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AN EPIDEMIOLOGIC STUDY OF LEUKEMIA IN OKLAHOMA, 1961-1965

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To Sharon

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

Figure | Page

AN EPIDEMIOLOGIC STUDY OF LEUKEMIA IN OKLAHOMA, 1961-1965

CHAPTER I

INTRODUCTION AND REVIEW OF LITERATURE

Leukemia as a definitive disease has a history of little more than one hundred years. It was first described by Velpeau (126) in 1827 when he described the blood of a deceased patient as being thick, "like gruel . . . resembling in consistency and color the yeast of red wine. . . . One might have asked if it were not rather laudable pus, mixed with blackish coloring matter, than blood." It was the appearance of the blood which first attracted the attention of early students of the disease. Barth (10) examined the blood microscopically. Donne (2) also examined leukemic blood by microscope and described "mucous globules" which could not be distinguished from pus corpuscles.

Bennett (13) and Virchow (129) recognized leukemia as a definite disease entity in simultaneous, independent publications in 1845. In 1852 Bennett published a monograph on "Leucocythaemia" in which he described thirty-seven

cases, seventeen of which had been diagnosed during life by means of blood examinations. Virchow during that time published a series of studies on the disease, introducing the term "leukemia."

In the century that has elapsed since the studies of Bennett and Virchow, progress has been made in the diagnosis, classification, and descriptive pathology of leukemia. Advances in therapy, including antibiotics, blood products, and chemotherapeutic agents, have resulted in prolonging life from weeks or months to several years in many leukemia patients. But the causes of leukemia remain obscure. Certain relatively consistent relationships have been established between leukemia and a number of proposed etiologic agents (51). It is well documented that exposure to ionizing radiation is associated with an increased risk of developing certain types of leukemia (14, 19, 24, 28, 56). Fairly convincing evidence has implicated benzene in human leukemia (32). Several other chemical agents, including some drugs, are suspect (12, 18, 34). The role of viruses in the development of leukemia in certain strains of laboratory rodents is well documented (3). Viruses are known to be implicated in many hyperplastic lesions in laboratory animals and in humans (3, 19). Evidence exists that suggests a virus may play a role in the development of human leukemia (95). Unusually large numbers of cases of leukemia have been noted to occur within

limited geographic areas in short periods of time, suggesting the possibility of an infectious agent (65, 85). Viral particles have been observed in electron micrographs of tissues from patients with leukemia and related malignancies (67). The geographic distribution of a similar malignant reticulosis, Burkitt's Lymphoma in Africa, suggests a possible vector dependent on specific climatic conditions and therefore suggests an infectious agent (20). The finding of a herpes-type virus in tissue homogenates and in serum of patients with Burkitt's Lymphoma further suggests a viral etiologic agent (38, 67). Videbaek (127), Heath (63), Anderson (7) and others have noted unusual familial aggregations of leukemia wherein a number of cases have occurred greatly exceeding the expected incidence and strongly suggesting a genetic mechanism or predisposition to the disease. Attempts to demonstrate excessive familiality in instances outside these unusually affected families have met with little success. Videbaek (5) noted an excessive incidence of leukemia, other cancers, and pernicious anemia in relatives of leukemic patients. However Videbaek's controls have been severely criticized, and most investigators have been unable to confirm his findings. Leukemia has been observed in well documented association with Down's Syndrome or Mongolism (94) and with other demonstrable chromosome abnormalities (87, 97). Sandberg, et al. (109, 110, 111) have consistently observed chromosome

abnormalities in peripheral blood and bone marrow preparations of patients with leukemia. Opinions differ as to whether this aneuploidy predisposes to, or is a product of, the leukemic process. The role of heredity in the development of human leukemia is still unclear.

The present paucity of knowledge concerning the etiology of leukemia is similar to that of 1938 which prompted Forkner (43) to observe that

> . . . almost nothing is known of the causes, either immediate or remote, of leukemia. In a minority of cases some disease or incident can be found in the patient's life to which the leukemia is sequential in time and to which, in some degree, it may be related. In the majority of cases no such antecedent is demonstrable. Those etiologic conditions which can be traced or suspected in some cases stand in a position with relation to the disease which is too uncertain to allow them to be considered as exciting or predisposing causes.

