNITY SES

The effect of community economic standing on HD incidence has been observed only among young persons. At older ages, HD rates show little variation. In these data, community SES was not significantly correlated with the peak old-age rate, as the lack of rate variation at these ages would predict. No other age-specific relationships with SES

Table 24. SPEARMAN RANK CORRELATION COEFFICIENTS AND ASSOCIATED P VALUES FOR CORRELATIONS* BETWEEN CHILDHOOD HODGKIN'S DISEASE RATES AND COMMUNITY-LEVEL SES VARIABLES

	Correlation Coefficients			
	AGES 5-14		AGES 0-9	
SES Variables	r_s	p	r_s	p
1960				
Pop Density	-.2485	.489	-.2848	.425
% Fam Inc <$3000	.1030	.777	.1515	.676
% Fam Inc >$10,000	-.0545	.881	-.1394	.701
Med Fam Inc	.0909	.803	.0545	.881
% Persons <5 yrs schooling	-.5515	.098	-.5636	.090
Med Yrs Ed	.4303	.214	.5152	.128
1970				
Pop Density	-.2485	.489	-.2848	.425
% Fam Inc <$3000	.3455	.328	.3818	.276
% Fam Inc <$5000	.2727	.446	.3576	.310
% Fam Inc >$15,000	-.4424	.200	-.3939	.260
% Fam Inc >$25,000	-.3455	.328	-.5515	.098
Med Fam Inc	-.2000	.580	-.2485	.489
% Persons <5 yrs schooling	-.3091	.385	-.3697	.293
% Persons > high school	.2727	.446	.1152	.751
Med Yrs Ed	.4909	.150	.5050	.138

* n = 10

were explored.

Thus the findings on the SES association with childhood and young adult rates concur with the earlier observations. They indicate a measurable effect of community-level SES on HD in the young even in a country with relatively uniform regional economic conditions.

Both historic (1960) and contemporary (1970) indicators of community economic level were significantly correlated with various rates. For some of these correlations, the directions of the associations were similar for measures of both income and education. In other cases, these two sets of variables showed correlations in opposite directions. This contradiction was anticipated from the divergent rank orders of these measures in certain regions (Chapter 3).

Testing associations in the SEER data is restricted by the small number of regions, the instability of some of the rates, and the general lack of variation in incidence and community SES. Despite these limitations, there were significant correlations that confirm the differences in HD intra- and internationally. In this country, the high risk to young adults affects a larger age range as it increases. Childhood disease lacks the independent incidence fluctuations noted internationally, varying instead with young adult risk. HD in older persons seems to operate separately from the disease in young adults but, for males, similarly

to disease in childhood. However, in its sensitivity to SES, HD incidence in all three age ranges varies in directions previously reported, showing a strong risk-enhancing effect of community SES only for young adults.

INCIDENCE FOR THE FOUR RYE HISTOLOGIC SUBTYPES: 1977-1980

At the regional level, histology-specific incidence for 1977-1980 retains the epidemiologic patterns noted in combined-area histology data. It also manifests some regional variations, which provide a histologic explanation for the unusual incidence patterns noted above. As with regional rates for all HD, however, the detailed age- and sex-specific distributions for each histologic type are more notable for their geographic consistency than for the few deviations.

AGE-ADJUSTED RATES

Table 25 lists the age-adjusted histology rates (the associated 95 percent confidence intervals are in Appendix Table C-9). Across all areas, these rates show the following features, which characterized histology incidence nationwide. 1) In every study location, NS rates are significantly higher than rates of the other three subtypes. 2) MC rates exceed those of LP and LD in most regions. 3) The male excess in MC, LP, and LD exists at almost every SEER site. In the NS subtype, male and female risks are consistently close, with relatively low male rates in Atlanta, Hawaii, Utah and New Orleans, all areas of low HD incidence.

While there was little striking geographic variation

Table 25. AVERAGE ANNUAL AGE-ADJUSTED RATES OF HODGKIN'S DISEASE BY HISTOLOGIC SUBTYPE, SEX AND REGION, 1977-80

Survey Region	NS	LP	MC	LD
BOTH SEXES				
San Fran.-Oak.	1.99	.14	.46 #!@	.15
Connecticut	1.97	.22	.77	.30
Atlanta	1.32 *+	.23	.48 #!	.08 +
Hawaii	1.43	.11	.34 #!	.18
Iowa	1.42 *+	.22	.88	.24
New Orleans ('74-77)	1.17 *+	.35	.76	.15
Detroit	1.39 *+	.21	.95	.19
New Mexico	1.42	.15	.62	.20
Utah	1.28 *+	.21	.52 #!	.17
Seattle-Puget S.	1.32 *+	.22	.77	.07 +!
MALES				
San Fran.-Oak.	2.11	.20	.73	.24
Connecticut	2.05	.37	.87	.43
Atlanta	1.08 *+	.39	.56 #	.15
Hawaii	1.29	.23	.36	.34
Iowa	1.32 *+	.33	1.19	.36
New Orleans ('74-77)	1.16 *+	.34	.82	.08 +
Detroit	1.45	.30	1.24	.24
New Mexico	1.68	.16	.80	.32
Utah	1.24 *	.28	.76	.26
Seattle-Puget S.	1.55	.34	.98	.10 +!
FEMALES				
San Fran.-Oak.	1.88	.09	.20 +#!@	.07
Connecticut	1.90	.09	.67	.19
Atlanta	1.54	.05	.36	-
Hawaii	1.60	-	.47	-
Iowa	1.56	.12	.61	.12
New Orleans ('74-77)	1.17	.31	.60	.20
Detroit	1.36	.12	.68	.16
New Mexico	1.17	.14	.44	.09
Utah	1.33	.14	.31	.08
Seattle-Puget S.	1.13 *+	.09	.60	.06

* Rate signif. lower ($p \leq 0.05$) than San Fran.-Oak. rate
\+ Rate signif. lower ($p \leq 0.05$) than Connecticut rate
\# Rate signif. lower ($p \leq 0.05$) than Detroit rate
! Rate signif. lower ($p \leq 0.05$) than Iowa rate
@ Rate signif. lower ($p \leq 0.05$) than Seattle-P.S. rate

in the incidence of any Rye type, the ranking of rates across areas and consequently, the locations between which differences were significant did vary some from subtype to subtype. Furthermore, these intersubtype regional relationships varied by sex, with more numerous rate differences for males than females. The most distinctive regional extremes in the age-adjusted rates are described below for each histologic category.

NS: San Francisco-Oakland and Connecticut had the highest incidence of NS, significantly exceeding rates in five other areas. The predominance of this most prevalent subtype in both males and females in these two areas is consistent with their high rates of HD overall. At 1.2 per 100,000, the NS rate in New Orleans is quite low. In Utah, the rate of NS in males is also unusually low.

LP: Rates for LP range from 0.11 per 100,000 in Hawaii to 0.23 per 100,000 in Atlanta, without any significant regional differences.

MC: Geographic rate rankings for this subtype are dissimilar to those for NS. The incidence of MC is highest in Detroit and Iowa, with rates significantly higher than in San Francisco-Oakland, Atlanta, Hawaii and Utah. The high NS-low MC pattern in San Francisco-Oakland is particularly pronounced in women, and, for both sexes, contrasts with Connecticut, which has high levels of all subtypes.

LD: Rates of LD are uniformly low. However, the rate in

Connecticut (0.3 per 100,000) is significantly higher than the low rates in Atlanta (0.08 per 100,000) and Seattle-Puget Sound (0.07 per 100,000).

Thus in the summary rates, regional histology-specific incidence parallels the geographic consistency of the regional overall rates, as well as the subtype distributions noted in combined-region data. For each histologic category, geographic variation is limited to differences among two or three regions. However, both the range of rates and their interregional rankings vary among the subtypes. As with data for all subtypes combined, female age-adjusted rates vary somewhat less than male rates, with fewer significant regional differences. Unusual incidence patterns occurred in San Francisco-Oakland, with low rates of LD and MC, especially in women; and in Utah, where NS incidence was depressed in males but not in females. Connecticut had high rates of all four subtypes.

GEOGRAPHIC COVARIATION OF SUBTYPE RATES

This intersubtype and intersex variability can be quantitatively evaluated by testing covariation between rates.

Covariation Between Subtypes: For one subtype, the ranking of rates by region does not seem to predict the rate ranking by region for other subtypes: e.g., a high rate of NS in an area does not indicate a high rate of LP. How independent are the intraregional orders of the four Rye categories? Table 26 presents rank correlation coefficients for

associations between rates for each pair of subtypes. The incidence of NS is negatively correlated with incidence of LP, and the MC subtype is weakly associated with LP. The inverse relationship between NS and LP parallels the patterns in nationwide data of high rates of NS and low rates of LP, and of their opposite secular trends in incidence from 1969 to 1980. There are no other significant relationships between histologic categories, indicating that the incidence of most subtypes occurs independently in these locations.

Intersubtype correlations are stronger in women. Female rates of LD are highly associated with rates of LP and MC. However, the inverse relationship between NS and LP found for both sexes is not statistically significant for women. There are no significant correlations among male rate ranks.

Covariation Between Sexes: The greater number of significant differences in male rates and their lack of intersubtype correlations suggest greater variation in histology-specific HD for men than women. How much similarity exists in the geographic distribution of male and female incidence by histologic type? The correlation coefficients for associations between male and female rates (Table 27) indicate that they are significantly correlated only for MC. The lack of strong intersex covariation for the other three subtypes is consistent with the differences in the extent of geographic

Table 26. SPEARMAN RANK CORRELATION COEFFICIENTS AND ASSOCIATED P VALUES FOR CORRELATIONS* BETWEEN RATES OF PAIRS OF HISTOLOGIC SUBTYPES, BY SEX, 1977-80

BOTH SEXES

	NS		LP		MC		LD	
	r_s	p	r_s	p	r_s	p	r_s	p
NS	-	-	-.5515	.049**	-.2121	.278	.4182	.115
LP	-	-	-	-	.4545	.093	-.0545	.441
MC	-	-	-	-	-	-	.3455	.164
LD	-	-	-	-	-	-	-	-

MALES

	NS		LP		MC		LD	
	r_s	p	r_s	p	r_s	p	r_s	p
NS	-	-	-.3576	.155	-.2606	.234	.3313	.173
LP	-	-	-	-	.2485	.244	-.2121	.278
MC	-	-	-	-	-	-	.0667	.427
LD	-	-	-	-	-	-	-	-

FEMALES

	NS		LP		MC		LD	
	r_s	p	r_s	p	r_s	p	r_s	p
NS	-	-	-.4182	.115	.0182	.480	-.0182	.480
LP	-	-	-	-	.0758	.414	.7660	.005**
MC	-	-	-	-	-	-	.5532	.049**
LD	-	-	-	-	-	-	-	-

* n = 10
** statistically significant at $p \leq 0.05$

Table 27. SPEARMAN RANK CORRELATION COEFFICIENTS AND ASSOCIATED P VALUES FOR CORRELATIONS* BETWEEN MALE AND FEMALE RATES OF EACH HISTOLOGY SUBTYPE

Correlation Pair	r_s	p
NS(males)-NS(females)	.2606	.234
LP(males)-LP(females)	-.2121	.278
MC(males)-MC(females)	.8061	.002 **
LD(males)-LD(females)	.1337	.356

* n = 10

** statistically significant at $p \leq 0.05$

variability in male and female rates frequently noted in these and other data.

AGE-SPECIFIC INCIDENCE

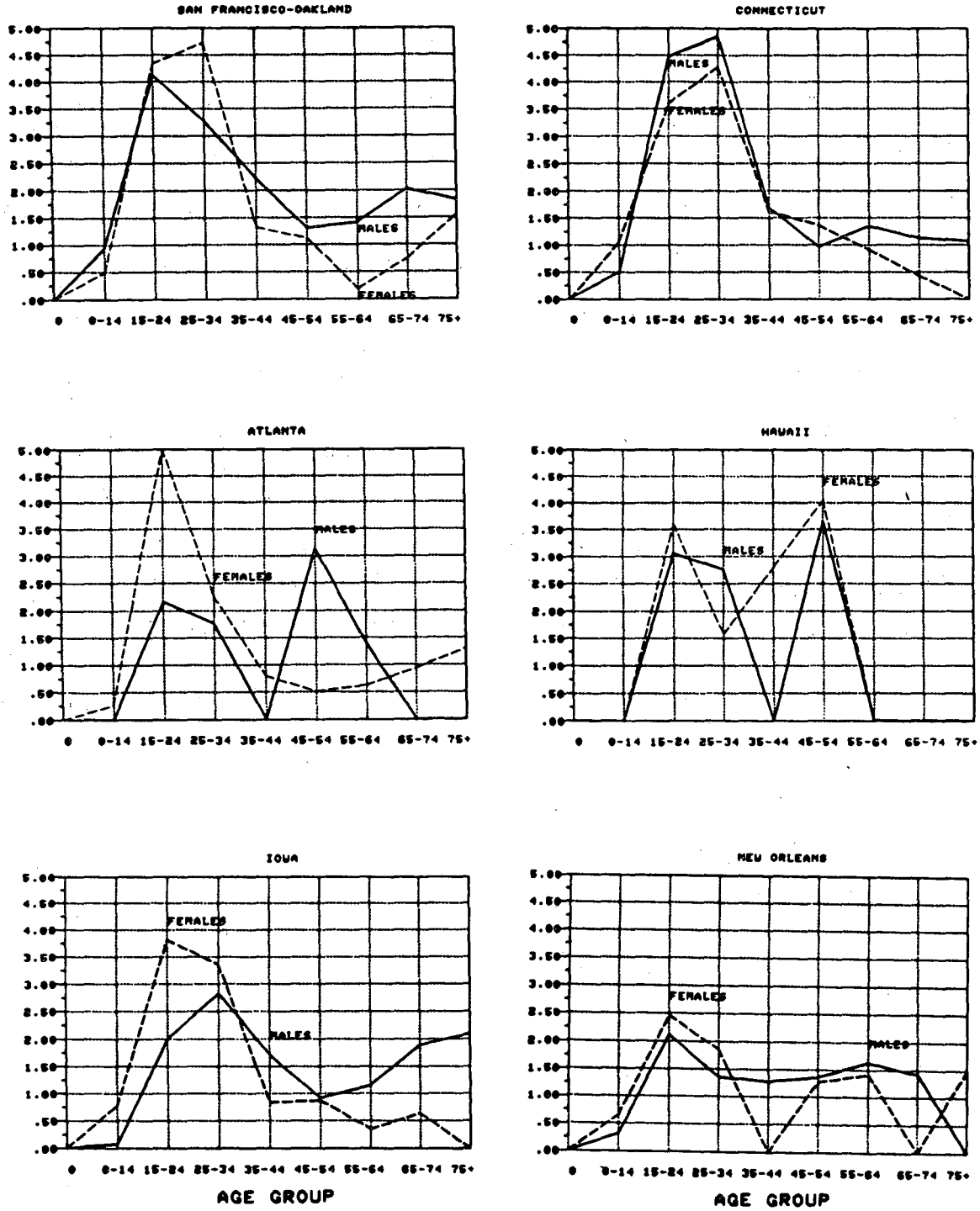
The age-incidence curves of each of the four histologic types show both the geographic uniformity and the few distinctive regional distributions observed in the regional age-adjusted histology rates and age-specific rates for all HD. The consistencies and anomalies in age-incidence are described by subtype.

NS: NS rates, graphed in Figure 21, form the characteristic prominent young adult peak in all SEER areas. The height of this peak varies by region, being particularly elevated in San Francisco-Oakland and Connecticut, and depressed in Utah. In persons over age 55, NS incidence seems to vary less geographically.

In young adults, NS rates are higher for women than for men in most locations. The contrasting female excess in San Francisco-Oakland and male excess in Connecticut have both been reported elsewhere (7,70). In Utah, male young adult rates of NS are particularly low, contributing to the low summary NS and overall incidence for males in this area in 1977-1980 (Figure 16). The male and female rate divergence over age 45, described in the nationwide NS incidence, also occurs in most regions.

LP: The age-specific rates of LP (Figure 22) are reasonably consistent from place to place, considering the instability from small numbers of cases. In most regions with reliable

Figure 21. AVERAGE ANNUAL AGE-, SEX-, AND HISTOLOGY-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE FOR EACH SEER REGION,
NODULAR SCLEROSIS
1977-1980



* rates per 100,000

Figure 21., continued

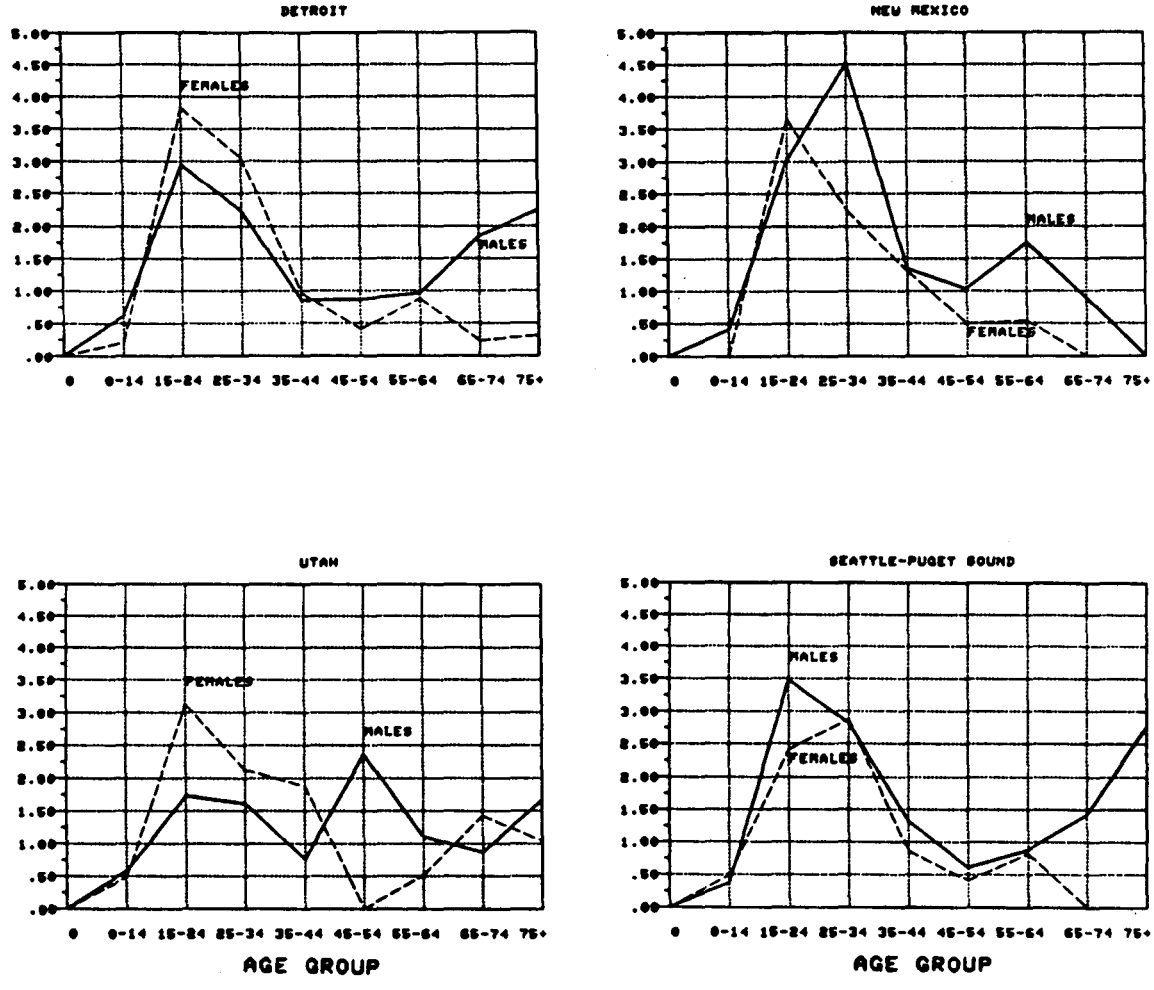
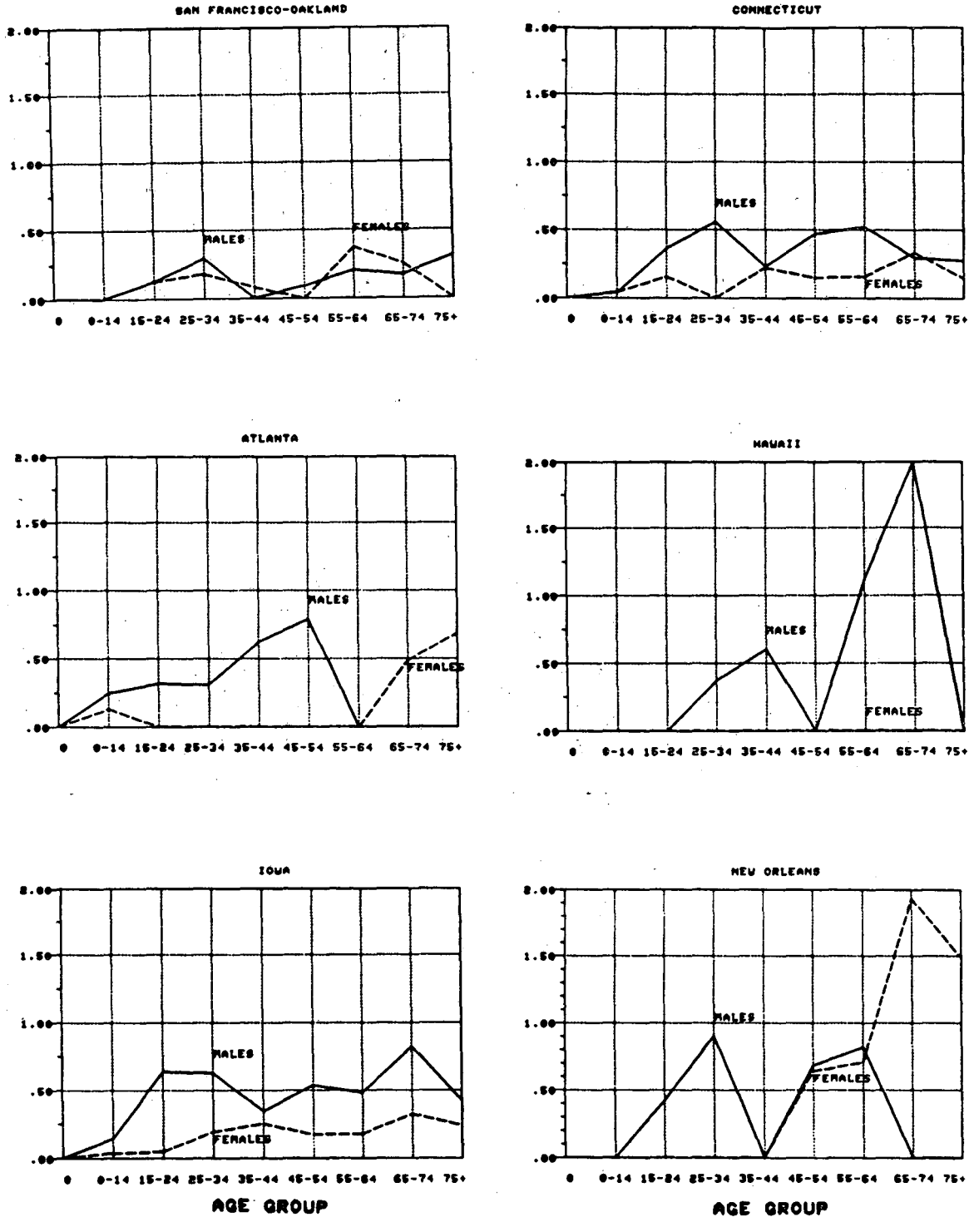
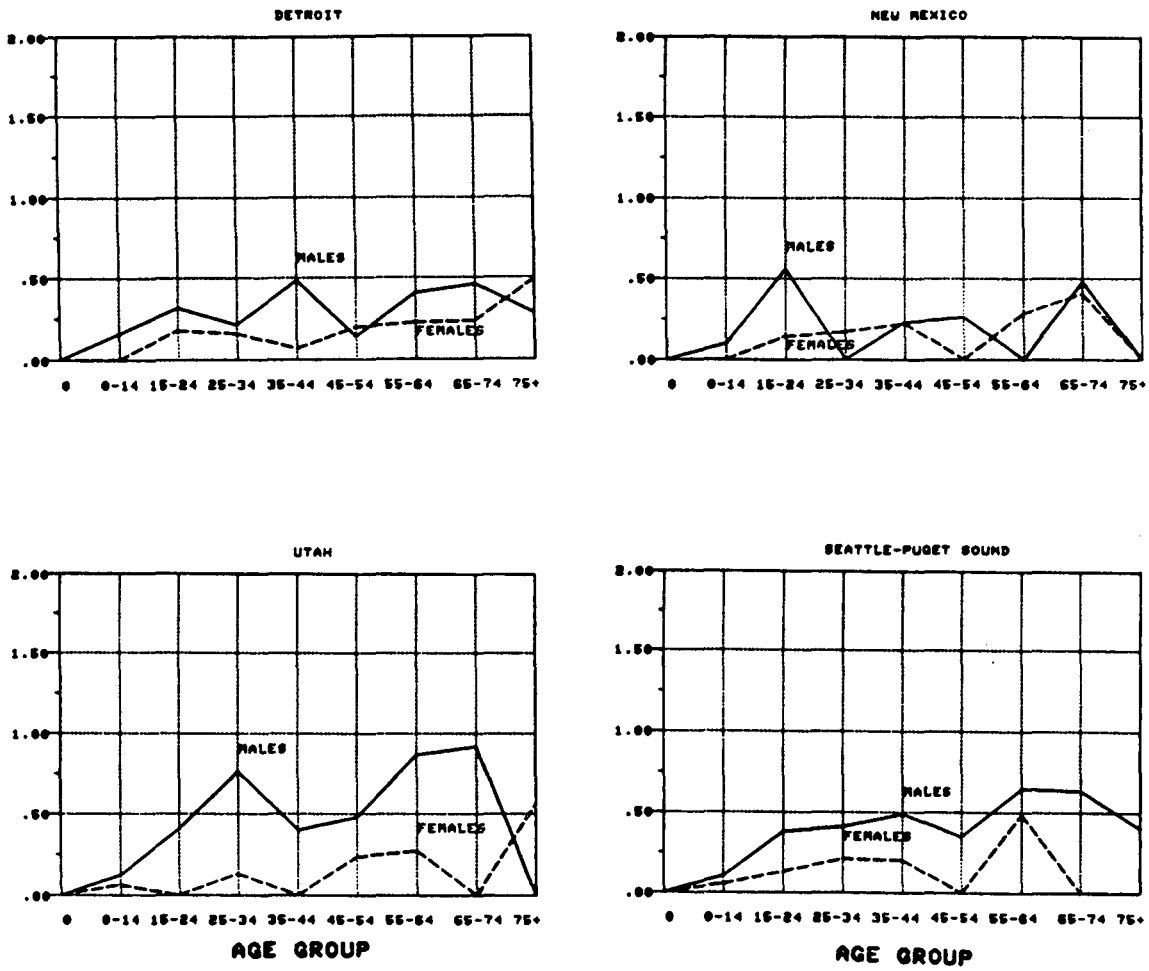


Figure 22. AVERAGE ANNUAL AGE-, SEX-, AND HISTOLOGY-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE FOR EACH SEER REGION.
LYMPHOCYTE PREDOMINANCE
1973-1980



* rates per 100,000

Figure 22., continued



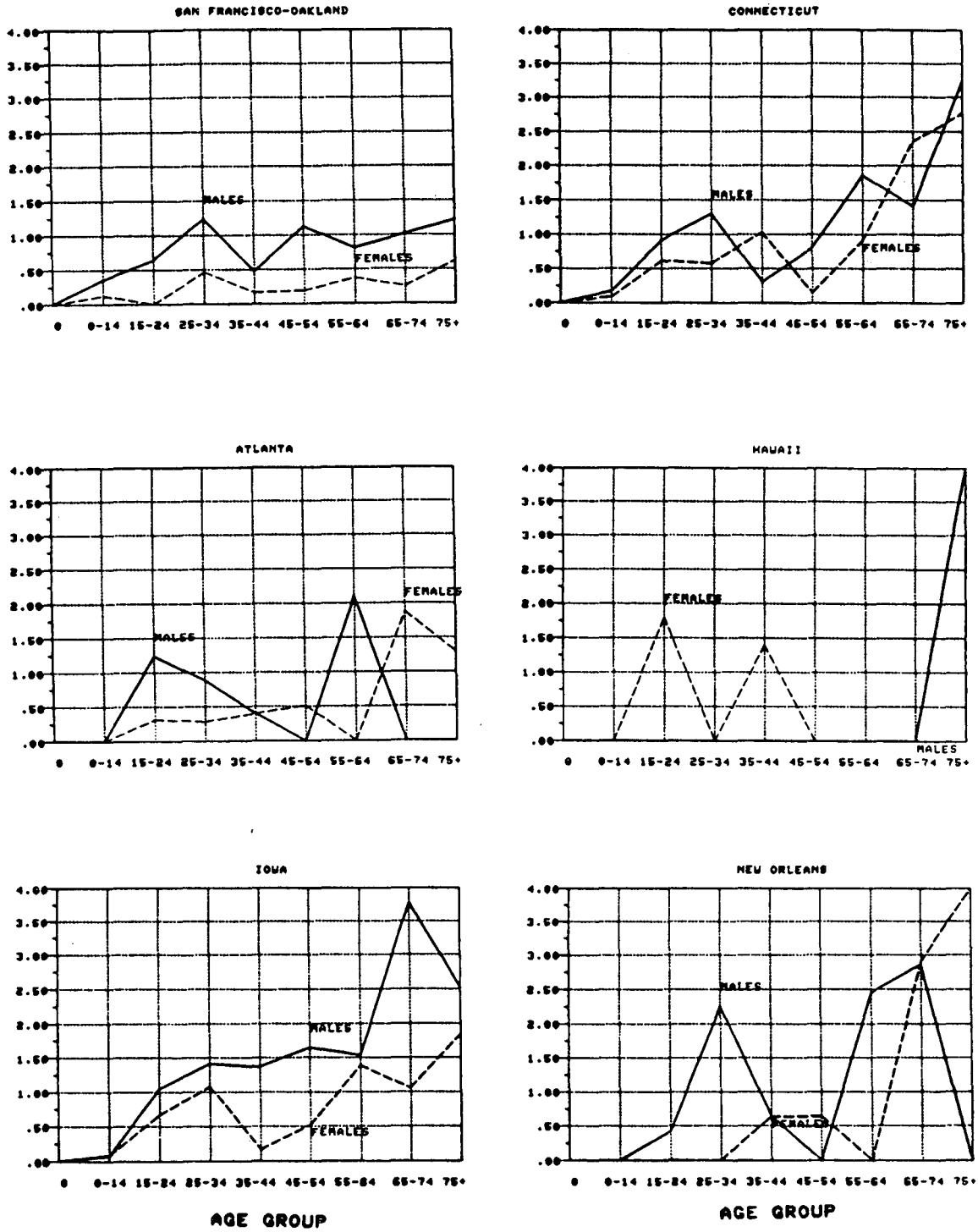
data, male incidence exceeds female incidence. However, in San Francisco-Oakland and New Mexico, this usually pronounced male excess is missing, with age-specific risk of LP similar for both sexes. The relatively low male rates contribute to the notably low age-adjusted rates of LP in these areas.

MC: The curves for MC (Figure 23) show somewhat greater geographic variability. In Connecticut, Detroit, Iowa, and Seattle-Puget Sound, rates are high and curves bimodal. In San Francisco-Oakland and New Mexico, the bimodality is less apparent. For San Francisco-Oakland in general, the incidence of MC is unusual. The relatively low level of these rates, particularly at older ages, contrast with data from Connecticut as well as from Alameda County, California for 1960-1969.

LD: The curves for LD show little variation for both sexes combined or by sex (Figure 24). Rates are highest in Connecticut but low in San Francisco-Oakland, again contradicting the patterns described in Alameda County.

Overall, age-specific incidence of the four histologic forms of HD varies minimally across these locations. The observed regional variation follows that seen in the summary rates. The histology-specific distributions stand out in San Francisco-Oakland, with its high female young adult NS rates and low incidence of LP, MD, and LD; and in Utah, where the rates of NS in males are very low. The age-, histology-specific irregularities for both areas help ex-

Figure 23. AVERAGE ANNUAL AGE-, SEX-, AND HISTOLOGY-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE FOR EACH SEER REGION,
MIXED CELLULARITY
1977-1980



* rates per 100,000

Figure 23., continued

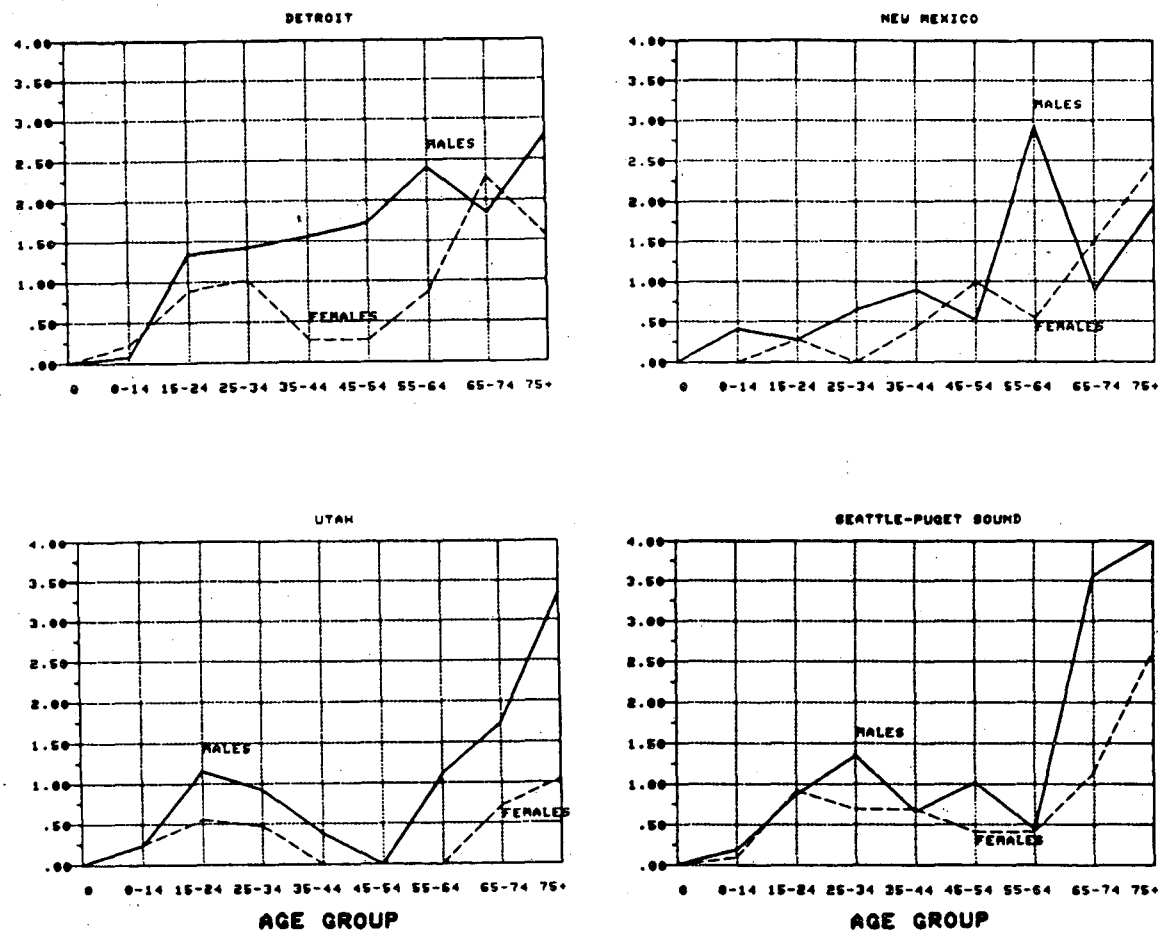
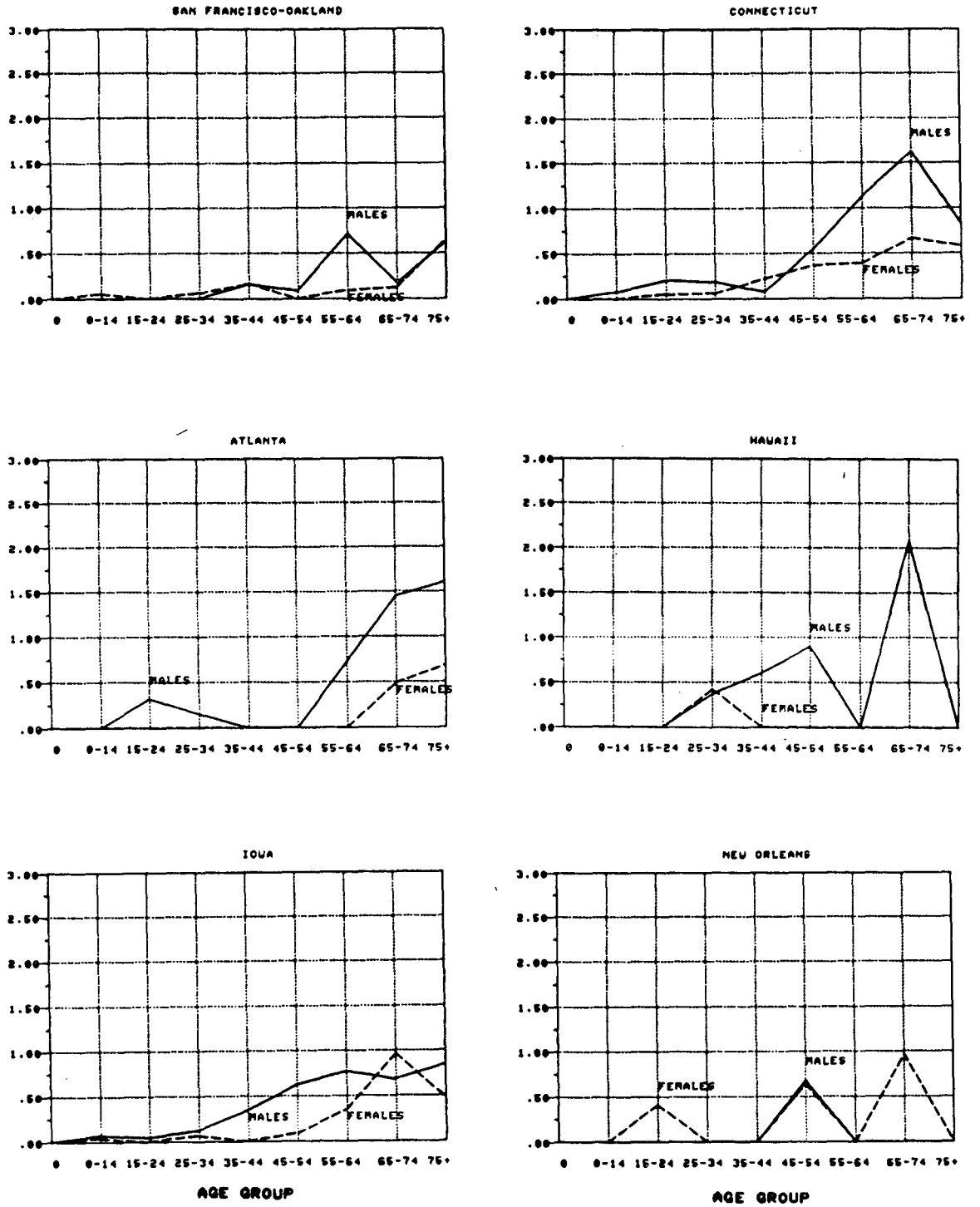


Figure 24. AVERAGE ANNUAL AGE-, SEX-, AND HISTOLOGY-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE FOR EACH SEER REGION.

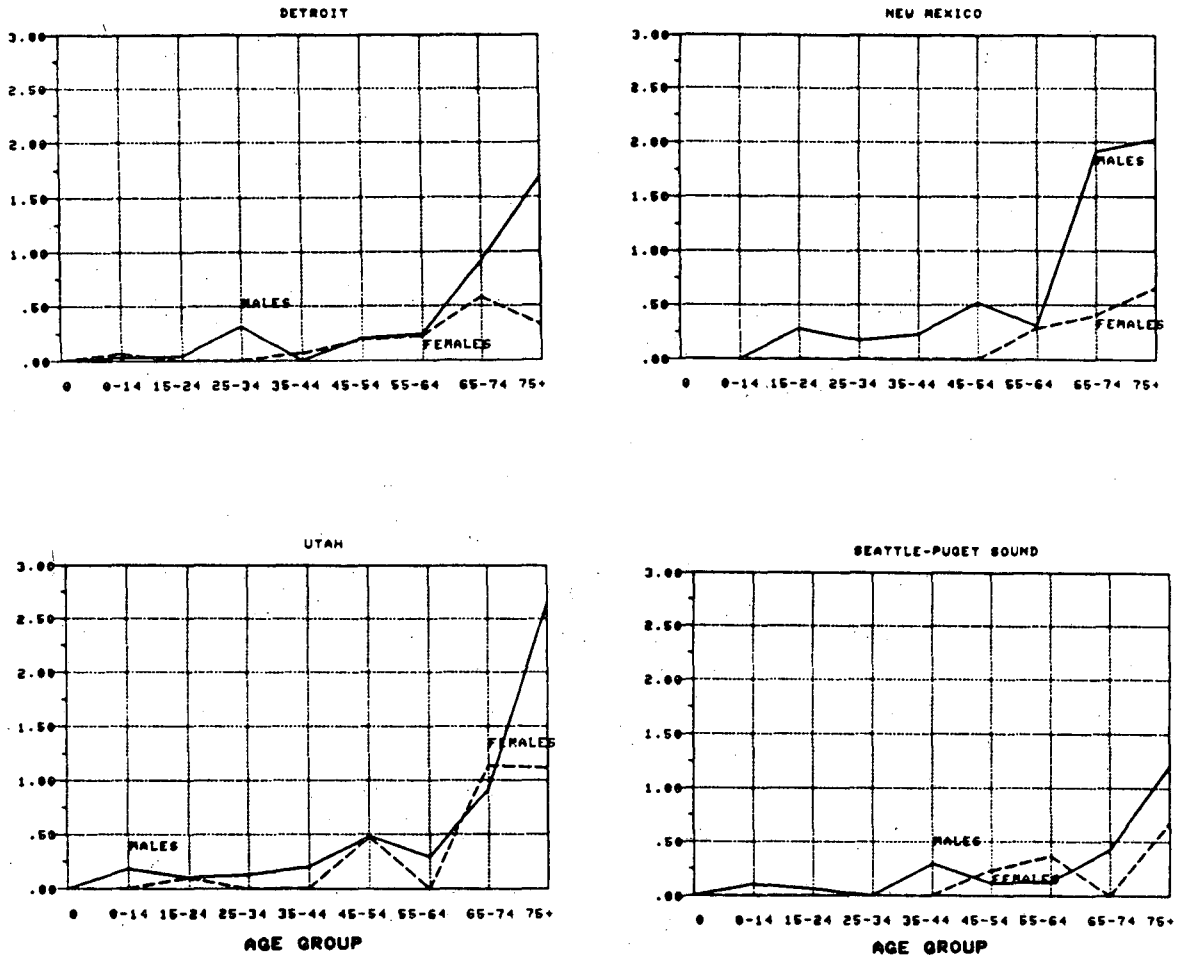
LYMPHOCYTE DEPLETION

1973-1980



* rates per 100,000

Figure 24., continued



plain the distinctive summary histology rates and overall HD incidence described above.

RELATIONSHIPS BETWEEN HISTOLOGY-SPECIFIC RATES AND COMMUNITY-WIDE ECONOMIC STATUS

Reviewing international data, Correa and O'Conor suggested that the histology-specific incidence of HD varied with economic status (4). They noted that in underdeveloped countries, MC and LD were the predominant subtypes, while in well-developed regions NS was most common. The high rates of NS for all SEER regions combined crudely support their impression. In addition, these patterns can be more precisely tested across the individual SEER areas.