Of all basic and clinical research being concentrated in this area at the present time, carefully designed and well executed epidemiologic studies hold a place of prime importance in describing potential etiologic relationships and directing other research efforts into more fruitful areas of endeavor.

Mortality rates for leukemia over the past twenty years in the United States indicate consistent increases in the occurrence of this disease (52). Some of this increase has been attributed to improved methods of diagnosis, advances made in the scope of disease certification, and improved therapeutic handling and resultant survival of

cases beyond the preleukemic phase with its tendency to infections and bleeding. However, the magnitude of the increase in death rates indicates more than improved detection and registering of cases, and is profoundly suggestive of increased exposure of the population to leukemogenic factors (44). In the United States the death rate from leukemia among males increased from 4.4 per 100,000 population in 1940 to 7.5 per 100,000 in 1960, and among women, from 3.1 in 1940 to 4.9 in 1960. Although all age groups have experienced consistently rising rates, the increase has been especially high in middle age and older individuals. For example, in men over fifty years of age, the death rate increased from 10.9 per 100,000 in 1940 to 22.6 per 100,000 in 1960, and for women over fifty years of age, from 7.4 per 100,000 in 1940 to 13.9 in 1960. After 1940, mortality statistics in the U.S. revealed the beginning of an age peak at 3 and 4 years that increased with time in U.S. whites, but which did not appear in U.S. non-whites. More recently, however, a peak has begun to appear at the age of 4 years in non-whites. This has been interpreted as an indication of "delayed exposure" of U.S. non-whites to some environmental leukemogen (26, 44, 52).

Often thought of as primarily a child's disease, leukemia kills more adults than children. White persons have a 50% greater risk of dying of leukemia than do negroes, and the disease is markedly more prevalent among

families of higher income. The Jewish people have a relatively low incidence of most forms of cancer but have an inordinately high incidence of leukemia (44, 54).

Recent observations by Fraumeni and Miller (44) concerning mortality statistics have, for the first time, shown a downturn in leukemia death rates in all ages from 1 to 74 years among the U.S. white population, but not among the U.S. non-white population, nor in England. While the decline has affected all ages between 1 and 74 years, it is most pronounced among children 1-4 years of age. It is yet too soon to say whether this downturn indicates a leveling off of the increases seen in leukemia mortality rates over the past several decades, or whether it is merely a random fluctuation in mortality patterns. In spite of the recently reported downturns in leukemia death rates, deaths from leukemia are still increasing each year among all age groups and races, and in both sexes (26, 44).

In marked contrast to the generally uniform distribution of leukemia cases in time and space, curious "clusters" of cases have been observed in which an unusually large number of leukemias occur within a small geographic area during a short period of time (85). Recently reports have come from Cheyenne, Wyoming; Niles, Illinois; Bergen County, New Jersey, and elsewhere of incidence levels of leukemia far above the expected (64, 65, 66). These spatial and temporal aggregations provide the analytic

epidemiologist a unique opportunity to study the disease within the environment which may have played a role in its genesis. Many workers feel that leukemia clusters indicate a high level of one or more leukemogenic factors in the environment, perhaps an infectious agent, and hence provide an unusual opportunity to identify and study these factors. The "cluster phenomenon" is given particular attention by proponents of the hypothesis that a viral or other infectious agent is implicated or responsible in the etiology and transmission of human leukemia (121). A number of investigators have suggested the possible etiologic role of viruses in human leukemia (65, 95). That viruses cause leukemia in a number of animal species is now well established (116). Recently, seroepidemiologic studies have revealed an association between antibodies to certain viruses and the occurrence of leukemia (67). These discoveries suggest the possibility of a causal relationship between certain filterable agents and leukemia in man.

In many instances however, leukemia "clusters" tend more to reflect: 1) the irregularity that is often observed with rare diseases and small numbers of cases; 2) after the fact drawing of time and space boundaries which serve to accentuate the grouping of cases; 3) exhaustive attempts to locate cases of leukemia in the suspected area compared to less complete reporting in neighboring areas; and, 4) variability in population density, migration, and race

distribution. Even in the more dramatic examples, as in Niles, Illinois, where eight cases of childhood leukemia were observed between September, 1957, and August, 1960, in a population of approximately 7,000 children, the aggregation may not indicate transmission by an infective agent, nor excessive concentrations in the environment of leukemogenic factors, but may instead be an unusual phenomenon which could occur by chance (66, 37, 53).