The correlations between histology-specific age-adjusted rates and community SES variables, presented in Table 28, quantitatively corroborate Correa and O'Conor's observations. For both sexes combined, rates of NS are positively associated with high levels of income and negatively correlated with low income. Rates of the other three subtypes show an opposite pattern, with higher incidence associated with lesser affluence.

These associations are more pronounced in women in several ways. 1) The correlation of NS with economic well-being is stronger, i.e., significant, or approaching signficance, for more SES variables, for females. Furthermore, only for females is NS correlated with both contemporary and historic levels of SES. 2) There is a negative

Table 28. SPEARMAN RANK CORRELATION COEFFICIENTS AND ASSOCIATED P VALUES FOR CORRELATIONS+ BETWEEN AGE-ADJUSTED RATES OF HODGKIN'S DISEASE AND COMMUNITY-LEVEL SES VARIABLES, BY HISTOLOGIC SUBTYPE AND SEX

Correlation Coefficients

BOTH SEXES

	NS		LP		MC		LD	
SES Variables	r_s	p	r_s	p	r_s	p	r_s	p
1960								
Pop Density	.0788	.829	.1394	.701	-.1152	.751	-.3455	-.328
% Fam Inc <$3000	-.5515	.098	.3212	.365	.2364	.511	.0303	.934
% Fam Inc >$10000	.6970	.025*	-.5152	.128	-.3818	.276	-.1152	.751
Med Fam Inc	.5515	.098	.3697	.293	-.1152	.751	-.1152	.751
% Persons <5 yrs schooling	.0545	.881	-.0182	.960	-.3455	.328	.0182	.960
Med Yrs Ed	.3455	.328	-.5394	.108	-.4061	.244	-.2484	.425
1970								
Pop Density	.0788	.829	.1394	.701	-.1152	.751	-.3455	.328
% Fam Inc <$3000	-.4182	.229	.1273	.726	-.1030	.777	-.0788	.829
% Fam Inc <$5000	-.4909	.150	.1758	.627	-.0303	.934	-.1030	.777
% Fam Inc >$15000	.3576	.310	-.2242	.533	-.1394	.701	-.1273	.726
% Fam Inc >$25000	.5515	.098	-.0788	.829	-.1879	.603	.0303	.934
Med Fam Inc	.4467	.174	-.2000	.580	.0788	.829	.0303	.934
% Persons <5 yrs schooling	.0424	.907	-.1394	.701	-.4182	.229	.0909	.803
% Persons > high school	.1515	.676	-.3333	.347	-.8061	.005*	-.6000	.067
Med Yrs Ed	.3091	.385	-.3576	.310	-.1758	.627	-.2121	.556

MALES

SES Variables	r_s	p	r_s	p	r_s	p	r_s	p
1960								
Pop Density	.0424	.907	.1758	.627	-.0788	.829	-.4545	.187
% Fam Inc <$3000	-.4788	.162	-.0182	.960	.1758	.627	-.1515	.676
% Fam Inc >$10000	.5394	.108	-.1758	.627	-.3212	.365	.1030	.777

\+ n = 10

* statistically significant at $p \leq 0.05$

Table 28. continued

	NS		LP		MC		LD	
SES Variables	r_s	p	r_s	p	r_s	p	r_s	p
Med Fam Inc	.6242	.054*	-.0545	.881	-.0424	.907	.0424	.907
% Persons <5 yrs schooling	-.2242	.533	-.1030	.777	-.3818	.276	-.1273	.726
Med Yrs Ed	.3091	.385	-.2485	.498	-.3333	.347	.1394	.701
1970								
Pop Density	.0424	.907	.1758	.627	-.0788	.829	-.4545	.187
% Fam Inc <$3000	-.3212	.365	-.2848	.425	-.1152	.751	-.2364	.511
% Fam Inc <$5000	-.3576	.310	-.2121	.556	-.0545	.881	-.2606	.467
% Fam Inc >$15,000	.1515	.676	.0788	.829	-.1152	.751	-.0424	.907
% Fam Inc >$25,000	.2848	.425	.2485	.489	-.1636	.651	.1758	.627
Med Fam Inc	.3939	.268	.1515	.676	.1152	.751	.1515	.676
% Persons <5 yrs schooling	-.1758	.627	-.2727	.446	-.4545	.187	-.0545	.881
% Persons > high school	.0061	.987	-.0667	.855	-.7939	.006*	-.2364	.551
Med Yrs Ed	.3576	.310	-.0909	.803	-.1030	.777	.1515	.676

FEMALES

SES Variables	r_s	p	r_s	p	r_s	p	r_s	p
1960								
Pop Density	.3697	.293	.1394	.701	-.0061	.9873	.1033	.776
% Fam Inc <$3000	-.5758	.082	.4424	.206	-.0545	.881	.1277	.725
% Fam Inc >$10,000	.5273	.117	-.6242	.054*	-.0788	.829	-.3587	.309
Med Fam Inc	.4303	.214	-.3818	.276	.0182	.960	-.1398	.700
% Persons <5 yrs schooling	-.0061	.987	-.1394	.701	.0303	.934	-.0243	.947
Med Yrs Ed	.2727	.446	-.4061	.244	-.4909	.150	-.5593	.093
1970								
Pop Density	.3697	.293	-.1394	.701	-.0061	.987	.1033	.776
% Fam Inc <$3000	-.5152	.128	.5394	.108	-.4303	.214	.1094	.763
% Fam Inc <$5000	-.6162	.060	.5273	.117	-.3576	.310	.0973	.789
% Fam Inc >$15,000	.5152	.128	-.5152	.128	.2000	.580	-.1824	.614
% Fam Inc >$25,000	.7333	.016*	-.6242	.054*	.2364	.511	-.1216	.738
Med Fam Inc	.5636	.090	-.4667	.174	.3212	.365	-.0790	.828
% Persons <5 yrs schooling	-.0909	.803	.0303	.934	-.1394	.701	-.0182	.960
% Persons > high school	.2364	.511	-.4909	.150	-.7939	.006*	-.7112	.021*
Med Yrs Ed	.3212	.365	-.3091	.385	-.3333	.347	-.3769	.283

* statistically significant at $p \leq 0.05$

association between MC and the number of post-high school years of education for males, but for females, such relationships occur for three subtypes--MC, LP and LD. 3) For women, rates of LP tended to decrease as affluence increased, but this effect was entirely absent in men.

These results confirm that in the United States, the incidence of NS increases with affluence, while the other Rye categories are associated with lower standards of living. They also suggest that the effect of economic conditions on histology-specific disease incidence may be stronger in women, affecting more subtypes and being particularly pronounced in NS and LP, although in opposite directions.

COMPARISONS WITH OTHER DATA

Age-specific histology rates based on a majority of HD cases are available for comparison from six areas. These are Connecticut (1965-1968)* (70); Alameda County, California (1960-1968) (NS and MC only) (7); Los Angeles County, California (1972-1975) (52); Norway (1968) (78); Finland (1961-1964) (77); and Western Australia (1960-1974) (74). For Connecticut and Alameda County, population rates were estimated from a sample of HD cases for which pathologic material was reread. No age-specific rates were published in these studies. Therefore, comparisons were made by visual inspection of age-specific rates included in Figures 25 and 26.

* For persons less than age 20 and greater than age 70, rates were based on data from a longer period--1950-1968.

CONNECTICUT 1965-1968, 1977-1980

The Connecticut rates from 1977-1980 are similar to those from ten years earlier, seen in Figure 25. There are two secular changes: 1) by 1977-1980, young adult rates of NS had increased, retaining their male excess. 2) In contrast, rates of young adult LP dropped in males over the decade. The age-histology distributions of MC and LD were basically unchanged.

ALAMEDA COUNTY, CALIFORNIA

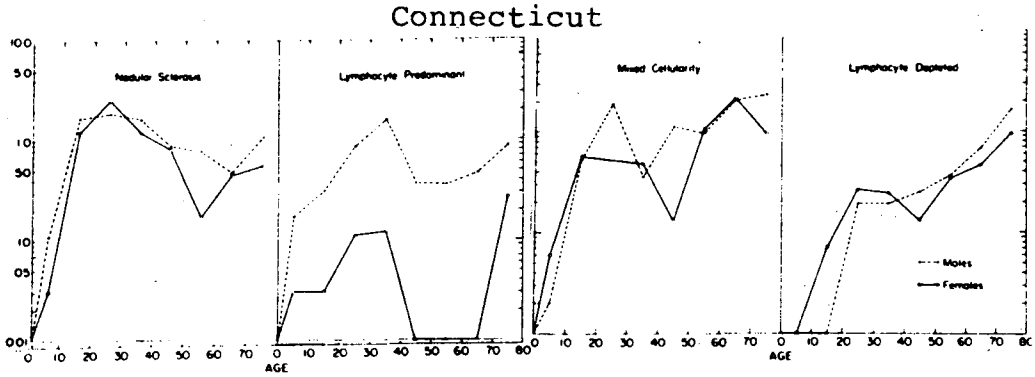
In San Francisco-Oakland, of which Alameda County is only one part, the 1977-1980 rates of young adult NS were higher for both sexes than seen earlier in Alameda County, but the female excess in this age range persisted (Figure 25). Rates of MC in older persons were considerably lower in the San Francisco-Oakland data, a finding consistent with the secular decrease in older age HD for San Francisco-Oakland seen in Figure 19. No age-specific rates were presented for LP or LD.

LOS ANGELES COUNTY, CALIFORNIA

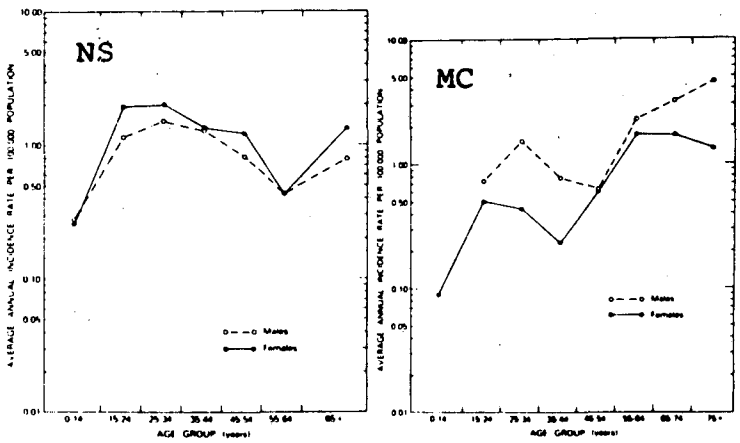
The rates for Los Angeles are similar overall to the SEER regional rates (Figure 25). Two minor features are worth noting. 1) The NS age-specific curve for this county is quite close to the curve for Connecticut for 1965-1968, particularly in the intermodal drop in male rates. 2) As in San Francisco-Oakland, rates of LP lack a male excess in the young adult years.

Figure 25. AVERAGE ANNUAL AGE- AND HISTOLOGY-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE FOR CONNECTICUT (1965-1968); ALAMEDA COUNTY, CALIFORNIA (1965-1968); AND LOS ANGELES COUNTY, CALIFORNIA (1972-1975)*

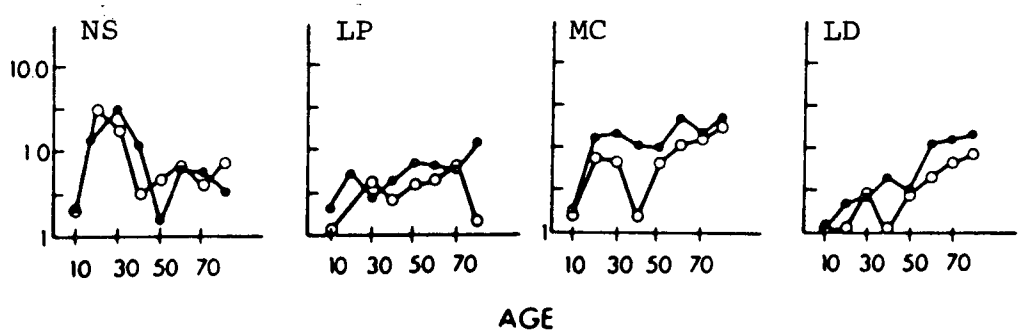
Connecticut



Alameda County, California



Los Angeles County, California



* from (70), (7), and (52), respectively

NORWAY

For each subtype, the age-specific curves in Norway, seen in Figure 26, generally resemble data from a similar time period in Connecticut and California, although Norwegian rates of MC are higher in older persons. Additional contrasts with the later SEER rates are 1) the lower level of young adult NS (compared to all areas except Utah), and 2) the lower incidence of both LP and LD, particularly at older ages.

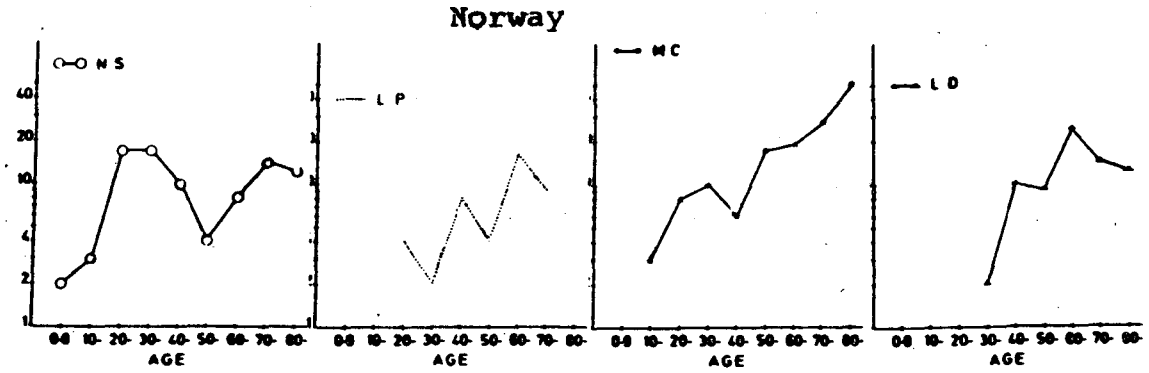
FINLAND

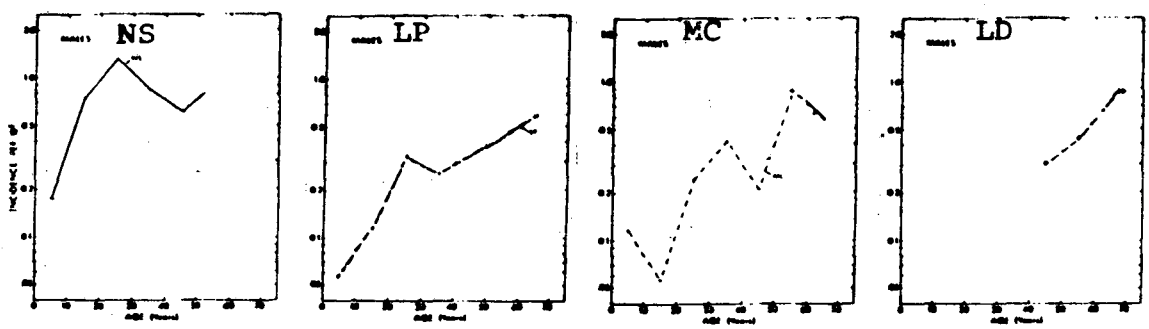
The age incidence in Finland is lower overall than in Norway and, consequently, than in the United States (Figure 26). However, the curves of all four subtypes have similar shapes and relative positions to the Norwegian curves. The incidence of MC in Finland is relatively lower than in Norway.

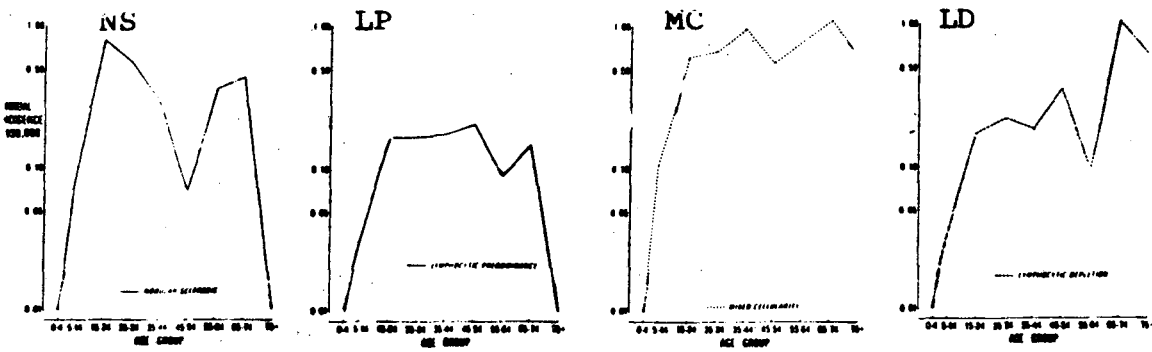
WESTERN AUSTRALIA

The distribution of HD in Western Australia follows a more Type II pattern of incidence, with a gentle, rather than pronounced, bimodal curve for all subtypes combined, and the highest subtype incidence occurring in MC (Figure 26). The age-specific rates of NS, LP, and MC are low, and the curve for NS, although bimodal, is lower than that for MC. In these characteristics the histology-specific incidence in Western Australia differs slightly from the patterns seen in the SEER and other United States and European

Figure 26. AVERAGE ANNUAL AGE- AND HISTOLOGY-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE FOR NORWAY (1968); FINLAND (1961-1964); AND WESTERN AUSTRALIA (1960-1974)*







* from (78), (77), and (74), respectively

data.

The variation in histology-specific data from these well-developed countries is more temporal than geographic. Incidence from the 1960s was similar across regions in having lower levels of NS, and higher rates of MC, LP and LD than seen later. Conversely, SEER data from 1977-80 were characterized by high rates of NS in young adults and much lower incidence of the other subtypes, especially LP and LD. This apparent evolution with time is similar to the pattern seen in secular data for the combined regions of the United States.

An interesting, albeit potentially coincidental, feature of young adult NS incidence is the persistent difference in the sex ratio in Connecticut and the San Francisco-Oakland region. Connecticut has had a male excess at these ages in both studies, while Alameda County and San Francisco-Oakland manifest a consistent, growing female excess. The reason for this difference is not clear.

SUMMARY

There is little pronounced geographic variation in the distribution of HD across the contemporary United States. Summary rates, male-female ratios, and age-specific curves show only slight regional differences either cross-sectionally or through time. Incidence follows the Type III pattern with associated secular trends described in Chapter 4. Over all regions, this pattern is further characterized

by a broadening of young adult risk across ages, with an unexpected positive covariation of childhood and young adult incidence; by an expected lack of association between young and older adult rates; and by a previously observed sensitivity in all three age groups to community SES.

Histology-specific rates were also geographically stable, and in most regions characterized by features discussed in Chapter 4. There were some variations in the rank order by region of the four subtypes. However, there was an inverse relationship in the levels of NS and LP, and stronger intersubtype correlations for women. Male and female rates were correlated only for MC. Histology-specific incidence varied as expected with community SES.

Rate differences among regions were slight, with relative levels of incidence consistent across histologic types in most areas. Incidence in San Francisco-Oakland was an exception: it was elevated overall and for NS, but had low levels of LP, MC and LD, and an unusual secular decrease. Another distinct regional pattern was the high level of MC in Detroit and Iowa, two areas of intermediate overall and NS incidence.

In general, the geographic consistency of HD is notable, given the potential for variation in diagnosis and data collection of this rare disease. The implications of the regional consistency as well as the unusual patterns are discussed in Chapter 6.

Chapter 6

DISCUSSION

The descriptive epidemiology of HD has been established since the seminal work of MacMahon (2,3) and Correa and O'Conor (4). To the substantial body of information about this disease, the present study makes three additions. 1) It describes the approximate nationwide incidence of HD, both for the present and over the past 30 years. 2) It establishes the extent of geographic variation across the United States. The regional data permit quantitative evaluation of incidence pattern variations, identification of any regional anomalies suggestive of varying environmental etiologies, and a demonstration of the accuracy of all-area summary rates as representations of regional experience. 3) Most significantly, this study partitions HD incidence into its histologic components, providing one of the first epidemiologic opportunities to document the incidence and establish the etiologic relevance of the Rye subtypes over a wide geographic range.

This final chapter will summarize the contribution of notable findings in these three areas to the understanding of HD, taking into consideration data limitations that might bias the results. It will review the applicability of the findings to the major causal theories. Last, it will mention further descriptive projects suggested by these

results.

I. HD ACROSS THE UNITED STATES: ALL REGIONS COMBINED

Most of the secular and contemporary distributions of HD in all regions combined conformed closely to patterns described in numerous other studies. The correlation analyses on regional-level data provided a more detailed characterization of nationwide incidence, which also confirmed previously reported observations, and in addition suggested some unexpected features.

SECULAR TRENDS

The secular changes in HD up to the 1970s contained few surprises. For both sexes, the trends are classic examples of a transition from Correa and O'Conor's Type II to Type III incidence patterns. Some part of these increases may reflect improvements in data accuracy. The Ten Cities Survey, TNCS and SEER programs attempted to insure thoroughness of case ascertainment by careful selection of registries and by quality control evaluations. However, Devesa et al. reported that data from the second Ten Cities Survey were less reliable than those from either the TNCS or SEER programs, by two measures of completeness and accuracy (89).* Therefore, some part of the observed increase in HD between 1947 and 1969 may represent an increase in ascertainment completeness over this period. However, the age-

* This analysis examined data from the five areas common to all three NCI surveys, considering percentage of incident cases reported by death certificate only, and proportion of cases with microscopic confirmation of diagnosis.

specific trends, and their occurrence with presumed economic improvements, clearly adhere to Correa and O'Conor's age- and sex-specific, socioeconomically modified model. Therefore these factors strongly suggest these early trends were real. The only feature of the time trend data not conforming to the Type II-Type III evolution was the lack of decrease in childhood rates, discussed below.

CONTEMPORARY STATUS OF HD

The more recent (SEER) rates were also generally consistent with prior descriptions of HD, both in overall and in histology-specific incidence. There were a few unexpected characteristics in rates of two of the three broad age groups (children, young adults and older persons), especially through time . There were also some previously undocumented trends in histology rates and in their associations with SES. And there were some subtle but unanticipated differences in male and female incidence trends. The following sections discuss these findings.

AGE-SPECIFIC TRENDS: Childhood

In well-developed countries, HD is quite rare in children. The low childhood rates in this study support this fact. However, in the SEER data, older children (ages 10-14) had relatively high and increasing disease rates, which were largely attributable to the NS subtype. One effect of this progressive prominence of NS in children was the secular stability of childhood rates mentioned above.

A second effect was the unexpected positive association between childhood and young adult rates across SEER regions. The inverse relationship in rates of these two age groups has been a distinctive epidemiologic feature of HD to date. This negative association has been observed in incidence and mortality data, cross-sectionally with international rates and secularly within a single country (2-4,35,44,48,76). The contradictory positive correlation in the SEER data resulted from a strongly positive association in rates of older children (age 10-14) and young adults, reflecting the relatively high incidence in the former.

While the consequences of these higher rates in older children--secular stability in childhood rates and positive covariation with young adult rates--were themselves unexpected, the higher, NS-associated, incidence itself was not surprising in an affluent environment. Differences in HD risk between younger and older children have been recognized previously. Miller, evaluating single-year age-specific HD mortality, identified a sharp increase in rates after age 11 (58). Recently Gutensohn and Shapiro suggested that older children had socioeconomic risks intermediate between those of younger children and young adults (43). These prior observations thus link HD risk in pre-teenage years to the risk of young adults. In the SEER data, childhood incidence patterns provided evidence of that shared susceptibility: rates in both older children and young adults seemed to be

elevated and rising in the contemporary United States.

The lack of a rate decrease in persons under age 10, and in the childhood rates of MC and LD, may also indicate that non-NS incidence has reached a baseline level at these younger ages. Perhaps that proportion of childhood disease resulting from early infectious exposure has already disappeared in this country under better economic conditions, leaving only those cases resulting from inherited susceptibility and unaffected by exogenous factors. If correct, this interpretation implies that the present levels of childhood incidence, especially for MC and LD, should remain unchanged in future years.

Thus these findings suggest new developments in the epidemiology of HD in children. Pre-teenage incidence, primarily of NS, seems to be responding to the same affluent environmental conditions promoting disease (also NS) in young adults. Rates in younger children have not changed, suggesting an endogenous etiology. These patterns are based on small numbers, which affect the rank order of rates for which correlations were calculated. However, although unexpected, the findings readily fit established explanations of HD causation.

AGE-SPECIFIC TRENDS: Young Adulthood

The incidence of young adult HD in the SEER population varied less from expected patterns than did childhood rates. The following characteristics are noteworthy.

High rates High rates of HD in young adults have been

considered a hallmark of its incidence in well-developed areas since Correa and O'Conor's 1971 paper (4). The elevated young adult incidence peak observed in nationwide and regional SEER data solidly concur with this observation.

Broad age range of young adult incidence Correlations across the ten SEER locations suggested a further element of contemporary young adult incidence: its tendency to increase in a wider range of ages (10 to 39) as its peak rates rise. Like all correlations in this study, this finding was based on only ten data points. It also achieved only borderline statistical significance. However, it suggests an epidemiologic behavior of HD incidence consistent with its observed sensitivity to economic status; namely, that under the conditions increasing risk to the most susceptible, risk also seems to increase for a broader age group. Thus susceptibility to young adult HD is not confined to persons between ages 20 and 30.

If correct, this finding confirms that HD in young persons is an environmental disease. Socioeconomic status has been causally implicated as one of the critical environmental factors in a variety of prior studies, and by its association with young adult rates in the SEER data, discussed next.

SES The positive ecologic association of young adult HD and socioeconomic status found here is not novel. However, most previous reports with international incidence data were

either observational (4,74,76), or used mortality data (54). What is interesting about the association in this study is its significant presence within a country where regional economic status is relatively high. In such circumstances, it indicates that even small changes in community economic well-being may alter risk of young adult HD.

The relationship of community-level SES with HD is obviously confounded by personal SES, known to increase disease risk in young persons (41,53). However, two factors validate region-wide economic conditions as an independent risk factor: 1) Correa and O'Conor's original observation that broad economic environment per se affected HD rates; and 2) the possibility of disease risk from both micro- and macro-socioeconomic status. For an infectious disease (which young adult HD has been proposed to be (3,48,75)), personal SES may affect risk by determining individual exposure and resistance to disease agents. However, the prevalence of such agents in the community might also depend on community factors like population density and sanitation. For HD, this interaction might function as follows: the affluent conditions in the United States may fail to support an etiologic agent in sufficient concentration to render the population immune in childhood, so that a much larger portion of the young adult population would be susceptible to the infection and its rare malignant outcome. In this way, socioeconomic status of the community may control HD incidence.

Thus the positive association of young adult HD with community SES in this study quantitatively corroborates past reports and raises the possibility of independent risk for region-wide economic conditions.

Relationship with older adult rates One of the premises on which the "two-disease hypothesis" was based was the apparent difference in geographic variation for young and older adult HD (2-4,54,73). The lack of significant covariation of peak rates of these two age ranges in the SEER data is consistent with this frequent observation.

However, the finding does contradict the results of the only quantitative evaluations of this relationship (75,76). The disagreement may reflect differences in age-group definitions or populations. The previous quantitative analyses correlated rates for broad age groups (ages 15-34 and over 50) from international data, while this project examined peak rates in each mode. Another study using similar broad age groups of United States mortality data also reported no apparent covariation of young and older adult HD (73). Therefore the lack of association of these two age groups seems not to be the result of age group definition but rather either a feature of HD in the United States, or the effect of biases in the rates of older persons, discussed below.

Secular increases Secular increases in young adult rates, such as those seen in the SEER data, have not often been

documented with other incidence data, but they have been anticipated from previous trends. These changes continue the dramatic secular increases in young adult mortality illustrated in Figure 4, and the trends in young adult incidence between 1947 and 1969-1971 recorded in Figure 10 and by Holly (34). They are similar to increases found in Boston between 1959-1963 and 1969-1973 (48). Gutensohn and Cole predicted such a pattern in 1977, saying that

> we may expect an increase in HD incidence in the United States during the next decade resulting from the current high level of living conditions and decrease in family size. (48, p.601)

The possibility that these increases may result from bias in numerators or denominators is small but is reviewed below.

Although the observed increases were not substantial, their consistency with past data suggests they were real. Type III incidence therefore appears not to be static but rather to evolve, with continued increases in young adult rates. The occurrence of this evolution over the relatively short eight-year study period agrees with an observation by Gutensohn and Cole that HD incidence can change rapidly, presumably in response to socioeconomic circumstances (35). Furthermore, it implies that the continuation of such circumstances will lead to higher rates of HD in persons ages 10 to 40 in the future.

Role of histologic subtypes in young adult incidence SEER histologic data reveal that the distinguishing features of young adult HD in these populations derived predominantly

from the NS subtype. While this form of HD has been previously understood to constitute most of young adult incidence, the more dynamic and detailed examination permitted by SEER histologic time trends identified several specific characteristics of young adult disease--its high and increasing rates, its female predominance (especially between ages 10 and 20), and its secular stability in childhood with the drop in childhood male excess--all of which could be attributed to NS.

In the present study, this subtype can also be linked indirectly to the increased risk of young adult HD with higher community SES. NS was the only category positively associated with community-level economic standing, a finding also noted ecologically by Henderson et al. and by Holly (34,52). All these correlations occurred with age-adjusted rates. However, the sequence of associations of NS with young adult disease, and young adult disease with community SES in these data, permits the conjecture that NS is the form of young adult HD that is sensitive to socioeconomic environmental conditions. While none of the case-control studies of HD in the United States has explicitly examined the effect of SES on subtype risk, a study in Israel did report elevations in the young adult risk of NS and MC with higher childhood social class (53).

The MC type of HD also has been noted elsewhere to have a pronounced young adult incidence. In the SEER data, young adult rates of MC are low and seem to have decreased

slightly in time. There is no clear reason for this change. It may represent the proposed evolving Type III incidence, although if so, it contradicts the positive association of MC with higher levels of SES in Israel.

The differences in secular trends by subtype also may reflect changes in histologic classification. There are no data on age-specific trends in assignment of the various Rye subtypes, but there have been several, more general studies of classification accuracy (7,70,77,79,92-98). These have shown that on expert pathologic review*, a substantial proportion (39-69 percent) of MC diagnoses were found to be incorrect, and the majority of these cases were reclassified as NS (95-97). If this particular pattern of reclassification occurred in young adult cases, and if it was instituted progressively through time by practicing pathologists educated through contact with the expert reviewers, then the apparent secular trends in young adult NS and MC could have been caused by such improvements.

This argument is conjectural and, as mentioned, cannot be checked with age-specific misclassification data. However, there is some suggestion that the educational impact of the LPPR has improved diagnostic accuracy of referring pathologists. Vélez-García et al. reported a

constant improvement in the degree of agreement [be-

* either in studies of misclassification (96), or, for cases entered in treatment study protocols, in reviews of diagnostic accuracy by expert pathologists participating in the Lymphoma Pathology Panel and Repository (LPPR) (95,97,98).

> tween initial and review diagnoses] which has been apparent over the years [1968 forward] since the system has been operational (97, p. 679).

Thus some of the secular increase in young adult NS may represent the reassignment of cases of MC. However, young adult HD, primarily composed of the NS subtype, showed increases independent of changes in intersubtype classification. Furthermore, the figures in Table 17 of this study indicate that the secular increases in NS were greater than the decreases in MC at almost all ages under 45. Therefore, it seems unlikely that young adult NS increases derived entirely from the inclusion of cases formerly called MC.

Summary The SEER data thus demonstrate an expected Type III distribution of young adult HD, with prominent rates. In addition, the geographic correlations and secular histologic data indicate that the pattern is not static but rather evolving. This evolution is characterized by: 1) slightly increasing incidence, which seems to affect a larger age group as it rises; 2) independence from disease in older persons; 3) increases in response to small increments in community economic status; and 4) occurrence over a relatively short period. As secular rate increases at these ages occurred only in the NS subtype, it is tempting to propose that the other epidemiologic features are also characteristic of the NS subtype, but the instability of the age-specific histologic rates prohibited direct evaluation

of these associations. However, a prominent and rising incidence of NS seems to be a further element of the evolving Type III distribution. If this pattern does represent changing incidence rather than classification of the disease, it suggests that rates at young adult ages will continue to increase in the future, as the conditions of affluence persist.

AGE-SPECIFIC TRENDS: Older Persons

The most unusual aspect of HD incidence in the SEER data was the decline in the rates of older persons. In previous studies, the primary age-specific variation, both geographically and secularly, occurred in childhood and young adult rates. In older persons, the disease tended to be stable (2,3,73). In this study, rates for persons over age 40 showed a decrease that was slight but pervasive, affecting all older age groups, both sexes and all four subtypes.

With the histologic heterogeneity of HD, a secular effect appearing in all subtypes leads to suspicion of bias. However, there are several possible explanations, including: 1) a cohort effect; 2) a depletion of susceptibles; 3) a diminishing of the risk factors for older age HD; 4) a change in classification of HD; and 5) an artifact of data collection procedures or denominator estimation.

Cohort Effect The possibility that the old-age rate decline represents a cohort effect is suggested by the age-specific behavior of the trend. In the twenty years between the 1947

and 1969-1971 surveys, the second incidence peak increased and shifted its location 15 to 20 years to an older age in both sexes. In the following decade, rates for all persons over age 40 dropped in magnitude but not location.

If a cohort phenomenon explains these changes, then the affected cohort would have been 40 to 70 years old in 1947. One experience common to this group was their status as teenagers and young adults (ages of relevance to HD) during World War I. However, the critical exposures would have had to have affected both men and women, which many wartime experiences did not. The effect of a post-War increase in parity on female rates is discussed later. The paucity of clues about causes of HD in older persons makes it difficult to project other potential etiologic exposures for this group, and thus to support a cohort effect as the explanation for the observed secular change.

Depletion of Susceptibles If HD has an infectious etiology at all ages, then the incidence decline in rates at older ages could have resulted from a progressive disappearance of susceptible persons over 40. The high rates of the disease usually observed in older persons may occur when the relatively low absolute rates of childhood and young adult disease leave a large segment of the population vulnerable to HD at older ages, perhaps at the point when their immune capacities and any existing protection against the cause of the disease have naturally decreased. Perhaps as environmen-

tal conditions change and delay relevant exposures until young adulthood, as may occur at present, the young adult nonimmune group, once exposed, develops HD in relatively large numbers (apparent as high young adult rates). This population at risk is then depleted not only of those persons previously likely to develop young adult disease, but also of those who, in other circumstances, would have been immune early in life but succumbed to HD in old age. The depletion of susceptibles before age 40 would thus produce the observed secular decreases in rates of older persons.

Arguing against this explanation, which is predicated on an infectious etiology, are 1) its lack of histologic specificity (in young adult HD, presumed to have an infectious cause, NS is the only subtype that increases with the environmental conditions thought to control infection); and 2) the lack of significant evidence that HD in older persons is in fact infectious.

At present, this hypothesis cannot be easily examined empirically, as there have been few data on secular trends of HD incidence under the supposedly etiologic conditions of prolonged economic affluence. SEER data from the future will be useful in investigating this issue.

Changing Risk Factors A related but more tenuous explanation of the older age incidence decline is a change in risk factors directly affecting persons over 40. This possibility is based on two observations: 1) the significant correlation between peak old age rates in males and rates in boys

across the SEER areas; and 2) its consistence with a Boston finding of shared socioeconomic risk factors in boys and men over 50 (43). If in fact the disease in children and older adults does covary because of common risk factors, and if the low childhood rates in all Type III regions reflect the disappearance of such conditions, then the secular decline in older persons might similarly reflect a decrease in the risk factors for this age group. This conclusion is based on limited evidence. A more convincing argument will require further elucidation of risk factors in older persons, and an explanation of the secular decline in female as well as male HD.

Changes in Classification of HD The unexpectedness of the old age rate declines, and their appearance in all subtypes raise the question of bias. With HD, misclassification is a particularly suspect source of error because of the well-recognized difficulty in establishing a precise diagnosis of this lymphoma, even histologically.

There are no data on secular trends in the age-specific misdiagnosis of HD. However, there have been a number of studies, some mentioned above, dealing with the differentiation of HD from other lymphomas (7,52,77,79,92-98). Many of these used nonrandom samples of cases (92-98) and restricted searchs for misdiagnosed cases of true HD to other lymphomas only (7,77,93-98), even though HD has been misclassified as inflammatory disease (92,98). Seven studies

are nevertheless very useful in this consideration of classification bias. Four reviewed pathologic diagnoses on complete samples of tumor registry, population-based cases (4,52,77,79), and three evaluated large numbers of lymphoma cases entered in treatment protocols (95-97).

These investigations revealed several classification errors germane to the current project. 1) There is a wide range in the degree of diagnostic accuracy. In nine studies, from 6 to 47 percent of cases had been incorrectly called HD (4,52,77,79,92,95-98). 2) When cases of true HD with other original diagnoses (mostly lymphomas) were retrieved, these "found" cases were fewer in number than those misdiagnosed as HD in every study. Although not all possible sources of such cases were searched, most error seems to be in differentiation with other lymphomas. Therefore on balance, HD is probably slightly overdiagnosed. 3) Of greatest significance here is that misdiagnosis was not uniform across ages but increased with age. In two separate studies of all HD cases from tumor registries in Alameda County, California, and Connecticut, Silverman et al. and O'Conor and colleagues found that 62 percent and 80 percent respectively of the cases falsely diagnosed as HD occurred in persons over ages 50-55 (4,52). This skew towards older ages reflected a more restrictive diagnosis of LD and a tendency for the misclassified cases to be reticulum cell sarcoma, a lymphoma affecting older persons. In a similar analysis, Franssila et al. calculated age-specific incidence

rates for Norwegian cases using both original and corrected diagnoses of HD (77). Graphed in Figure 27, these curves indicate a greater loss of cases and subsequent drop in rates at older ages following correction of diagnosis.

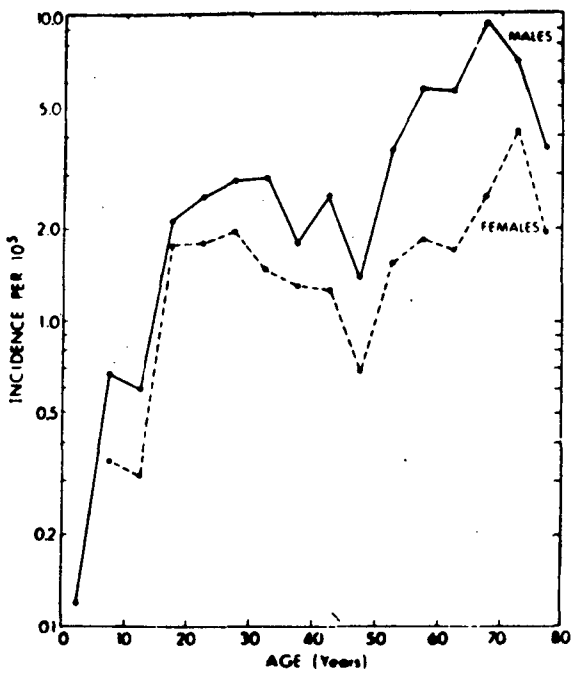
The significance of these findings is clear: the secular decline in older age rates seen in the SEER data may have resulted from improved diagnostic accuracy of lymphomas. This possibility cannot be evaluated directly, in the absence of data on time trends in misclassification. However, such a change may have occurred, if the expert review system has indeed had an impact on the accuracy of lymphoma diagnoses over time. As the LPPR system was established in 1968, such an effect could have been manifest as secular declines in the late 1970s. However, it cannot be quantitatively demonstrated at present.

Examination of secular trends in nonHodgkin's lymphomas provides an independent, though similarly indirect, check on the likelihood of diagnostic accuracy affecting time trends. TNCS and SEER data show that rates of these lymphomas have risen slightly between 1969-1971 and 1973-1977, particularly at older ages * (12,13). This increase cannot be attributed here to any specific cause, such as improvement in the differentiation between HD and other lymphomas, but it is consistent with the findings and arguments presented above that suggest that development.

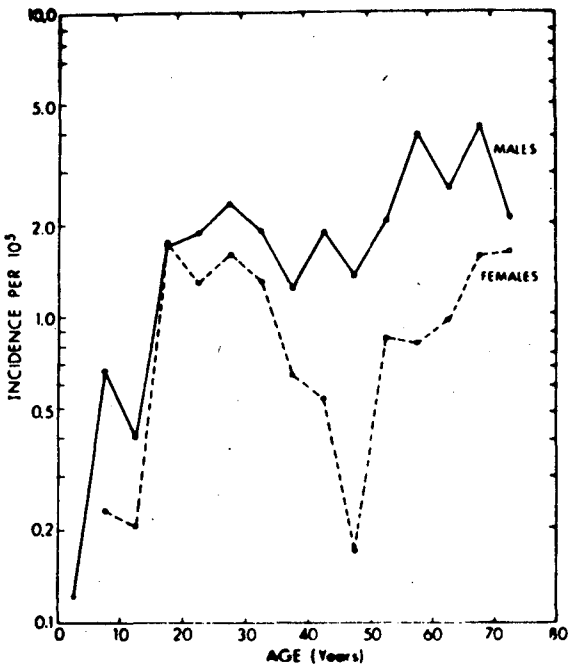
* data not shown here

Figure 27. AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE IN FINLAND, 1960-1964, BEFORE AND AFTER REEXAMINATION OF HISTOLOGIC DIAGNOSES*

BEFORE REEXAMINATION



AFTER REEXAMINATION



* from (77)

These studies of misclassification raise three cautions in interpreting secular trends in HD. 1) All rates may be slightly overestimated, especially those at older ages. 2) The secular decreases in rates for persons over age 40 in some part may reflect improvements in diagnostic accuracy in the 1970s. 3) The slight increases noted in young adult rates oppose the apparent effects of misclassification at these ages (Figure 27). Therefore they cannot be attributed to diagnostic changes and may in fact have been greater than observed, given misclassification.

Other numerator and denominator errors The recent secular trends in HD at all ages could result from two other types of error: 1) differences in the thoroughness of case ascertainment in the contributing surveys; and 2) inaccurate estimates of SEER rate denominators from use of linear interpolation.

(1) Two studies comparing TNCS and SEER data quality concluded that relability in both surveys was high (88,89). However, DeVesa et al. noted that the SEER system of annual retrospective updating of case reports for all previous years tended to leave recent data the least complete (89). Knowlden et al. demonstrated substantial shifts in the slopes of rate trends after the updated incidence material was included (99).

These findings suggest that later cases used in this HD study may be underrepresented by as much as 5 percent,

according to DeVesa et al. While underreporting could contribute to the rate decline observed after 1977, the presence of opposing secular trends in young adult and older age incidence makes such a possibility unlikely. Age-related ascertainment bias itself also seems an inadequate explanation of either trend, as it would require both a diminishing attention to diagnosis of the elderly in time and some difference in completeness of case identification by sex.

(2) SEER rates may also be affected by bias in the estimated denominators. While the impact of small numerators on rates is apt to be greater than the effect of nonsystematic denominator inaccuracies, there are conceivable errors from use of a linear model, which could produce the observed secular rate trends.

The increase in young adult HD between the two SEER periods could occur spuriously under the following conditions:

(1) If population growth in this age range was constant from 1970 until mid-decade and then increased at a greater rate, 1977-1980 population levels would be underestimated by linear interpolation. The 1977-1980 rate using this artificially low estimated denominator would be overstated and falsely indicate a secular increase in rates.

(2) Similarly, if the actual population count lagged below the level predicted by the linear model each year from 1970 until the 1977-1980 period, the 1973-1976 denominator

would be artificially high relative to the 1977-1980 denominator. Then the earlier rate would be erroneously low and again falsely suggest a secular increase.

(3) Both these population trends could occur simultaneously, producing an S-shaped curve and rates falsely demonstrating a secular increase.

In older persons, nonlinear rates of population growth in patterns opposite those above could explain the decrease in HD incidence at these ages.