If environmental factors are responsible for leukemia trends, these factors should increase or decrease concomitantly with changes in leukemia death rates. Such is not the case with ionizing radiation. Since radiation can induce acute leukemia or chronic myelogenous leukemia, but not chronic lymphatic leukemia, and since there is a linear relationship between radiation dosage and incidence, one would expect the decrease in per capita exposure over the past decade to be reflected in leukemia mortality rates (28). A study of leukemia mortality by cell types should also indicate whether recent trends are attributable to the decreasing exposure to radiation. However, a study of these data does not support the hypothesis that the declining mortality is correlated with radiation exposure. Several other comparisons of mortality trends and exposure to environmental factors have been equally unrewarding. However, because leukemia clusters may reflect unusual environmental factors,

continued study and investigation may yet yield important epidemiological information (35, 53).

CHAPTER II

METHODS

The purpose of this study is to determine the incidence and distribution of leukemia in Oklahoma for the period January 1, 1961, through December 31, 1965, and to carry out controlled descriptive studies in areas characterized by sharply elevated incidence, hereafter referred to as "cluster areas." The "cluster area" has been arbitrarily defined as any county in the state whose five year average mortality or incidence rate is greater than twice the national average of seven cases per 100,000 population per year, or whose mortality or incidence rate exceeds twice the national average for any single year when, in addition, striking temporal and spatial case-clustering occurs within the county unit.

Annual mortality from leukemia closely approximates the incidence of the disease. This approximation is of course greater with time since all cases eventually die. Since mortality records are relatively complete in their coverage of all deaths from this cause, mortality is used in this study as one estimate of leukemia incidence.

Mortality data was supplied by the Statistics Division of the Oklahoma State Department of Health. This information was analyzed by sex, race, age, clinical and/or pathological diagnosis, county of residence and year of diagnosis. This data is of relatively good quality due to near universal registry of leukemia deaths.

The ability of mortality information to estimate true incidence is limited by several factors. Mortality data, while including virtually all cases occurring, often gives little or no information as to the time of onset, or the place of residence of the patient at onset. Incidence estimated by mortality does not include leukemia cases still living. In that leukemia is a universally fatal disease, with death usually occurring within a very few months or years from onset, these limitations are somewhat minimized. Data obtained through examination of death registration certificates are usually accurate and complete with regard to age, sex, race, residence, clinical diagnosis, immediate cause of death, and secondary causes and complications. The number of cases of leukemia missed in death registration data is small. But it is clear that mortality data leave much to be desired in pinpointing the occurrence of cases in time and space, making it difficult to determine the occurrence of elevated incidence and to correlate elevated incidence with possible etiological factors.

To obtain the additional information needed to determine the incidence and distribution of leukemia, hospital records of leukemia cases occurring in Oklahoma during the study period were examined. Examination of medical records yields valuable information such as age, date and residence at onset, medical and/or pathological diagnosis, clinical data and background information which might be of epidemiologic importance. This information permits the formulation of reasonably accurate incidence statistics unobtainable from mortality data due to the variability in the period of time elapsing between diagnosis and death, and the relocation of the patient from one to another geographic area. Leukemia is particularly amenable to this type of study since virtually all cases require hospitalization in facilities of size and quality sufficient to cope with the myriad of therapeutic problems encountered. Some leukemia cases may, however, escape detection. A young patient, in acute leukemic crisis, might expire before definitive diagnosis was made and not be autopsied. The aged person in the terminal stages of a more immediately life threatening disease, or a case with bizarre manifestations might evade diagnosis. Hospital record data is necessarily dependent upon the accuracy and completeness of the medical records examined and upon the ability of the hospital to retrieve all such records. Some cases are missed because of referral to famous specialty treatment

facilities in other states. Other patients, especially those in the extreme northwestern and southeastern sectors of Oklahoma, may seek medical attention in facilities in neighboring states.