However, for such population dynamics to produce HD trends, they would have to have occurred simultaneously in the appropriate directions in both young adult and older adult age ranges. In addition, they would have to explain the contradictory age-specific trends of the four subtypes. These conditions seem improbable. Therefore the observed HD time trends are not likely to be artifacts of an inaccurate interpolation model, although some geographic variation may reflect regional differences in the appropriateness of linear estimates.

Summary Thus the secular decline in HD in older persons is slight but notable in its departure from the expected distribution. If the trend is real, several factors, presented above, may have contributed to it. Determining the exact causes will require more information about the etiology of this disease in persons over 40. While errors in case ascertainment and denominator estimation do not seem likely

sources of any age-specific trend, changing accuracy in the differentiation of HD from other lymphomas may well be responsible for some of the rate decreases at older ages.

HISTOLOGY-SPECIFIC INCIDENCE AND TRENDS

The histology-specific rates derived in this investigation are important in two ways. 1) They are reasonably complete (including a large majority of all HD cases) and geographically broad-based. Previous studies have either relied on histology data from a limited proportion of cases (34) or focussed on single regions (7,52,70,74,77,78). 2) They allowed a preliminary examination of secular trends. This combination of completeness and secular detail permitted a more dynamic examination of the contributions of the four subtypes to overall incidence than was previously possible.

Like HD incidence overall, the histology-specific rates generally agreed with prior reports of subtype distributions. For NS, they detailed and confirmed the pronounced association of this subtype with HD in young persons. More significantly, they indicated that NS is the only form of the disease presently increasing in this country.

Rates of the other subtypes, particularly LP, were relatively low and decreased slightly. The factors producing these distributions are not clear from the limited detail in this study. However, there are a few explanatory clues to the secular changes.

Explanations of Secular Trends

Common risk factors The first, suggested by correlations across SEER areas, is that factors increasing the NS risk may decrease risk of LP. The rates of these two subtypes are inversely correlated and seem to have opposite associations with community SES, at least in women. These findings are tentative. The SES association is based on significant correlations in one sex only. The negative association between NS and LP contradicts previous observations in international data of positive covariation of these subtypes (4). However, the possibility that an inverse NS-LP relationship characterizes an affluent society is supported by a similar observation in Alameda County, California (7). The authors of that study proposed that the low incidence of LP in their population might represent "another feature of the evolution of the Type III epidemiologic pattern" (7, p.1763).

Changes in histologic classification A second explanation of the secular trends in subtype incidence is changes in histologic classification. The studies of diagnostic accuracy in HD have emphasized the difficulties in establishing Rye diagnoses of this disease. The considerable interobserver error is felt to reflect differences in experience, interpretation of guidelines, and quality of diagnostic materials, while intraobserver error indicates the subjectivity involved in diagnostic decisions.

Certain findings from these studies are relevant to interpretation of SEER histologic rates. 1) Diagnostic

accuracy varied considerably with histologic category. While no subtype was classified with 100 percent reliability, NS had been shown repeatedly to be the easiest to diagnose, and LP and LD the most difficult. These differences are illustrated in Table 29, which presents for each histologic subtype the proportion of final (expert) diagnoses contributed by the initial diagnoses in three studies. Expert clasification of NS agreed with the great majority of the original diagnoses, while the final diagnoses of the other subtypes used half or less of the initial classifications. 2) There were prominent changes in the relative frequencies of the subtypes, following diagnostic reevaluation. The proportions of NS increased (from 47 to 65 percent in one study (95), and from 33 to 57 percent in another (97)), while there were decreases for both MC (35 to 26 percent (95), and 39 to 24 percent (97)) and LP. The percentages of LD did not change notably.

There are several consequences of these observations for the SEER histologic data. 1) The rates of all subtypes are inaccurate to some degree, in addition to their representing less than 100 percent of all cases (discussed below). Therefore both all-area rates and regional differences should be interpreted cautiously. 2) Rates of NS are likely to be more accurate than rates of MC, LP and LD. 3) Secular changes may reflect improvements in diagnostic accuracy under the same arguments about the impact of expert

Table 29. PERCENT OF REREVIEWED DIAGNOSES CONTRIBUTED BY ORIGINAL DIAGNOSES, BY SUBTYPE, FROM THREE STUDIES

Percent of Final Diagnoses from Original Diagnoses

	NS			LP			MC			LD		
	Studies			Studies			Studies			Studies		
	A*	B+	C#	A	B	C	A	B	C	A	B	C
NS	@(88)	(97)	(87)	29	50	50	40	19	37	23	-	18
LP	-	-	-	(29)	-	(18)	2	6	1	-	-	-
MC	8	3	5	43	50	18	(48)	(69)	(39)	15	-	12
LP	2	-	2	-	-	-	3	6	5	(31)	(100)	(45)

Number of Final Diagnoses from Original Diagnoses

	NS			LP			MC			LD		
	Studies			Studies			Studies			Studies		
	A	B	C	A	B	C	A	B	C	A	B	C
NS	(77)	(34)	(161)	-	1	17	7	3	82	2	-	9
LP	2	-	-	(2)	-	(6)	3	1	2	-	-	-
MC	26	1	9	1	1	6	(31)	(11)	(86)	2	-	6
LP	3	-	3	-	-	-	2	1	11	(4)	(4)	(23)

* from (95)
\+ from (96)
\# from (97)
@ numbers in parentheses represent initial diagnoses confirmed on review

diagnoses presented above. The changes in subtype-specific relative frequencies after expert review are entirely consistent with the direction of SEER data secular trends.

Three factors argue against classification changes as the entire explanation of the observed time trends. 1) As indicated in Table 17, simple transfer of diagnoses among subtypes does not explain the secular changes in every age group. 2) The increases in NS rates occur too disproportionately across ages and between sexes to result only from greater use of this category. 3) The young adult increases in NS paralleled a rise in young adult rates for all HD, which was itself independent of intersubtype diagnostic trends. Nevertheless, the effect of classification changes and other sources of bias discussed next should be considered in examining histology-specific rates in this or any study where pathologic diagnoses have not been rereviewed.

Other sources of bias to histologic rates Two final sources of bias to histology-specific incidence come from the changing prevalence of Rye scheme usage. 1) The infrequent implementation of this classification in the early 1970s bases histology-specific rates from those periods on a small and nonrepresentative portion of all HD cases. Therefore these early rates grossly underrepresent the true incidence, describing it only for a sample of the cases. 2) This sample is known to be biased toward inclusion of young persons (Tables 9 and 10). Consequently histologic rates at

these ages are both more reliable and more representative than rates for older persons. Factors influencing the use of Rye diagnoses in older age groups could also bias their rates by basing them on nonrandom as well as small proportions of cases. However, sources of error for rates of older persons were not investigated here.

The relative overrepresentation of young persons would also affect the age-adjusted histology rates, especially from 1973-1976. In particular, it would contribute to the higher summary rates of NS and MC, subtypes of young adults. However, the age imbalance is not likely to have caused TNCS and SEER rates and proportions of NS to be high relative to data from other areas. Such bias would not be systematically limited to these surveys, for which data were accumulated post hoc from a range of areas and diagnostic situations.

Thus, data incompleteness and bias toward youth in the numerators may introduce some error into all histology-specific rates, especially those from the earlier years. Some potential inaccuracy in their magnitude was artificially eliminated through use of estimated rates, although such rates themselves contain and magnify any biases inherent in selection for Rye subtyping. The predominant use of rates from 1977-1980, when the proportion of cases with Rye detail was high at all ages, also minimizes the problems of both incompleteness and age bias.

Summary The histology rates in this study indicate that

incidence of the NS form of HD is rising in young persons, presumably as socioeconomic and other conditions of risk for this subtype persist. Incidence of MC, LD, and particularly LP are declining. Whether these decreases represent real incidence changes, possibly in response to the same environmental conditions, or the artifactual consequences of changing classification practices or prevalence of usage, will require more detailed study of both subtype-specific risk factors and trends in the usage of the Rye scheme.

MALE-FEMALE DIFFERENCES

As with other variables, the distribution of HD incidence by sex is consistent with previous observations. In the SEER data, male rates were higher than females rates, and varied somewhat more both regionally and secularly, as reported by Correa and O'Conor (4). The sex differences in the early secular trends (1947-1969) offer particularly clear examples of the patterns these authors described, with female rates assuming a bimodal form under all conditions.

Incidence Patterns Pronounced in Women

In spite of the generally lower and less variable female incidence, certain secular trends were unexpectedly pronounced in women. Both young adult increases and older rate decreases were slightly more prominent in women, although the opposite was anticipated. On a regional basis, this trend produced a somewhat greater homogeneity in female age-specific incidence across areas (noted in the 1977-

1980 rates). Most correlations between rates and between rates and socioeconomic status were also stronger, or significant only, in women.

One particular female pattern--the high levels of the NS subtype--may explain these findings. As discussed above, NS incidence was relatively elevated and rising in these populations. A secular increase in rates of this female-dominated form of HD would produce the more pronounced time trends in women, and the stronger correlations for HD overall, as these associatons all focussed on young adult disease, where NS is the prominent subtype.

Similarly, the strong role of NS in female HD may explain both the smaller secular and geographic variation traditionally characteristic of female incidence, and the greater female homogeneity in the most recent SEER regional incidence patterns. It is established that women are more prone to develop NS than the other subtypes. If NS is in fact the form of HD resulting from an infection with a ubiquitous agent, as Gutensohn and Cole proposed (48), then the past and present lack of variation in female rates may reflect the uniform distribution of the cause of this form of HD, which women are more likely to develop.

Low HD Rates in Older Women

Why rates of HD in older females decreased as much as or more than male rates is not clear. Certain explanations offered above for the old age decline pertain to these sex-specific differences. In particular a larger decline in

rates of older women resulting from rising young adult incidence of NS, to which women are especially susceptible, would nicely fit the hypothesis of the depletion of susceptibles. Misclassification and other biases could also contribute to this female secular trend, although the effect of such errors should be seen equally in both sexes.

The possible protective effect of parity (three or more children) noted in Israel (62), may also contribute to these trends. Such a hypothesis suggests a cohort effect, with a substantial increase in parity between the 1920s and the 1960s producing the present low HD incidence in women. The post-World War II "baby boom" may have elevated parity sufficiently, and the childbearing cohort it affected would have been appropriately middle-aged by the mid-1970s. Detecting trends in earlier birth rates to explain the rate drops in the oldest women would require a more detailed examination of demographic trends.

Grufferman suggests that parity, diminished by the lower birth rate and increasing use of contraceptives, may have contributed to the greater female increases in HD in Boston between 1959 and 1973 (8). While this explanation does not apply well to age-specific data from Boston (presented by Gutensohn and Cole (48)) in which young adult rates showed markedly more secular increase in males than in females, it is another reasonable explanation for the more pronounced increase in female than male young adult rates in

the SEER data.

A further possible reason for sex differences in disease is occupation. The low intermodal female rates and the secular declines at older ages might both reflect the lack of work-related etiologic exposures in women. However, the few occupations associated with HD increased risk relatively little. A preliminary study of occupational exposures and female risk of HD found no incidence differences between housewives and employed women (8,72). Therefore this factor is not a likely explanation of the low female rates of HD.

Sex Differences in Histologic Incidence

Two sex-specific patterns in histology rates also deserve mention. One is the observation that male and female rates covary only for MC, suggesting that factors affecting risk and/or disease response may be similar in both sexes only for this subtype. The other is the inverse relationship between rates of LP and community-level SES, present only among women. While this finding may have etiologic significance, its limitation entirely to one sex is unusual. There are no apparent explanations for these correlations, besides the possibility that they are spurious findings resulting from small numbers. However, they may serve as clues for more detailed studies of histology-specific risks.

Summary of Male-Female Differences

Thus these findings offer evidence that the incidence of HD is becoming more prominent in young adult women,

while declining in older women. The former finding results from an increase in the incidence of the NS subtype, which may partly reflect the lower parity of recent years. The latter observation can be explained only by those factors affecting both sexes, although it may also result at least partly from the higher parity of the past. If accurate, however, these sex-specific patterns imply a greater similarity between the sexes in HD incidence in the future, as the rate of NS continues to increase. Why women are considerably less susceptible than men to three subtypes of HD (MC, LP and LD), but equally or more susceptible to NS, remains unanswered.

II. HD BY REGION

The regional data in this study provide a unique opportunity to compare HD incidence for a single time period in a number of locations across the United States. Unfortunately, the reliance by the TNCS and SEER programs on local data collection diminishes the uniformity of data quality. Ascertainment may vary with regional procedures and may not be as thorough as in a special study of a disease. There may also be geographic differences in diagnostic practices and application of the Rye classification, which may contribute in particular to the greater variation of the histology-specific rates.

In the face of these possible biases, the regional consistency of HD rates is noteworthy, although it does

confirm similarities in age-adjusted rates among countries noted in Chapter 2. The absence of geographic variation in age-specific rates differs from the international findings. However, this pattern, too, was expected, given the narrower variation in SES in this country than throughout the world. In general, the stability in all SEER HD rates reiterates the likelihood of uniform distribution or ubiquitousness of the causes of the disease. It provides little evidence of varying environmental etiologies beyond those socioeconomic factors already identified.

DISTINCTIVE REGIONAL PATTERNS IN INCIDENCE

There were some regional rate differences, mostly representing a range of the expected distributions. With the aforementioned potential for variation in data collection and classification, these relatively minor interregional variations may be insignificant. However, a few distinctive patterns can be examined further. These include the high but differing levels of HD in San Francisco-Oakland and Connecticut; the low rates of HD in males from Utah; the low levels of disease in Hawaii (and in Atlanta and New Orleans); and the high incidence of MC in Detroit and Iowa.

SAN FRANCISCO-OAKLAND, CONNECTICUT

The elevated San Francisco-Oakland and Connecticut rates of HD, particularly for young adults and for the NS subtype, may reflect two causes in common. The first is a high risk environment. These two regions are the most affluent in the SEER constellation. Such economic standing

has been associated with the high incidence of young adult, particularly NS, disease observed here.

The second explanation for the similarity in rates is data collection. Both regions have long-established tumor registries, which may have more thorough case ascertainment. The effect of diligence in data collection on higher rates of HD has been recently mentioned by Boston researchers, who noted elevated rates in their special study of this disease (8).

Difference in Rates Between San Francisco-Oakland and Connecticut

San Francisco-Oakland and Connecticut also have marked differences in childhood rates, in relative magnitudes of histology-specific rates (all high in Connecticut, but only NS high in San Francisco-Oakland), and in secular changes among older persons (considerably more pronounced in San Francisco-Oakland). Some differences, such as the low rates of LP, and the small but consistent female excess in young adult rates in the San Francisco-Oakland region, were noted in a previous comparison of HD between these areas (7). However, in neither that study nor the present one are reasons for these discrepancies clear.

Two regional differences could contribute to the varying incidence patterns. 1) Stanford University Medical Center, which has pioneered in the research and treatment of HD for many years, is located near the San Francisco-Oakland

SMSA. Local diagnostic practice may well reflect the direct or indirect contribution of the pathologists at Stanford. Based on the comparisons of initial and expert diagnoses of HD, this effect may explain: a) the relatively low rates of HD among older persons in the area, and b) the particular distribution of the four histologic subtypes (high NS, and low MC, LD and especially LP (see Table 29).

(2) San Francisco-Oakland and Connecticut also differ in their degree of urbanness. However, rural rates of HD have been noted to be lower than urban rates (35), so the uniformly higher incidence in Connecticut seems unlikely to result from the more rural environment.

Thus there are several potential explanations of both the similarities and differences in rates from these two regions, but they do not completely explicate their distinctive incidence patterns.

UTAH

In males over age 14 in Utah, HD showed a substantial secular decline, unusual both in its degree and in its occurrence in young adults. This pattern seemed to reflect a pronounced deficit of NS in males in 1977-1980. Its restriction to one sex and one subtype tends to rule out data collection biases as the cause, but there are no other apparent explanations.

HAWAII, ATLANTA AND NEW ORLEANS

HD incidence was quite low in Hawaii, particularly among women in 1973-1976, and for the LP and MC subtypes.

The depressed levels and unusual age-specific distributions may be affected by four factors.

Small Numbers

This state has a small population and consequently reported few cases of HD. The rates are therefore less stable and may produce low and irregular incidence patterns.

Denominator Inaccuracy

The denominators interpolated for this study were 16.6 percent larger than extrapolated population counts projected by the state (see Table 7) and if inaccurate, could artificially yield relatively low rates. However, rates using both types of denominators were quite similar for both sexes and for males (13). A discrepancy in the female rates could be explained by the slightly difference time periods covered by the two sources. Therefore, denominator inaccuracy does not seem to explain the low incidence of HD on this island.

Racial Misclassification

The diverse racial composition of Hawaii may create problems of classification that could bias rates. Racial categories in health and census surveys may not have accurately enumerated the large complex non-Caucasian population (61 percent in 1970 *) in Hawaii. HD has a low incidence among Asians, particularly the Japanese (who make up 25 percent of all Hawaiians *). Consequently misclassification

* from Bureau of the Census files in SEEDIS

of even a few non-Caucasians as whites could lower white rates, as they are based on small numbers.

Racial Susceptibility

In addition, the racial composition of the state may control levels of incidence by affecting genetic susceptibility of a critical portion of the population. If HD has an infectious etiology, and if the low rates among the Japanese are determined by their lower susceptibility to such a causative agent, then a community with a large proportion of nonsusceptibles might support the disease agent poorly. Incidence in all groups, including whites, would then be lower than expected. This explanation has also been proposed by Kolonel to explain certain cancer incidence patterns in Hawaii (100).

SES

Although lower HD rates have been associated with poverty, the low levels of the disease in Hawaii cannot be attributed to its economic status, which is intermediate for the SEER regions. However, for Atlanta and New Orleans, low community SES may partly explain the low rates.

DETROIT AND IOWA

The relatively high rates of the MC subtype in Detroit and Iowa are of interest. With the intermediate levels of HD overall and among young adults, and the low community-average levels of education and income in these regions, such a pattern recalls a more Type II distribution of the disease.

SUMMARY OF REGIONAL INCIDENCE PATTERNS

Thus the regional SEER rates are primarily noteworthy for their homogeneity. The unexpected regional deviations seem most likely due to differences in case ascertainment and classification, particularly for the histology-specific rates, and to regional differences in the appropriateness of a linear model to estimate denominators. The low rates in Hawaii, Atlanta and New Orleans, and the particular histologic frequencies in Detroit, Iowa, San Francisco-Oakland and Connecticut, may all reflect regional economic environments. With the exception of Hawaii, these regional situations are consistent with previously established relationships of HD incidence and socioeconomic environments. They provide no new clues to environmental etiology.

The lack of pronounced geographic variation implies that the all-regions rates closely approximate incidence for almost all regions. However, 71 percent of all HD cases in this study were equally contributed by four regions--San Francisco-Oakland, Connecticut, Detroit, and Iowa. The nationwide rates thus primarily reflect the incidence in these areas, and the unusual distributions in Hawaii, Utah and the Southern regions are less exactly represented.

OTHER LIMITATIONS OF ANALYSES

There are two final warnings in interpreting findings from this study. The first is the use of many statistical tests. With pair-wise comparisons, such as the correlations between all pairs of subtype-specific rates, the p value of

the specific tests may be set, but the significance of the entire series is unknown. Also, in the many comparisons of 95 percent confidence intervals, the small but present possibility that the observed significant differences are random may be realized over the numerous tests. With HD, whose epidemiologic features are so well known, consistency with previous findings is a useful guide in differentiating real and spurious significant results.

A second aspect of this study, its geographic or ecological nature, requires mention. Associations between rates of different groups, or between rates and characteristics of groups, cannot be interpreted reliably as evidence of shared risks, because they may be caused by unrecognized confounding factors. However, again, the established epidemiology of HD provides a standard against which to interpret such relationships. Unexpected associations should be evaluated for their potential relevance and suggestions of hypotheses.

APPLICATION OF RESULTS TO ETIOLOGIC THEORIES

Both the secular trends and histologic detail of the SEER data provide potentially useful evidence for evaluating the appropriateness of the existing etiologic theories. In particular, information about histologic incidence has been considered promising for this task because of the natural divisions of HD clinically and epidemiologically along histopathologic lines. Prior to this study, however, there

have been few opportunities to apply dynamic histologic data from the United States to the question of etiology.

How do the findings from this project fit with the "two-disease" and "host-susceptibility" theories of HD cause presented in Chapter 2? Unfortunately, while the data do offer additional detail to each hypothesis, they are consistent with either.

"TWO-DISEASE" HYPOTHESIS

The "two-disease" hypothesis interprets the young and older adult incidence peaks, with their lack of geographic or secular covariation, their sex-specific differences and their differing anatomic distributions, as indicating separate illnesses, one inflammatory and the other malignant. Considerable subsequent evidence of an infectious etiology for young adult HD is felt to support this theory. Fransila and coworkers further proposed that NS, with its characteristic histologic and anatomic appearances, and occurrence at young adult ages, was a specific entity representing one of the two diseases (77).

The SEER data reveal several distinct patterns in the incidence of younger and older persons consistent with this hypothesis. These two age groups have differences in sex ratios, secular trends, and associations with community socioeconomic status, and they do not covary across regions. The attribution of overall incidence to its histologic components uncovered the most pertinent observation, namely, the occurrence of most of the young adult disease traits in

the NS subtype alone. This finding associates the characteristics of young adult disease, which are different from those in older persons, primarily to a single histologic form of HD. The fact that NS incidence is increasing in these ages in distinct contrast to rates of the other subtypes is particularly strong evidence that an independent condition is creating the first incidence peak.

However, the SEER data provide no contradiction to a major argument against this age-based theory, i.e., the occurrence of all histologic forms of HD at all ages. In every subtype except LD, there is also some elevation of incidence in young adults. Furthermore, in these populations, the incidence of NS in older men, while low, seems to be increasing with time. This apparent trend is slight and may simply represent random variation based on small numbers. While the presence of all subtypes at all ages does not disprove their separate etiologies, neither the bimodality of three subtypes, nor a rising incidence of NS in the elderly is concordant with the hypothesis that the disease of young adults is a separate condition consisting of NS.

The possible role of misclassification in the observed secular trends places a further constraint on the usefulness of these findings to the two-disease theory. If the decline in older persons or the limitation of secular increases to the NS subtype did result from changes in either the differentiation of HD and other lymphomas, or the accurate sub-

classification of the disease, then the primary evidence supporting this hypothesis is invalidated.

Thus the SEER findings can be easily interpreted to indicate that HD is two diseases, one affecting young persons and increasing, and the other a disease of older persons, disappearing in time. However, this interpretation requires that the study results on which it is based reflect true incidence changes and not improvements in diagnostic accuracy.

"HOST-SUSCEPTIBILITY" HYPOTHESIS

The alternate theory of HD causation interprets the two incidence peaks and their differences, especially in histologic composition, as expressions of a single disease whose manifestations represent differing age-specific responses to environmental conditions affecting both host and agent. Under this hypothesis, the NS subtype is felt to be the disease response of the healthier (therefore mostly younger) host, and its high incidence is explained as a reaction to an affluent environment.

The young adult, especially NS, increases and the older age declines in the SEER secular data are all consistent with this theory under the assumptions made to explain the depletion of susceptibles. If the high levels of economic well-being in the country paradoxically leave increasing proportions of young adults susceptible to an infection from which HD is a rare consequence, while either reducing the high risk environments, or depleting the population at risk,

for disease at older ages, then the observed age-, sex- and histology-specific secular trends are entirely consistent with a single etiology. While this study did not demonstrate a SES risk for young adult NS per se, it does support the likelihood of this critical association.

Thus while the data in this study allow a more detailed consideration of these primary ideas about HD etiology, they do not favor either theory. A better discrimination between these hypotheses will require more information about risk factors in all age groups, but particularly persons over 50.

ADDITIONAL DESCRIPTIVE PROJECTS

Epidemiologic research to date has advanced the understanding of HD to the point where most of the remaining issues need evaluation at the analytic level. However, there are still several descriptive questions to be asked:

1) What will be the secular trends of the disease in coming years, particularly for the four histologic types? Will they extend the trends presented here? The on-going SEER program is a valuable source of data for answering these questions, especially with the continued improvement in the quality and prevalence of histologic information in time.

2) What is the relationship between personal-level SES and community-wide economic conditions on the development of HD? Are these risk factors independent? Information

on this subject would essentially provide additional evidence on the likelihood of an infectious etiology and would help characterize the nature of both agent and disease response.

3) How do socioeconomic risk factors operate at the histologic level? Few case-control studies have considered SES and histologic type, and findings have been inconclusive. The limited availability of adequate histologic diagnosis in incidence surveys has previously prevented analysis of the role of community-level SES, except for the study of HD in Los Angeles county, where numbers were too small for age-specific consideration (52).

4) Is HD incidence among whites lower in areas where the white population is in the minority, as may be the case with the data from Hawaii? Does this phenomenon contribute to the lower incidence rates in the South? Evidence of such a mechanism would also indicate an infectious cause of the disease.

5) Are there secular trends in the age-specific misclassification of HD that explain the decrease among older persons in this study? Investigation of this issue requires the rereading of pathologic material from an adequate time period.

6) Is the recent decline of HD in older persons a cohort effect, reflecting a loss of susceptible individuals to an increase in disease at earlier ages, or, for women, to the protection of higher post-War birth rates?

Answers to these questions would help establish the validity of the findings of this study and further elucidate the behavior of HD at the community level.

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Appendix A.

MATERIALS AND METHODS

Supplemental Tables

Appendix Table A-1.
AGE-SPECIFIC PROPORTIONS OF HODGKIN'S DISEASE CASES CLASSIFIED BY THE RYE HISTOLOGIC SCHEME IN TWO TIME PERIODS; AND AGE-SPECIFIC PERCENT CHANGE IN OVERALL HODGKIN'S DISEASE RATES BETWEEN 1973-1976 AND 1977-1980

Age Group	Proportion of Cases Rye-Classified		% Change in Overall Rates
	1973-76	1977-80	
0 -14	.76	.93	.026
15-24	.70	.95	.049
25-34	.70	.95	.107
35-44	.68	.89	.028
45-54	.63	.91	-.279
55-64	.64	.88	-.232
65-74	.56	.83	-.182
75+	.59	.78	-.030
TOTAL	.66	.91	-.046

Age Group	Proportion of Cases Rye-Classified			
	1973-76		1977-80	
	MALES	FEMALES	MALES	FEMALES
0 -14	.73	.79	.95	.91
15-24	.70	.70	.95	.94
25-34	.70	.69	.94	.96
35-44	.70	.66	.88	.89
45-54	.62	.64	.93	.89
55-64	.67	.59	.86	.93
65-74	.52	.62	.86	.79
75+	.61	.58	.76	.81

Appendix B.

HODGKIN'S DISEASE INCIDENCE ACROSS ALL REGIONS COMBINED

Supplemental Tables

Appendix Table B-1.

AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES
OF HODGKIN'S DISEASE FOR ALL SURVEY REGIONS
BY SEX AND TIME PERIOD

	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44
TOTALS '73-'80	.08	.50	1.61	4.04	5.10	5.11	3.88	2.83	2.13
TOTALS '69-'71	.10	.40	1.20	3.20	5.20	5.00	2.80	3.50	2.90
TOTALS '73-'76	.10	.44	1.61	3.86	5.07	4.99	3.50	2.72	2.21
TOTALS '77-'80	.06	.57	1.61	4.21	5.14	5.23	4.22	2.94	2.06
MALES '73-'80	.06	.74	1.45	3.85	5.67	5.46	4.64	3.48	2.66
FEMALES '73-'80	.10	.25	1.78	4.22	4.54	4.76	3.12	2.18	1.61
MALES '47	.00	.70	1.70	2.50	2.30	2.80	3.30	3.30	3.70
FEMALES '47	.20	.20	1.30	.90	4.40	2.60	3.70	2.70	2.70
MALES '69-'71	.10	.60	1.20	3.40	5.70	5.80	3.90	4.60	3.80
FEMALES '69-'71	.00	.20	1.10	3.00	4.80	4.20	1.80	2.50	2.00
MALES '73-'76	.08	.62	1.41	3.72	5.86	5.50	4.35	3.44	2.88
FEMALES '73-'76	.12	.25	1.83	4.01	4.30	4.47	2.66	2.00	1.54
MALES '77-'80	.04	.87	1.50	3.98	5.49	5.43	4.90	3.53	2.43
FEMALES '77-'80	.09	.25	1.72	4.44	4.78	5.03	3.53	2.35	1.69

Appendix Table B-1., continued

	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	AAR
TOTALS '73-'80	2.55	2.89	2.99	4.11	4.30	5.98	6.25	5.39	4.24	3.00
TOTALS '69-'71	3.30	4.00	4.50	5.90	6.80	7.00	9.70	7.20	6.60	3.40
TOTALS '73-'76	2.76	3.54	3.51	4.52	4.98	6.28	7.01	5.42	2.82	3.07
TOTALS '77-'80	2.31	2.22	2.49	3.71	3.66	5.70	5.53	5.37	5.44	2.92
MALES '73-'80	3.32	3.80	4.10	5.44	5.61	7.79	8.17	8.00	5.46	3.54
FEMALES '73-'80	1.80	2.02	1.98	2.91	3.23	4.68	5.06	4.00	3.71	2.52
MALES '47	5.80	5.50	6.10	7.30	9.90	8.40	6.00	6.60	.00	3.40
FEMALES '47	2.80	3.60	4.20	4.10	3.80	3.50	4.50	2.20	4.30	2.50
MALES '69-'71	4.50	4.80	6.10	7.60	7.20	8.20	11.10	11.50	9.30	4.10
FEMALES '69-'71	2.20	3.10	3.10	4.50	6.40	6.10	8.70	4.60	5.20	2.70
MALES '73-'76	3.30	4.70	4.75	5.79	6.56	7.72	7.78	7.64	3.73	3.62
FEMALES '73-'76	2.25	2.43	2.35	3.39	3.71	5.25	6.52	4.20	2.40	2.57
MALES '77-'80	3.36	2.88	3.47	5.11	4.73	7.87	8.54	8.35	6.96	3.46
FEMALES '77-'80	1.30	1.59	1.58	2.45	2.78	4.14	3.67	3.82	4.79	2.47

Appendix Table B-2. 95% LOWER AND UPPER CONFIDENCE INTERVALS FOR FIVE-YEAR AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE, FOR FOUR TIME PERIODS, BY SEX, ALL SURVEY AREAS COMBINED

FEMALES: 1947, 1969-1971

	Age Groups							
LIMITS	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39
Lower 1947	-.18	-.21	.18	-.01	2.61	1.28	2.08	1.29
Upper 1947	.58	.61	2.42	1.81	6.19	3.92	5.32	4.12
				*				
Lower 1969-71	.00	-.10	.42	1.83	3.28	2.64	.67	1.14
Upper 1969-71	.00	.50	1.78	4.17	6.32	5.76	2.93	3.86

	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85PL
Lower 1947	1.22	1.22	1.72	1.99	1.67	1.16	.41	.09	-2.15	-4.15
Upper 1947	4.18	4.39	5.49	6.41	6.53	6.44	6.59	8.91	6.55	12.75
Lower 1969-71	.84	1.00	1.61	1.51	2.42	3.68	3.19	5.31	.93	.48
Upper 1969-71	3.16	3.40	4.59	4.70	6.58	9.12	9.01	12.09	8.27	9.92

FEMALES: 1969-71, 1977-80

	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39
Lower 1969-71	.00	-.10	.42	1.83	3.28	2.64	.67	1.14
Upper 1969-71	.00	.50	1.78	4.17	6.32	5.76	2.93	3.86
Lower 1977-80	-.03	.05	1.22	3.69	4.01	4.22	2.82	1.70
Upper 1977-80	.20	.45	2.22	5.20	5.54	5.85	4.24	2.99

	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85PL
Lower 1969-71	.84	1.00	1.61	1.51	2.42	3.68	3.19	5.31	.93	.48
Upper 1969-71	3.16	3.40	4.59	4.70	6.58	9.12	9.01	12.09	8.27	9.92
						*		*		
Lower 1977-80	1.09	.77	1.02	1.02	1.69	1.91	2.96	2.40	2.26	2.87
Upper 1977-80	2.28	1.83	2.16	2.15	3.21	3.65	5.33	4.94	5.38	6.70

* Confidence intervals of rates for two time periods do not overlap

Appendix Table B-2., continued

MALES: 1947, 1969-71

	Age Groups								
LIMITS	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	
Lower 1947	.00	-.06	.44	.96	.95	1.39	1.73	1.69	
Upper 1947	.00	1.46	2.96	4.04	3.65	4.21	4.87	4.91	
Lower 1969-71	-.12	.10	.50	2.15	3.93	3.95	2.23	2.73	
Upper 1969-71	.32	1.10	1.90	4.65	7.48	7.66	5.58	6.47	

	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85PL
Lower 1947	1.94	3.52	3.20	3.48	4.09	5.45	3.18	.11	-2.59	.00
Upper 1947	5.46	8.08	7.81	8.72	10.51	14.35	13.62	11.89	15.79	.00
Lower 1969-71	2.18	2.74	2.89	3.77	4.72	3.95	4.19	5.55	3.98	.56
Upper 1969-71	5.43	6.26	6.71	8.43	10.48	10.46	12.21	16.65	19.02	18.04

MALES: 1969-71, 1977-80

	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39
Lower 1969-71	-.12	.10	.50	2.15	3.93	3.95	2.23	2.73
Upper 1969-71	.32	1.10	1.90	4.65	7.48	7.66	5.58	6.47
Lower 1977-80	-.04	.51	1.05	3.28	4.67	4.59	4.07	2.74
Upper 1977-80	.12	1.24	1.95	4.69	6.31	6.26	5.74	4.32

	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85PL
Lower 1969-71	2.18	2.74	2.89	3.77	4.72	3.95	4.19	5.55	3.98	.56
Upper 1979-71	5.43	6.26	6.71	8.43	10.48	10.46	12.21	16.65	19.02	18.04
Lower 1977-80	1.71	2.49	2.09	2.60	3.95	3.47	5.94	6.07	5.14	3.44
Upper 1977-80	3.15	4.22	3.66	4.34	6.26	6.00	9.79	11.01	11.56	10.48

* Confidence intervals of rates for two time periods do not overlap

Appendix Table B-3.
RATIOS OF MALE AND FEMALE AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE, FOR THREE TIME PERIODS

	Ratios		
Age Group	'69-'71	'77-'80	'73-'80
0-4	1.8	1.4	.6
5-9	3.7	2.7	3.0
10-14	2.4	1.8	.8
15-19	1.1	.9	.9
20-24	1.2	1.2	1.3
25-29	1.4	1.1	1.2
30-34	2.2	1.4	1.5
35-39	1.8	1.5	1.6
40-44	1.9	1.4	1.7
45-49	2.1	2.6	1.8
50-54	1.6	1.8	1.9
55-59	2.0	2.2	2.1
60-64	1.7	2.1	1.9
65-69	1.1	1.7	1.8
70-74	1.3	1.9	1.7
75-79	1.3	2.3	1.6
80-84	2.5	2.2	2.0
85+	1.8	1.5	1.5

Appendix Table B-4.

95% LOWER AND UPPER CONFIDENCE LIMITS FOR
AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE BY SEX,
FOR EACH HISTOLOGIC SUBTYPE,
ALL SEER REGIONS COMBINED, 1977-1980

		AGE GROUPS							
		00-14	15-24	25-34	35-44	45-54	55-64	65-74	75PL
NODULAR SCLEROSIS									
FEMALES	Lower	.36	3.15	2.84	.86	.50	.36	.21	.12
	Upper	.69	4.11	3.80	1.54	1.08	.88	.74	.69
								*	*
MALES	Lower	.30	2.68	2.58	.99	.83	.80	.94	.98
	Upper	.60	3.56	3.48	1.71	1.55	1.55	2.02	2.59
LYMPHOCYTE PREDOMINANCE									
FEMALES	Lower	.00	.02	.03	-.01	-.01	.09	.02	.09
	Upper	.00	.16	.22	.16	.18	.42	.37	.62
		*	*	*	*				
MALES	Lower	.03	.22	.28	.19	.15	.10	.23	-.04
	Upper	.17	.52	.63	.57	.53	.46	.90	.60
MIXED CELLULARITY									
FEMALES	Lower	.04	.42	.45	.24	.14	.43	.96	1.23
	Upper	.20	.82	.87	.66	.51	.99	1.86	2.42
				*		*	*		
MALES	Lower	.08	.71	.93	.52	.73	1.12	1.46	1.73
	Upper	.26	1.19	1.50	1.08	1.42	1.98	2.74	3.71
LYMPHOCYTE DEPLETION									
FEMALES	Lower	-.01	.00	-.01	.00	-.01	.09	.29	.30
	Upper	.04	.00	.09	.20	.18	.42	.89	1.02
			*						
MALES	Lower	.02	.01	.04	.03	.11	.35	.62	.70
	Upper	.14	.15	.24	.27	.46	.89	1.53	2.12

* confidence intervals of male and female rates do not overlap

Appendix Table B-5.

AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES
OF HODGKIN'S DISEASE FOR ALL REGIONS
BY RYE HISTOLOGIC SUBTYPE AND TIME PERIOD,
FOR BOTH SEXES COMBINED

	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+
LP '73-'76	.08	.25	.26	.24	.25	.43	.40	.18
MC '73-'76	.11	.61	.94	.59	.74	.95	1.39	1.78
LD '73-'76	.04	.08	.09	.11	.34	.37	.59	.61
NS '73-'76	.34	2.18	1.70	.74	.64	.79	.75	.75
LP '77-'80	.05	.24	.29	.23	.21	.27	.36	.33
MC '77-'80	.14	.79	.94	.63	.70	1.11	1.71	2.14
LD '77-'80	.05	.04	.09	.13	.18	.43	.80	.92
NS '77-'80	.49	3.37	3.17	1.28	.99	.89	.91	.89

Appendix Table B-6.

AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES
OF HODGKIN'S DISEASE FOR ALL REGIONS,
BY RYE HISTOLOGIC SUBTYPE AND TIME PERIOD,
FOR MALES

	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+
LP '73-'76	.14	.54	.53	.40	.56	.91	.84	.48
MC '73-'76	.19	1.06	2.05	1.09	1.51	2.02	3.13	3.71
LD '73-'76	.06	.17	.20	.25	.65	.77	1.35	1.45
NS '73-'76	.35	2.98	2.21	1.41	1.25	1.49	1.67	1.29
LP '77-'80	.11	.39	.49	.43	.37	.32	.66	.37
MC '77-'80	.18	1.00	1.29	.91	1.16	1.80	2.44	3.58
LD '77-'80	.08	.08	.15	.17	.30	.72	1.25	1.85
NS '77-'80	.47	3.28	3.22	1.54	1.28	1.37	1.73	2.35

Appendix Table B-7.

AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES
OF HODGKIN'S DISEASE FOR ALL REGIONS
BY RYE HISTOLOGIC SUBTYPE AND TIME PERIOD,
FOR FEMALES

	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+
LP '73-'76	.08	.16	.20	.30	.24	.45	.60	.19
MC '73-'76	.11	.68	.66	.64	.84	1.00	1.94	2.60
LD '73-'76	.05	.07	.06	.08	.44	.40	.80	.77
NS '73-'76	.55	3.25	2.68	.76	.80	1.00	1.07	1.25
LP '77-'80	.00	.10	.13	.08	.09	.27	.25	.44
MC '77-'80	.13	.66	.68	.50	.37	.76	1.80	2.25
LD '77-'80	.01	.00	.04	.11	.09	.27	.75	.81
NS '77-'80	.58	3.86	3.46	1.35	.89	.67	.60	.50

Appendix Table B-8.

OBSERVED AND EXPECTED* INCIDENCE RATES OF HODGKIN'S DISEASE
BY RYE HISTOLOGIC SUBTYPE AND AGE
FOR ALL SEER REGIONS COMBINED, 1977-1980

	AGE GROUPS								
	00-14	15-24	25-34	35-44	45-54	55-64	65-74	75PL	AAR
NODULAR SCLEROSIS									
Observed	.49	3.37	3.17 **	1.28	.99	.89	.91	.89	1.54
Expected *	.43	3.10	2.55	1.00	.67	.83	.91	.96	1.33
LYMPHOCYTE PREDOMINANCE									
Observed	.05	.24	.29	.23	.21	.27	.36	.33	.20
Expected *	.10	.35	.38	.32	.26	.46	.49	.23	.28
MIXED CELLULARITY									
Observed	.14	.79	.94 **	.63	.70	1.11	1.71	2.14	.73
Expected *	.14	.87	1.42	.80	.77	1.01	1.68	2.28	.82
LYMPHOCYTE DEPLETION									
Observed	.05	.04	.09	.13	.18	.43	.80	.92	.19
Expected *	.05	.12	.13	.15	.36	.39	.71	.78	.22

* Expected under the null hypothesis of no histology-specific differences in secular change between 1973-1976 and 1977-1980

** 95 percent confidence intervals do not overlap

Appendix Table B-9.

95% LOWER AND UPPER CONFIDENCE LIMITS FOR OBSERVED AND EXPECTED AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE FOR EACH HISTOLOGIC SUBTYPE, BOTH SEXES ALL SEER REGIONS COMBINED, 1977-1980

	AGE GROUPS							
	00-14	15-24	25-34	35-44	45-54	55-64	65-74	75PL
NODULAR SCLEROSIS								
FOR FOR OBSERVED RATES								
Lower Limit	.38	3.05	2.85	1.03	.76	.66	.63	.55
Upper Limit	.60	3.70	3.50 *	1.52	1.22	1.11	1.19	1.22
FOR EXPECTED RATES								
Lower Limit	.32	2.79	2.26	.78	.48	.61	.63	.61
Upper Limit	.53	3.41	2.85	1.22	.86	1.05	1.19	1.31
LYMPHOCYTE PREDOMINANCE								
FOR OBSERVED RATES								
Lower Limit	.02	.15	.19	.12	.10	.14	.18	.13
Upper Limit	.09	.32	.39	.33	.31	.39	.53	.53
FOR EXPECTED RATES								
Lower Limit	.05	.25	.27	.20	.14	.29	.28	.06
Upper Limit	.15	.46	.50	.45	.38	.62	.69	.40
MIXED CELLULARITY								
FOR OBSERVED RATES								
Lower Limit	.08	.63	.76	.45	.50	.86	1.33	1.62
Upper Limit	.20	.94	1.12 *	.80	.89	1.36	2.10	2.66
FOR EXPECTED RATES								
Lower Limit	.08	.71	1.20	.60	.56	.77	1.30	1.75
Upper Limit	.20	1.04	1.64	.99	.97	1.25	2.06	2.82
LYMPHOCYTE DEPLETION								
FOR OBSERVED RATES								
Lower Limit	.01	.01	.03	.05	.08	.27	.54	.58
Upper Limit	.08	.08	.14	.20	.28	.59	1.06	1.26
FOR EXPECTED RATES								
Lower Limit	.02	.06	.07	.07	.22	.24	.47	.46
Upper Limit	.09	.18	.20	.24	.49	.54	.96	1.09

* Confidence intervals for observed and expected rates do not overlap

Appendix Table B-10.