The medical records of Oklahoma hospitals accredited with the Joint Committee on Accreditation of Hospitals (JCAH) were examined to obtain the incidence information utilized in this study. Because of the uniform geographic distribution of these fifty-two hospitals across the state, the superiority of their records systems in terms of content and retrieval capability, and the practice of hospitalization of leukemia patients in large, more modern facilities for care, this method is considered reliable for obtaining reasonably thorough coverage of the Oklahoma leukemia population. Permission was obtained from the administrators of each of these hospitals to examine their medical records; each administrator was notified prior to the arrival of the investigators and was requested to retrieve the records of all leukemia patients hospitalized from 1961 to 1965. Each record was examined and information regarding name, age, sex, race, address, date of onset, clinical and pathological diagnosis and other pertinent information (e.g. history of exposure to insecticides, radiation; other cases of leukemia or other cancers in immediate family, congenital abnormalities, and previous illnesses was recorded). The Case Record Form in Appendix A

was used for recording this information. This information was later coded and transcribed to data processing cards which were filed by Hill-Burton area, by county, by year of diagnosis, and by name. Filing by name prevented duplication of cases treated in more than one hospital.

Since the county unit often provides a population base too small for a completely satisfactory study of a disease with a low incidence rate, such as leukemia, a larger population unit was used in addition to counties. The ten regions defined by the Hill-Burton program for hospital construction have been used since they 1) utilize existent county boundaries, 2) are comprised of a number of counties representing definite geographic areas with common economic, trade, and other characteristics, 3) have at least one general hospital of not less than 100-bed capacity, and a sufficiency of related health facilities for the central city to assume the characteristics of a medical center, and 4) provide a population base of sufficient size for more meaningful rate calculation. Complete descriptions of these ten regions are included in Appendix C.

The data obtained from the examination of mortality statistics and medical records of leukemia patients were used to compute mortality and incidence rates for the seventy-seven counties, the ten regions, and for the state. Age adjusted mortality and incidence rates were computed for the state for the five year period; and age, race, and

sex specific rates were computed for the ten regions by year. These rates have been analyzed and compared, and regions of elevated mortality and incidence examined for unusual age, sex, or race composition and distribution.

Counties with elevated incidence have been studied in depth. Descriptive profiles were constructed including pertinent information regarding geographic characteristics, mineral and other geological aspects, description of vegetation and animal life (domestic and wild), meteorological variables and climate, economical and social parameters, occupation data, health status (mortality and morbidity experience), and medical resources. (See Appendix C.) In addition, an interview with a member of the patient's family was conducted. A Case Investigation Form (Appendix B) designed to extract epidemiological information concerning the patient's personal and social history, environment, medical history, and other factors possibly associated with his leukemia, was completed.

The complete profiles of leukemia patients from within the cluster areas were compared with 1) case profiles of apparently normal, non-leukemic controls from within the cluster areas, matched for age, sex, and race; 2) case profiles of leukemia patients from matched non-cluster areas; and 3) case profiles of apparently normal, non-leukemic controls from non-cluster areas, matched for age, sex, and race with non-cluster area leukemia cases. Information

concerning the four groups studied was compared for differences in pertinent epidemiological factors. These differences will be discussed later and related to possible etiologic determinants. Factors responsible for such differences will be discussed relative to sampling errors, chance, or true differences in the environment which might affect the incidence and distribution of the disease. The methods used in this study were developed and tested in a pilot study in Hughes County, Oklahoma.

CHAPTER III

R E S U L T S

Oklahoma's annual leukemia mortality rates have been slightly higher than the national average throughout the 1961-1965 period. The average five-year crude rate for Oklahoma, 1961-1965 was 8.5 deaths per 100,000 population per year. The age-adjusted rate was 7.9 per 100,000 per year. Figure 1 shows Oklahoma and U.S. rates for the 1961-1965 period. Oklahoma rates are slightly higher than the U.S. rates and show an increase over the five-year period, whereas U.S. rates have remained approximately the same. The effect of age-adjustment (direct method) in lowering state mortality rates is demonstrated also.

Figure 2 and Table 1 show mortality from respective types of leukemia. Acute leukemia is observed most frequently in all years except 1963. The over-all trend for acute leukemia and chronic lymphocytic leukemia is a gentle increase over the five-year period. The other types do not show this increase. Perhaps the most interesting difference seen in Figure 2 is the increasing

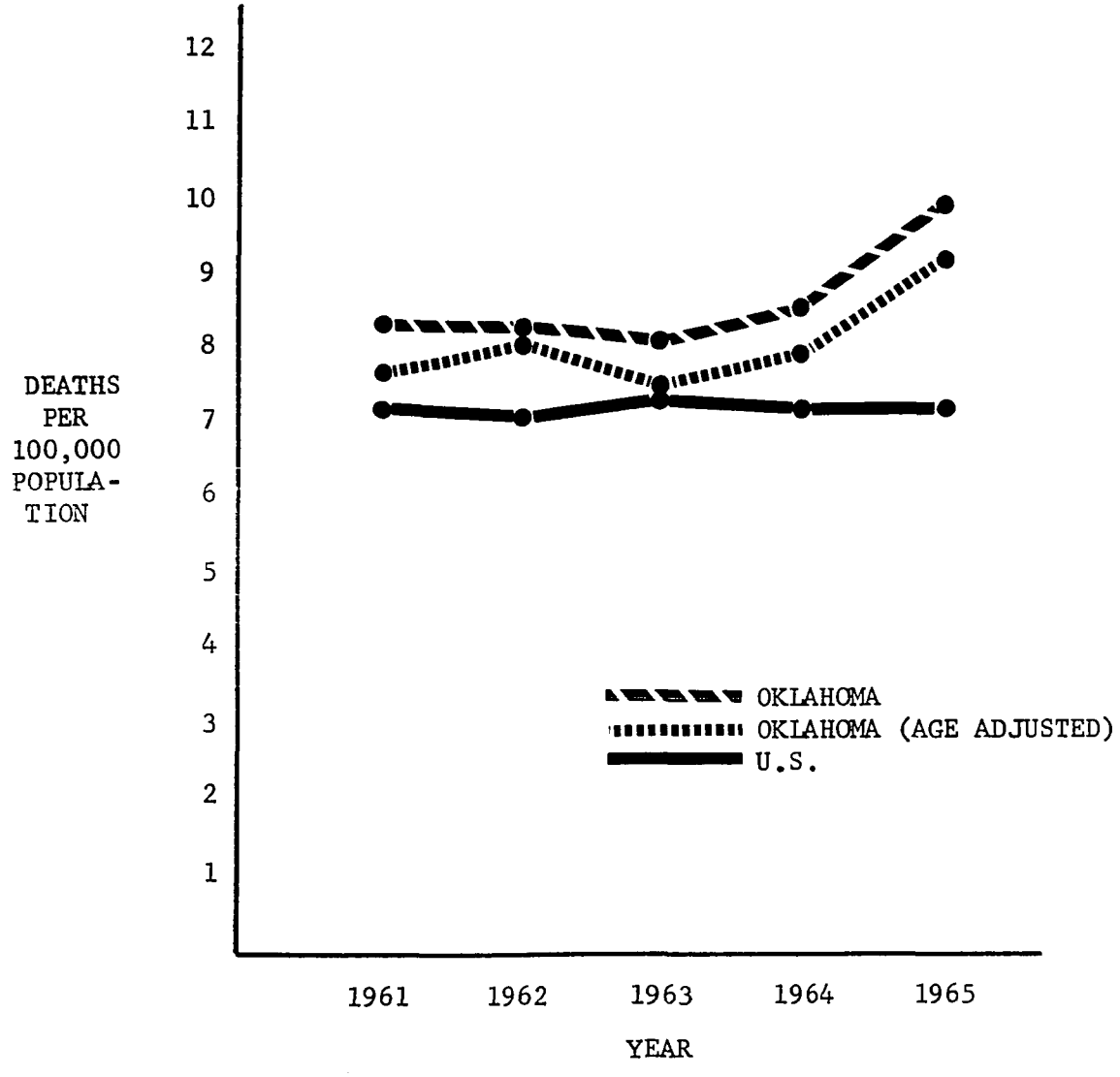

Fig. 1.--Oklahoma and U.S. mortality rates from leukemia for 1961-1965.