AVERAGE ANNUAL AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE ESTIMATED FOR 100 PERCENT OF CASES, BY SEX, TIME PERIOD AND RYE HISTOLOGIC SUBTYPE, ALL SEER REGIONS COMBINED

	AGE GROUPS								
MALES	00-14	15-24	25-34	35-44	45-54	55-64	65-74	75PL	AAR
1973-1976									
NS	.35	2.98	2.21	1.41	1.25	1.49	1.67	1.29	1.48
LP	.14	.54	.53	.40	.56	.91	.84	.48	.46
MC	.19	1.06	2.05	1.09	1.51	2.02	3.13	3.71	1.30
LD	.06	.17	.20	.25	.65	.77	1.35	1.45	.38
1977-1980									
NS	.47	3.28	3.22	1.54	1.28	1.37	1.73	2.35	1.74
LP	.11	.39	.49	.43	.37	.32	.66	.37	.33
MC	.18	1.00	1.29	.91	1.16	1.80	2.44	3.58	1.07
LD	.08	.08	.15	.17	.30	.72	1.25	1.85	.32
FEMALES									
1973-1976									
NS	.55	3.25	2.68	.76	.80	1.00	1.07	1.25	1.43
LP	.08	.16	.20	.30	.24	.45	.60	.19	.22
MC	.11	.68	.66	.64	.84	1.00	1.94	2.60	.71
LD	.05	.07	.06	.08	.44	.40	.80	.77	.21
1977-1980									
NS	.58	3.86	3.46	1.35	.89	.67	.60	.50	1.63
LP	.00	.10	.13	.08	.09	.27	.25	.44	.11
MC	.13	.66	.68	.50	.37	.76	1.80	2.25	.60
LD	.01	.00	.04	.11	.09	.27	.75	.81	.13

Appendix Table B-11.

95% LOWER AND UPPER CONFIDENCE LIMITS FOR
AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE
ESTIMATED FOR 100 PERCENT OF CASES FOR EACH HISTOLOGIC SUBTYPE
BY SEX AND TIME PERIOD, FOR ALL SEER REGIONS

	AGE GROUPS							
MALES NS	00-14	15-24	25-34	35-44	45-54	55-65	65-74	75PL
1973-1976								
Lower Limit	.22	2.54	1.81	1.04	.89	1.06	1.08	.59
Upper Limit	.47	3.41	2.62 *	1.78	1.61	1.92	2.26	1.99
1977-1980								
Lower Limit	.32	2.83	2.76	1.15	.91	.97	1.14	1.43
Upper Limit	.62	3.73	3.69	1.92	1.65	1.77	2.31	3.27
LP	00-14	15-24	25-34	35-44	45-54	55-65	65-74	75PL
1973-1976								
Lower Limit	.06	.36	.33	.20	.32	.58	.42	.06
Upper Limit	.22	.73	.73	.60	.80	1.25 *	1.25	.91
1977-1980								
Lower Limit	.03	.23	.31	.22	.17	.13	.30	.01
Upper Limit	.18	.54	.67	.63	.56	.52	1.01	.74
MC	00-14	15-24	25-34	35-44	45-54	55-65	65-74	75PL
1973-1976								
Lower Limit	.10	.80	1.65	.76	1.12	1.52	2.32	2.53
Upper Limit	.28	1.32 *	2.44	1.41	1.91	2.52	3.93	4.90
1977-1980								
Lower Limit	.08	.75	1.00	.62	.80	1.34	1.75	2.45
Upper Limit	.27	1.25	1.59	1.21	1.51	2.26	3.13	4.72
LD	00-14	15-24	25-34	35-44	45-54	55-65	65-74	75PL
1973-1976								
Lower Limit	.01	.06	.07	.10	.39	.46	.82	.71
Upper Limit	.12	.27	.32	.41	.91	1.08	1.89	2.19
1977-1980								
Lower Limit	.02	.01	.05	.04	.12	.43	.75	1.04
Upper Limit	.14	.16	.25	.30	.49	1.01	1.74	2.67

Appendix Table B-11., continued

FEMALES

	AGE GROUPS							
NS	00-14	15-24	25-34	35-44	45-54	55-65	65-74	75PL
1973-1976								
Lower Limit	.39	2.80	2.23	.49	.52	.66	.66	.73
Upper Limit	.71	3.70	3.13	1.03	1.09	1.34	1.48	1.77
1977-1980								
Lower Limit	.40	3.37	2.97	.99	.59	.40	.30	.19
Upper Limit	.75	4.36	3.94	1.70	1.20	.94	.90	.81

LP	00-14	15-24	25-34	35-44	45-54	55-65	65-74	75PL
1973-1976								
Lower Limit	.017	.062	.077	.132	.087	.223	.293	-.010
Upper Limit	.135 *	.266	.323	.474	.395	.675	.913	.396
1977-1980								
Lower Limit	.000	.023	.035	-.006	-.006	.101	.055	.146
Upper Limit	.000	.185	.223	.174	.190	.447	.443	.728

MC	00-14	15-24	25-34	35-44	45-54	55-65	65-74	75PL
1973-1976								
Lower Limit	.04	.48	.43	.40	.56	.66	1.39	1.85
Upper Limit	.18	.89	.88	.89	1.13 (*)	1.34	2.50	3.34
1977-1980								
Lower Limit	.05	.46	.47	.28	.17	.47	1.28	1.59
Upper Limit	.22	.87	.90	.72	.57	1.05	2.32	2.91

LD	00-14	15-24	25-34	35-44	45-54	55-65	65-74	75PL
1973-1976								
Lower Limit	.00	.00	-.01	-.01	.23	.19	.45	.36
Upper Limit	.09	.14	.12	.16	.65 *	.61	1.16	1.18
1977-1980								
Lower Limit	-.01	.00	-.01	.01	-.01	.10	.41	.42
Upper Limit	.04	.00	.09	.22	.19	.45	1.09	1.21

* Confidence intervals of rates for two time periods do not overlap

Appendix C.

HODGKIN'S DISEASE INCIDENCE BY SURVEY REGION

Supplemental Tables

Appendix Table C-1.

95 PERCENT LOWER AND UPPER CONFIDENCE LIMITS
FOR AGE-ADJUSTED INCIDENCE RATES OF HODGKIN'S DISEASE
BY TIME PERIOD, SEX AND REGION

	Lower and Upper Confidence Limits		
1973-1980*	TOTALS	MALES	FEMALES
San Fran.-Oak.	2.99 - 3.49	3.37 - 4.15	2.44 - 3.08
Connecticut	3.35 - 3.84	3.82 - 4.58	2.75 - 3.39
Atlanta '75-'80	2.08 - 2.82	1.97 - 3.09	1.89 - 2.91
Hawaii	1.44 - 2.62	1.56 - 3.57	.93 - 2.40
Iowa	2.80 - 3.25	3.24 - 3.95	2.24 - 2.82
New Orleans '74-'77	2.11 - 3.34	1.97 - 3.78	1.64 - 3.24
Detroit	2.79 - 3.21	3.26 - 3.94	2.22 - 2.75
New Mexico	2.39 - 3.14	2.89 - 4.12	1.62 - 2.53
Utah	2.38 - 3.06	2.85 - 3.97	1.72 - 2.53
Seattle-P.S. '74-'80	2.37 - 2.86	2.76 - 3.53	1.84 - 2.45
1973-1976*	TOTALS	MALES	FEMALES
San Fran.-Oak	3.14 - 3.87	3.37 - 4.49	2.63 - 3.59
Connecticut	3.23 - 3.93	3.68 - 4.77	2.57 - 3.46
Atlanta '75-77	2.12 - 3.24	1.85 - 3.57	1.97 - 3.54
Hawaii	1.20 - 2.92	1.41 - 4.64	.42 - 2.08
Iowa	2.68 - 3.32	3.15 - 4.17	1.99 - 2.79
New Orleans '74-'77	2.11 - 3.34	1.97 - 3.78	1.64 - 3.24
Detroit	2.65 - 3.24	3.10 - 4.05	2.02 - 2.76
New Mexico	2.23 - 3.32	2.66 - 4.45	1.42 - 2.72
Utah	2.49 - 3.54	3.11 - 4.89	1.56 - 2.76
Seattle-P.S. '74-'76	2.32 - 3.08	2.58 - 3.77	1.78 - 2.76
1977-1980*	TOTALS	MALES	FEMALES
San Fran.-Oak	2.64 - 3.33	3.06 - 4.15	1.97 - 2.83
Connecticut	3.26 - 3.95	3.64 - 4.71	2.66 - 3.58
Atlanta '78-80	1.73 - 2.71	1.64 - 3.10	1.40 - 2.69
Hawaii	1.23 - 2.88	.95 - 3.50	.87 - 3.28
Iowa	2.71 - 3.34	3.02 - 4.01	2.24 - 3.06
Detroit	2.75 - 3.36	3.14 - 4.12	2.19 - 2.96
New Mexico	2.21 - 3.25	2.59 - 4.25	1.44 - 2.69
Utah	2.02 - 2.90	2.19 - 3.61	1.53 - 2.64
Seattle-P.S. '74-'76	2.24 - 2.87	2.63 - 3.63	1.66 - 2.44

* unless otherwise indicated

Appendix Table C-2.

AVERAGE ANNUAL INCIDENCE RATES OF HODGKIN'S DISEASE FOR BOTH SEXES, BY SEER REGION, 1973-1980

Region	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	AAR
SAN FRANCISCO-O.	.92	5.27	5.30	2.64	2.40	3.40	5.10	5.64	3.24
CONNECTICUT	.82	5.46	5.90	3.23	3.29	4.41	5.64	5.07	3.59
ATLANTA	.69	4.52	2.72	1.65	2.34	3.07	4.06	3.84	2.45
HAWAII	.33	2.71	3.34	1.64	2.85	2.88	2.01	4.11	2.03
IOWA	.82	4.15	4.53	2.37	3.18	3.40	5.76	5.66	3.02
NEW ORLEANS	.48	3.33	3.90	1.28	4.30	3.41	5.19	7.14	2.73
DETROIT	.68	4.88	4.16	2.61	2.77	3.46	4.81	6.00	3.00
NEW MEXICO	.84	4.22	3.52	2.24	2.68	3.96	4.17	4.80	2.77
UTAH	.83	3.91	3.61	2.28	2.25	3.08	5.40	6.16	2.72
SEATTLE-P.S.	.68	3.96	4.63	2.34	1.68	2.70	3.97	5.63	2.61

Appendix Table C-2., continued

AVERAGE ANNUAL INCIDENCE RATES OF HODGKIN'S DISEASE
FOR MALES, BY SEER REGION
1973-1980

Region	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	AAR
SAN FRANCISCO-O.	1.06	5.49	5.68	3.35	3.23	4.58	6.88	5.61	3.76
CONNECTICUT	.66	6.11	6.99	3.30	3.82	6.16	7.53	6.64	4.20
ATLANTA	.37	4.14	2.62	1.65	3.43	4.36	3.61	4.82	2.53
HAWAII	.32	1.51	4.07	1.21	3.60	5.56	4.15	10.62	2.56
IOWA	.71	4.02	5.04	3.27	4.66	4.63	7.24	8.05	3.59
NEW ORLEANS	.31	3.81	5.88	1.93	4.10	4.91	4.29	.00	2.87
DETROIT	.75	5.09	4.58	3.58	3.71	4.31	5.80	9.59	3.60
NEW MEXICO	1.36	4.61	4.50	2.96	3.39	5.18	4.30	8.11	3.51
UTAH	.91	4.06	4.09	2.79	3.37	4.05	7.82	10.56	3.41
SEATTLE-P.S.	.72	4.37	4.85	3.04	2.09	3.51	6.37	7.66	3.14

Appendix Table C-2., continued

AVERAGE ANNUAL INCIDENCE RATES OF HODGKIN'S DISEASE
FOR FEMALES, BY SEER REGION
1973-1980

Region	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	AAR
SAN FRANCISCO-0.	.78	5.05	4.92	1.90	1.59	2.32	3.80	5.66	2.76
CONNECTICUT	.98	4.82	4.84	3.16	2.79	2.82	4.22	4.24	3.07
ATLANTA	1.03	4.90	2.82	1.64	1.28	1.93	4.37	3.42	2.40
HAWAII	.34	4.48	2.51	2.15	2.01	.00	.00	.00	1.66
IOWA	.93	4.28	4.01	1.51	1.79	2.28	4.61	4.31	2.53
NEW ORLEANS	.65	2.86	1.86	.63	4.48	2.12	5.80	10.43	2.44
DETROIT	.59	4.68	3.73	1.66	1.88	2.68	4.05	3.92	2.49
NEW MEXICO	.30	3.83	2.55	1.55	2.00	2.83	4.05	2.64	2.08
UTAH	.76	3.76	3.12	1.77	1.17	2.17	3.41	3.36	2.12
SEATTLE-P.S.	.65	3.54	4.41	1.62	1.28	1.95	2.05	4.49	2.14

Appendix Table C-3. 95 PERCENT LOWER AND UPPER CONFIDENCE LIMITS FOR INCIDENCE RATES OF HODGKIN'S DISEASE IN CHILDREN AGES 0-9, BY SEX AND REGION

Region	Confidence Limits					
	TOTALS		MALES		FEMALES	
	Lower	Upper	Lower	Upper	Lower	Upper
San Fran.-Oak.	.16	.70	.26	1.26	-.09	.26
Connecticut	.04	.35	-.03	.41	-.03	.43
Atlanta	-.10	.29	-.19	.57	.00	.00
Hawaii	-.23	.72	-.45	1.40	.00	.00
Iowa	.11	.46	.10	.67	-.02	.37
New Orleans	-.24	.73	.00	.00	-.49	1.50
Detroit	.10	.42	.12	.68	-.04	.25
New Mexico	.05	.72	.01	1.19	-.15	.47
Utah	.17	.71	.05	.80	.06	.84
Seattle-P.S.	.08	.50	.05	.75	.-07	.40

Appendix Table C-4.
95 PERCENT LOWER AND UPPER CONFIDENCE LIMITS
FOR AGE-ADJUSTED INCIDENCE RATES OF HODGKIN'S DISEASE
BY SEX, TIME PERIOD AND REGION

	Lower and Upper Confidence Limits	
TOTALS	1973-1976 *	1977-1980*
San Fran.-Oak	3.14 - 3.87	2.64 - 3.33
Connecticut	3.23 - 3.93	3.26 - 3.95
Atlanta '75-80	2.12 - 3.24	1.73 - 2.71
Hawaii	1.20 - 2.92	1.23 - 2.88
Iowa	2.68 - 3.32	2.71 - 3.34
New Orleans '74-77	2.11 - 3.34	
Detroit	2.65 - 3.24	2.75 - 3.36
New Mexico	2.23 - 3.32	2.21 - 3.25
Utah	2.49 - 3.54	2.02 - 2.90
Seattle-P.S. '74-80	2.32 - 3.08	2.24 - 2.87
MALES	1973-1976 *	1977-1980*
San Fran.-Oak	3.37 - 4.49	3.06 - 4.15
Connecticut	3.68 - 4.77	3.64 - 4.71
Atlanta '75-80	1.85 - 3.57	1.64 - 3.10
Hawaii	1.41 - 4.64	.95 - 3.50
Iowa	3.15 - 4.17	3.02 - 4.01
New Orleans '74-77	1.97 - 3.78	
Detroit	3.10 - 4.05	3.14 - 4.12
New Mexico	2.66 - 4.45	2.59 - 4.25
Utah	3.11 - 4.89	2.19 - 3.61
Seattle-P.S. '74-80	2.58 - 3.77	2.63 - 3.63
FEMALES	1973-1976 *	1977-1980*
San Fran.-Oak	2.63 - 3.59	1.97 - 2.83
Connecticut	2.57 - 3.46	2.66 - 3.58
Atlanta '75-80	1.97 - 3.54	1.40 - 2.69
Hawaii	.42 - 2.08	.87 - 3.28
Iowa	1.99 - 2.79	2.24 - 3.06
New Orleans '74-77	1.64 - 3.24	
Detroit	2.02 - 2.76	2.19 - 2.96
New Mexico	1.42 - 2.72	1.44 - 2.69
Utah	1.56 - 2.76	1.53 - 2.64
Seattle-P.S. '74-80	1.78 - 2.76	1.66 - 2.44

* unless otherwise indicated

Appendix Table C-5.

AVERAGE ANNUAL INCIDENCE RATES OF HODGKIN'S DISEASE
FOR MALES, BY SEER REGION
1973-1976

Region	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	AAR
SAN FRANCISCO-O.	.87	5.21	5.97	3.53	3.60	4.71	9.11	6.36	3.93
CONNECTICUT	.44	6.23	5.96	3.83	4.39	6.42	9.59	4.55	4.22
ATLANTA	.24	3.92	1.93	2.55	2.67	4.52	7.55	6.70	2.71
HAWAII	.61	.00	5.59	1.24	1.78	11.98	4.64	11.75	3.02
IOWA	1.02	4.15	5.27	2.59	5.26	5.43	5.26	7.70	3.66
NEW ORLEANS	.31	3.81	5.88	1.93	4.10	4.91	4.29	.00	2.87
DETROIT	.75	5.26	4.49	3.35	4.21	4.28	4.86	9.09	3.57
NEW MEXICO	1.66	5.11	2.24	3.23	4.73	3.19	5.16	10.66	3.55
UTAH	.51	4.72	5.14	3.78	3.92	4.85	10.77	11.20	4.00
SEATTLE-P.S.	.58	3.94	4.86	2.88	2.16	6.02	6.85	4.86	3.17

Appendix Table C-5., continued

AVERAGE ANNUAL INCIDENCE RATES OF HODGKIN'S DISEASE
FOR FEMALES, BY SEER REGION
1973-1976

Region	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	AAR
SAN FRANCISCO-O.	.90	5.47	4.37	1.98	1.67	3.16	6.18	7.41	3.11
CONNECTICUT	.76	5.02	4.69	2.64	3.27	3.23	3.70	4.03	3.02
ATLANTA	1.75	4.47	3.11	1.69	1.56	3.33	5.04	2.90	2.75
HAWAII	.65	3.58	3.58	.00	.00	.00	.00	.00	1.25
IOWA	.85	3.37	2.98	1.84	2.16	2.30	5.43	5.24	2.39
NEW ORLEANS	.65	2.86	1.86	.63	4.48	2.12	5.80	10.43	2.44
DETROIT	.55	4.38	2.94	1.68	2.48	3.03	3.52	3.78	2.39
NEW MEXICO	.57	3.16	2.18	1.34	2.51	3.57	5.28	.00	2.07
UTAH	.79	3.46	3.47	1.24	1.91	2.86	3.24	2.42	2.16
SEATTLE-P.S.	.73	3.51	4.82	1.48	1.61	2.08	2.11	5.02	2.27

Appendix Table C-5., continued

AVERAGE ANNUAL INCIDENCE RATES OF HODGKIN'S DISEASE FOR MALES, BY SEER REGION 1977-1980

Region	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	AAR
SAN FRANCISCO-O.	1.30	5.79	5.41	3.17	2.82	4.45	4.72	4.88	3.61
CONNECTICUT	.93	5.99	7.93	2.76	3.22	5.91	5.65	8.63	4.17
ATLANTA	.51	4.34	3.25	.80	4.17	4.20	.00	3.09	2.37
HAWAII	.00	3.06	2.76	1.17	5.48	.00	3.74	9.69	2.22
IOWA	.37	3.91	4.84	3.94	4.03	3.84	9.18	8.40	3.52
DETROIT	.76	4.91	4.67	3.84	3.16	4.33	6.75	10.09	3.63
NEW MEXICO	1.02	4.12	6.46	2.69	2.07	7.01	3.56	5.80	3.42
UTAH	1.27	3.47	3.23	1.90	2.83	3.33	5.20	10.00	2.90
SEATTLE-P.S.	.83	4.68	4.85	3.15	2.04	1.76	6.05	9.65	3.13

Appendix Table C-5., continued

AVERAGE ANNUAL INCIDENCE RATES OF HODGKIN'S DISEASE
FOR FEMALES, BY SEER REGION
1977-1980

Region	0-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	AAR
SAN FRANCISCO-O.	.62	4.60	5.42	1.82	1.50	1.48	1.49	4.05	2.40
CONNECTICUT	1.24	4.62	4.97	3.68	2.28	2.43	4.71	4.42	3.12
ATLANTA	.27	5.32	2.55	1.59	1.02	.62	3.74	3.89	2.04
HAWAII	.00	5.39	1.57	4.20	4.04	.00	.00	.00	2.07
IOWA	1.01	5.15	4.92	1.17	1.39	2.26	3.80	3.45	2.65
DETROIT	.65	4.97	4.48	1.65	1.22	2.33	4.57	4.06	2.58
NEW MEXICO	.00	4.49	2.89	1.75	1.49	2.15	3.01	4.87	2.07
UTAH	.73	4.04	2.84	2.26	.46	1.55	3.57	4.17	2.09
SEATTLE-P.S.	.58	3.56	4.15	1.72	1.02	1.85	2.01	4.14	2.05

Appendix Table C-6. 95% LOWER AND UPPER CONFIDENCE INTERVALS FOR AGE-SPECIFIC HISTOLOGY RATES BY STATE, AND TIME PERIOD

BOTH SEXES

		00-14	15-24	25-34	35-44	45-54	55-64	65-74	75PL
SAN FRANCISCO-OAKLAND									
1973-1976	Lower	.48	4.22	4.07	1.84	1.70	2.69	5.37	4.61
	Upper	1.29	6.45	6.29	3.70	3.54	5.11	9.48	9.49
1977-1980	Lower	.49	4.06	4.33	1.63	1.27	1.86	1.61	2.48
	Upper	1.44	6.34	6.50	3.39	3.03	3.94	4.12	6.18
CONNECTICUT									
1973-1976	Lower	.30	4.56	4.18	2.26	2.78	3.51	4.44	2.41
	Upper	.89	6.69	6.46	4.19	4.85	5.99	8.00	6.02
1977-1980	Lower	.66	4.29	5.23	2.27	1.83	2.96	3.57	3.82
	Upper	1.50	6.33	7.63	4.20	3.64	5.20	6.66	7.87
ATLANTA									
1975-1977	Lower	.30	2.59	1.29	.81	.65	1.59	2.30	.08
	Upper	1.65	5.82	3.77	3.43	3.56	6.19	9.79	8.01
1978-1980	Lower	-.05	3.13	1.62	.24	.98	.60	.05	.07
	Upper	.83	6.53	4.16	2.16	4.17	4.02	4.42	7.23
HAWAII									
1973-1976	Lower	-.2	.0	1.9	-.6	-.9	.8	-2.1	-4.4
	Upper	1.5	2.8	7.4	2.0	2.8	11.6	6.6	13.6
1977-1980	Lower	.0	1.6	.4	.1	.6	.0	-1.8	-3.6
	Upper	.0	6.4	4.0	5.1	9.0	.0	5.4	11.0
IOWA									
1973-1976	Lower	.58	2.91	3.09	1.36	2.57	2.63	3.77	4.21
	Upper	1.29	4.61	5.16	3.06	4.77	4.95	6.94	8.07
1977-1980	Lower	.37	3.62	3.82	1.63	1.72	1.98	4.49	3.48
	Upper	1.00	5.44	5.94	3.45	3.64	4.03	7.84	6.92

Appendix Table C-6., continued

MICHIGAN									
1973-1976	Lower	.38	3.90	2.83	1.70	2.42	2.58	2.66	3.60
	Upper	.92	5.72	4.59	3.29	4.22	4.68	5.55	7.96
1977-1980	Lower	.40	4.02	3.63	1.87	1.40	2.30	3.84	4.03
	Upper	1.02	5.86	5.52	3.58	2.93	4.26	7.17	8.40
NEW MEXICO									
1973-1976	Lower	.49	2.63	.96	.86	1.71	1.39	2.14	.53
	Upper	1.77	5.65	3.45	3.68	5.48	5.39	8.31	8.08
1977-1980	Lower	.07	2.79	2.97	.84	.46	2.29	1.00	1.36
	Upper	.98	5.82	6.37	3.59	3.09	6.68	5.52	9.10
UTAH									
1973-1976	Lower	.2	2.8	2.8	1.1	1.3	1.7	3.3	1.8
	Upper	1.0	5.3	5.8	3.9	4.5	5.9	10.0	9.9
1977-1980	Lower	.5	2.6	1.9	.9	.4	.8	1.8	2.4
	Upper	1.5	4.9	4.2	3.3	2.8	4.0	6.8	10.4
SEATTLE-PUGET SOUND									
1974-1976	Lower	.27	2.67	3.56	1.18	.90	2.45	2.27	2.36
	Upper	1.04	4.78	6.12	3.20	2.87	5.52	6.16	7.56
1977-1980	Lower	.35	3.19	3.51	1.56	.76	.95	2.29	3.70
	Upper	1.07	5.08	5.50	3.34	2.31	2.67	5.33	8.47

Appendix Table C-6., continued

MALES

		00-14	15-24	25-34	35-44	45-54	55-64	65-74	75PL
SAN FRANCISCO-OAKLAND									
1973-1976	Lower	.3	3.7	4.3	2.1	2.1	2.8	5.6	2.4
	Upper	1.4	6.8	7.6	5.0	5.1	6.6	12.6	10.3
1977-1980	Lower	.5	4.1	3.9	1.8	1.4	2.6	2.2	1.5
	Upper	2.1	7.5	6.9	4.6	4.2	6.3	7.2	8.3
CONNECTICUT									
1973-1976	Lower	.1	4.6	4.2	2.3	2.8	4.3	6.2	1.4
	Upper	.8	7.8	7.7	5.3	6.0	8.5	13.0	7.7
1977-1980	Lower	.4	4.5	6.0	1.5	1.8	4.0	3.2	4.4
	Upper	1.5	7.5	9.8	4.0	4.6	7.9	8.1	12.9
ATLANTA									
1975-1977	Lower	-.2	1.7	.4	.5	.3	.9	.9	-2.6
	Upper	.7	6.1	3.5	4.6	5.0	8.1	14.2	16.0
1977-1980	Lower	-.2	2.1	1.3	-.3	1.3	.8	.0	-3.0
	Upper	1.2	6.6	5.2	1.9	7.1	7.6	.0	9.1
HAWAII									
1973-1976	Lower	-.6	.0	1.4	-1.2	-1.7	1.5	-4.5	-11.3
	Upper	1.8	.0	9.7	3.7	5.3	22.5	13.7	34.8
1977-1980	Lower	.0	.4	.1	-1.1	-.7	.0	-3.6	-9.3
	Upper	.0	5.7	5.5	3.5	11.7	.0	11.1	28.7
IOWA									
1973-1976	Lower	.5	2.9	3.6	1.3	3.4	3.4	2.9	4.1
	Upper	1.5	5.4	6.9	3.9	7.1	7.4	7.6	11.3
1977-1980	Lower	.0	2.7	3.4	2.3	2.3	2.2	6.1	4.7
	Upper	.7	5.1	6.3	5.6	5.7	5.5	12.3	12.1
DETROIT									
1973-1976	Lower	.3	3.9	3.1	2.0	2.7	2.6	2.5	4.6
	Upper	1.2	6.6	5.9	4.7	5.7	5.9	7.2	13.5
1977-1980	Lower	.3	3.6	3.3	2.4	1.8	2.7	3.9	5.4
	Upper	1.2	6.2	6.0	5.3	4.5	6.0	9.6	14.8

Appendix Table C-6., continued

NEW MEXICO									
1973-1976	Lower	.6	2.8	.4	.8	1.6	.4	.6	1.3
	Upper	2.7	7.5	4.0	5.6	7.8	6.0	9.7	20.0
1977-1980	Lower	.1	2.0	3.6	.5	.0	3.0	.1	-.8
	Upper	1.9	6.2	9.3	4.8	4.1	11.0	7.1	12.4
UTAH									
1973-1976	Lower	.0	2.7	2.8	1.3	1.2	1.5	4.4	2.2
	Upper	1.0	6.7	7.5	6.2	6.6	8.2	17.1	20.2
1977-1980	Lower	.5	1.9	1.5	.2	.6	.7	1.0	2.0
	Upper	2.0	5.1	4.9	3.6	5.1	6.0	9.4	18.0
SEATTLE-PUGET SOUND									
1973-1976	Lower	.1	2.4	3.1	1.2	.7	3.3	3.1	.6
	Upper	1.1	5.5	6.7	4.5	3.7	8.7 *	10.6	9.1
1977-1980	Lower	.3	3.3	3.4	1.7	.8	.5	3.2	4.6
	Upper	1.4	6.1	6.3	4.6	3.3	3.0	8.9	14.7

Appendix Table C-6., continued

FEMALES

		00-14	15-24	25-34	35-44	45-54	55-64	65-74	75PL
SAN FRANCISCO-OAKLAND									
1973-1976	Lower	.3	3.9	2.9	.9	.6	1.7	3.7	4.3
	Upper	1.5	7.1	5.8	3.1	2.7	4.7	8.7 *	10.5
1977-1980	Lower	.1	3.1	3.9	.7	.5	.5	.3	1.8
	Upper	1.2	6.1	7.0	2.9	2.5	2.5	2.7	6.2
CONNECTICUT									
1973-1976	Lower	.3	3.6	3.2	1.4	1.9	1.8	1.9	1.8
	Upper	1.2	6.4	6.2	3.9	4.6	4.7	5.5	6.2
1977-1980	Lower	.6	3.3	3.5	2.2	1.1	1.2	2.7	2.3
	Upper	1.9	6.0	6.5	5.1	3.4	3.6	6.7	6.6
ATLANTA									
1975-1977	Lower	.5	2.1	1.2	.0	-.2	.4	.6	-1.1
	Upper	3.1	6.8	5.0	3.3	3.3	6.3	9.5	6.9
1977-1980	Lower	-.3	2.8	.9	.0	-.4	-.6	.1	-.5
	Upper	.8	7.8	4.2	3.2	2.4	1.8	7.4	8.3
HAWAII									
1973-1976	Lower	-.6	.1	.1	.0	.0	.0	.0	.0
	Upper	1.9	7.1	7.1	.0	.0	.0	.0	.0
1977-1980	Lower	.0	1.1	-.6	-.6	-1.6	.0	.0	.0
	Upper	.0	9.7	3.8	9.0	9.6	.0	.0	.0
IOWA									
1973-1976	Lower	.4	2.2	1.7	.8	1.0	1.1	3.3	3.0
	Upper	1.3	4.5	4.2	2.9	3.3	3.6	7.6	7.5
1977-1980	Lower	.5	3.8	3.4	.3	.4	1.0	2.1	1.7
	Upper	1.6	6.5	6.4	2.0	2.4	3.5	5.6	5.2

Appendix Table C-6., continued

DETROIT									
1973-1976	Lower	.2	3.2	1.8	.8	1.4	1.7	1.7	1.6
	Upper	.9	5.6	4.0	2.6	3.6	4.4	5.3	6.0
1977-1980	Lower	.2	3.7	3.2	.7	.4	1.2	2.6	1.8
	Upper	1.1	6.3	5.8	2.6	2.0	3.5	6.6	6.3
NEW MEXICO									
1973-1976	Lower	-.1	1.3	.4	-.2	.3	.7	1.1	.0
	Upper	1.2	5.0	3.9	2.9	4.7	6.4	9.5	.0
1977-1980	Lower	.0	2.3	1.0	.0	-.2	.0	.1	.1
	Upper	.0	7.7	4.8	3.5	3.2	4.3	6.0	9.6
UTAH									
1973-1976	Lower	.2	1.8	1.5	-.2	.0	.4	.1	-.9
	Upper	1.4	5.1	5.4	2.7	3.8	5.4	6.4	5.8
1977-1980	Lower	.2	2.4	1.2	.5	-.4	-.2	.4	.1
	Upper	1.3	5.7	4.5	4.1	1.4	3.3	6.7	8.3
SEATTLE-PUGET SOUND									
1973-1976	Lower	.2	2.0	3.0	.3	.3	.5	.3	1.7
	Upper	1.3	5.0	6.6	2.7	2.9	3.6	4.0	8.3
1977-1980	Lower	.1	2.3	2.8	.7	.1	.6	.5	1.7
	Upper	1.0	4.8	5.5	2.8	1.9	3.1	3.5	6.6

* Confidence intervals for two time periods do not overlap

Appendix Table C-7. 95% LOWER AND UPPER CONFIDENCE INTERVALS FOR AGE-ADJUSTED RATES FOR FOUR REGIONS, BY TIME PERIOD AND SEX

Region		Confidence Interval LOWER LIMIT		UPPER LIMIT
SAN FRANCISCO-OAKLAND				
Totals	1969-1971	3.59	-	4.48
	1973-1976	3.14	-	3.87
	1977-1980	2.64	-	3.33
Males	1969-1971	4.25	-	5.70
	1973-1976	3.37	-	4.49
	1977-1980	3.06	-	4.15
Females	1969-1971	2.67	-	3.78
	1973-1976	2.63	-	3.59
	1977-1980	1.97	-	2.83
ATLANTA				
Totals	1969-1971	2.32	-	3.60
	1975-1977	2.12	-	3.24
	1978-1980	1.73	-	2.71
Males	1969-1971	2.45	-	4.55
	1975-1977	1.85	-	3.57
	1978-1980	1.64	-	3.10
Females	1969-1971	1.68	-	3.26
	1975-1977	1.97	-	3.54
	1978-1980	1.40	-	2.69
IOWA				
Totals	1969-1971	2.86	-	3.64
	1973-1976	2.68	-	3.32
	1977-1980	2.71	-	3.34
Males	1969-1971	3.35	-	4.61
	1973-1976	3.15	-	4.17
	1977-1980	3.02	-	4.01
Females	1969-1971	2.09	-	3.06
	1973-1976	1.99	-	2.79
	1977-1980	2.24	-	3.06

Appendix Table C-7., continued

DETROIT		LOWER LIMIT		UPPER LIMIT
Totals	1969-1971	2.77	-	3.48
	1973-1976	2.65	-	3.24
	1977-1980	2.75	-	3.36
Males	1969-1971	3.06	-	4.18
	1973-1976	3.10	-	4.05
	1977-1980	3.14	-	4.12
Females	1969-1971	2.24	-	3.15
	1973-1976	2.02	-	2.76
	1977-1980	2.19	-	2.96

Appendix Table C-8. 95% LOWER AND UPPER CONFIDENCE INTERVALS FOR AGE-SPECIFIC INCIDENCE RATES OF HODGKIN'S DISEASE BY REGION, SEX AND TIME PERIOD

Region		AGE GROUP							
SAN FRANCISCO-OAKLAND									
BOTH SEXES		00-14	15-24	25-34	35-44	45-54	55-64	65-74	75PL
1969-1971	Lower	.5	4.7	4.2	2.0	2.1	3.6	5.4	5.9
	Upper	1.3	7.4	6.9	4.3	4.3	6.9	10.4	12.6
1977-1980	Lower	.5	4.1	4.3	1.6	1.3	1.9	1.6	2.5
	Upper	1.4	6.3	6.5	3.4	3.0	3.9	4.1	6.2
MALES									
1969-1971	Lower	.3	4.0	5.0	2.8	2.7	4.7	4.7	7.3
	Upper	1.4	7.7	9.4	6.8	6.5	10.3	12.9	21.3
1977-1980	Lower	.5	4.1	3.9	1.8	1.4	2.6	2.2	1.5
	Upper	2.1	7.5	6.9	4.6	4.2	6.3	7.2	8.3
FEMALES									
1969-1971	Lower	.3	4.4	2.2	.4	.7	1.5	4.0	3.0
	Upper	1.6	8.1	5.5	2.7	3.2	5.0	10.3	10.0
1977-1980	Lower	.1	3.1	3.9	.7	.5	.5	.3	1.8
	Upper	1.2	6.1	7.0	2.9	2.5	2.5	2.7	6.2
ATLANTA									
BOTH SEXES		00-14	15-24	25-34	35-44	45-54	55-64	65-74	75PL
1969-1971	Lower	.0	2.0	2.1	.3	1.4	1.0	4.9	1.6
	Upper	.9	5.0	5.4	2.6	5.2	5.6	15.6	14.1
1978-1980	Lower	-.1	3.1	1.6	.2	1.0	.6	.0	.1
	Upper	.8	6.5	4.2	2.2	4.2	4.0	4.4	7.2

Appendix Table C-8., continued

MALES

1969-1971	Lower	.0	1.7	2.6	-.2	.7	.6	.1	-1.6
	Upper	1.7	6.5	8.4	3.1	6.0	8.4	14.7	26.1
1978-1980	Lower	-.2	2.1	1.3	-.3	1.3	.8	.0	-3.0
	Upper	1.2	6.6	5.2	1.9	7.1	7.6	.0	9.1

FEMALES

1969-1971	Lower	.0	1.0	.2	-.2	.7	-.3	4.6	-.8
	Upper	.0	5.0	3.7	3.1	5.9	5.0	19.5	12.3
1978-1980	Lower	-.3	2.8	.9	.0	-.4	-.6	.1	-.5
	Upper	.8	7.8	4.2	3.2	2.4	1.8	7.4	8.3

IOWA

BOTH SEXES		00-14	15-24	25-34	35-44	45-54	55-64	65-74	75PL
1969-1971	Lower	.2	2.9	2.6	2.1	2.2	3.7	4.1	6.8
	Upper	.7	4.9	5.1	4.5	4.5	6.9	8.0	12.6
1977-1980	Lower	.4	3.6	3.8	1.6	1.7	2.0	4.5	3.5
	Upper	1.0	5.4	5.9	3.4	3.6	4.0	7.8	6.9

MALES

1969-1971	Lower	.3	2.9	1.9	2.2	2.0	5.5	4.6	5.2
	Upper	1.2	6.1	5.5	6.1	5.6	11.3	11.4	14.6
1977-1980	Lower	.0	2.7	3.4	2.3	2.3	2.2	6.1	4.7
	Upper	.7	5.1	6.3	5.6	5.7	5.5	12.3	12.1

FEMALES

1969-1971	Lower	-.1	2.0	2.2	1.0	1.4	.9	2.2	5.9
	Upper	.3	4.7	5.9	3.9	4.5	3.9	6.8	13.3
1977-1980	Lower	.5	3.8	3.4	.3	.4	1.0	2.0	1.7
	Upper	1.6	6.5	6.4	2.0	2.4	3.5	5.6	5.2

Appendix Table C-8., continued

DETROIT

		00-14	15-24	25-34	35-44	45-54	55-64	65-74	75PL
BOTH SEXES									
1969-1971	Lower	.3	3.1	2.3	3.1	2.4	2.4	4.5	3.7
	Upper	.8	5.1	4.4	5.4	4.4	4.9	8.7	9.3
1977-1980	Lower	.4	4.0	3.6	1.9	1.4	2.3	3.8	4.0
	Upper	1.0	5.9	5.5	3.6	2.9	4.3	7.2	8.4
MALES									
1969-1971	Lower	.1	2.9	2.7	3.2	2.4	2.4	3.6	4.6
	Upper	.8	5.7	6.0	6.8	5.5	6.3	10.0	15.4
1977-1980	Lower	.3	3.6	3.3	2.4	1.8	2.7	3.9	5.4
	Upper	1.2	6.2	6.0	5.3	4.5	6.0	9.6	14.8
FEMALES									
1969-1971	Lower	.2	2.6	1.2	2.1	1.6	1.4	3.6	1.3
	Upper	1.0	5.2	3.6	5.0	4.1	4.5	9.3	7.0
1977-1980	Lower	.2	3.7	3.2	.7	.4	1.2	2.6	1.9
	Upper	1.1	6.3	5.8	2.6	2.0	3.5	6.6	6.3

Appendix Table C-9. 95% LOWER AND UPPER CONFIDENCE INTERVALS FOR AGE-ADJUSTED INCIDENCE RATES OF HODGKIN'S DISEASE BY SEX, HISTOLOGIC SUBTYPE AND REGION, 1977-1980

BOTH SEXES

		LOWER LIMIT		UPPER LIMIT
NS:	San Francisco-Oakland	1.70	-	2.27
	Connecticut	1.71	-	2.23
	Atlanta	.95	-	1.69
	Hawaii	.77	-	2.08
	Iowa	1.20	-	1.64
	New Orleans	.76	-	1.58
	Detroit	1.18	-	1.59
	New Mexico	1.05	-	1.79
	Utah	.97	-	1.60
	Seattle-Puget Sound	1.10	-	1.55
LP:	San Francisco-Oakland	.07	-	.21
	Connecticut	.13	-	.31
	Atlanta	.07	-	.40
	Hawaii	-.11	-	.33
	Iowa	.13	-	.30
	New Orleans	.13	-	.56
	Detroit	.13	-	.29
	New Mexico	.03	-	.27
	Utah	.07	-	.34
	Seattle-Puget Sound	.12	-	.31
MC:	San Francisco-Oakland	.32	-	.60
	Connecticut	.61	-	.93
	Atlanta	.25	-	.70
	Hawaii	-.03	-	.71
	Iowa	.71	-	1.05
	New Orleans	.43	-	1.08
	Detroit	.78	-	1.12
	New Mexico	.37	-	.89
	Utah	.32	-	.71
	Seattle-Puget Sound	.60	-	.95
LD:	San Francisco-Oakland	.07	-	.22
	Connecticut	.21	-	.40
	Atlanta	-.01	-	.16
	Hawaii	-.09	-	.45
	Iowa	.15	-	.33
	New Orleans	.00	-	.29
	Detroit	.11	-	.26
	New Mexico	.06	-	.34
	Utah	.05	-	.29
	Seattle-Puget Sound	.02	-	.13

Appendix Table C-9., continued

MALES

		LOWER LIMIT		UPPER LIMIT
NS:	San Francisco-Oakland	1.69	-	2.54
	Connecticut	1.68	-	2.43
	Atlanta	.61	-	1.55
	Hawaii	.48	-	2.10
	Iowa	1.02	-	1.62
	New Orleans	.59	-	1.74
	Detroit	1.14	-	1.75
	New Mexico	1.12	-	2.25
	Utah	.79	-	1.69
	Seattle-Puget Sound	1.21	-	1.89
LP:	San Francisco-Oakland	.08	-	.32
	Connecticut	.21	-	.52
	Atlanta	.09	-	.70
	Hawaii	-.22	-	.68
	Iowa	.18	-	.48
	New Orleans	.04	-	.64
	Detroit	.16	-	.44
	New Mexico	-.02	-	.33
	Utah	.06	-	.49
	Seattle-Puget Sound	.17	-	.51
MC:	San Francisco-Oakland	.48	-	.98
	Connecticut	.63	-	1.12
	Atlanta	.22	-	.91
	Hawaii	-.35	-	1.08
	Iowa	.90	-	1.48
	New Orleans	.34	-	1.30
	Detroit	.96	-	1.52
	New Mexico	.38	-	1.22
	Utah	.40	-	1.11
	Seattle-Puget Sound	.69	-	1.26
LD:	San Francisco-Oakland	.10	-	.37
	Connecticut	.26	-	.60
	Atlanta	-.03	-	.33
	Hawaii	-.17	-	.85
	Iowa	.20	-	.53
	New Orleans	-.07	-	.23
	Detroit	.11	-	.37
	New Mexico	.05	-	.59
	Utah	.04	-	.48
	Seattle-Puget Sound	.00	-	.20

Appendix Table C-9., continued

FEMALES

		LOWER LIMIT		UPPER LIMIT
NS:	San Francisco-Oakland	1.49	-	2.26
	Connecticut	1.54	-	2.27
	Atlanta	.98	-	2.10
	Hawaii	.54	-	2.66
	Iowa	1.24	-	1.89
	New Orleans	.61	-	1.74
	Detroit	1.08	-	1.65
	New Mexico	.70	-	1.64
	Utah	.89	-	1.77
	Seattle-Puget Sound	.84	-	1.42
LP:	San Francisco-Oakland	.01	-	.17
	Connecticut	.01	-	.17
	Atlanta	-.05	-	.14
	Hawaii	.0	-	.0
	Iowa	.03	-	.20
	New Orleans	-.01	-	.64
	Detroit	.04	-	.20
	New Mexico	-.02	-	.29
	Utah	-.02	-	.30
	Seattle-Puget Sound	.01	-	.16
MC:	San Francisco-Oakland	.08	-	.33
	Connecticut	.47	-	.87
	Atlanta	.08	-	.63
	Hawaii	-.10	-	1.04
	Iowa	.42	-	.80
	New Orleans	.11	-	1.09
	Detroit	.49	-	.88
	New Mexico	.15	-	.74
	Utah	.10	-	.51
	Seattle-Puget Sound	.39	-	.82
LD:	San Francisco-Oakland	.00	-	.13
	Connecticut	.09	-	.29
	Atlanta	.0	-	.0
	Hawaii	.0	-	.0
	Iowa	.05	-	.20
	New Orleans	-.03	-	.44
	Detroit	.06	-	.26
	New Mexico	-.04	-	.22
	Utah	-.03	-	.20
	Seattle-Puget Sound	-.01	-	.12

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