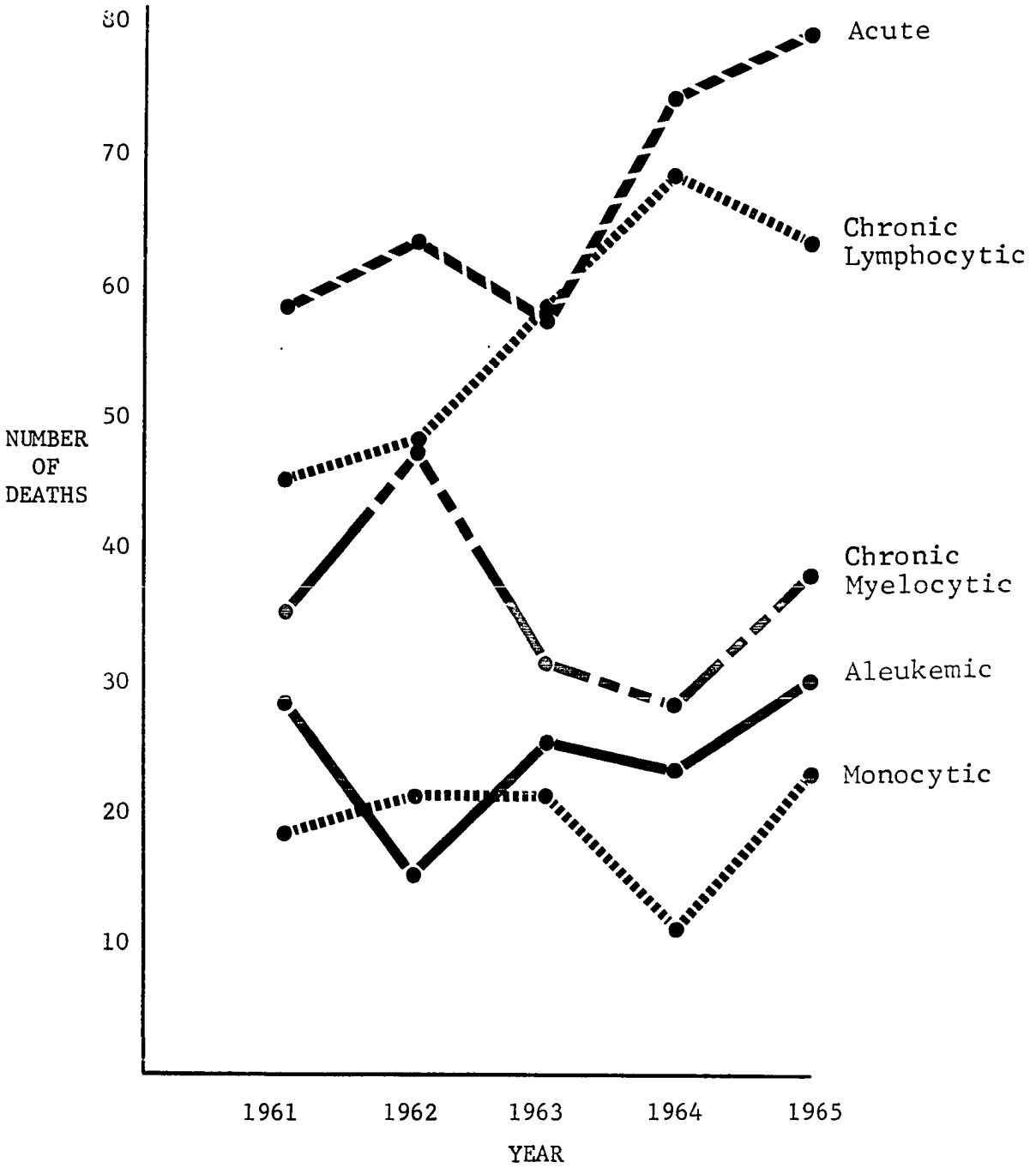

Fig. 2.--Leukemia mortality by year and by type in Oklahoma, 1961-1965.

TABLE 1

OKLAHOMA LEUKEMIA MORTALITY BY CELL TYPE, 1961-1965

Year	Acute	Chronic Lympho-cytic	Chronic Myelo-cytic	Mono-cytic	Aleu-kemic	Total	Rate[a]
1961	59	45	34	17	29	184	7.5
1962	63	48	47	21	15	194	7.9
1963	57	58	31	21	25	192	7.4
1964	73	68	28	11	23	203	7.8
1965	79	63	38	23	30	233	9.1
Total	331	282	178	93	122	1006[b]	7.9

[a]Age-adjusted mortality rate (per 100,000).

[b]Four cases of unspecified diagnosis omitted.

difference between chronic lymphocytic leukemia and chronic myelocytic leukemia with time. In 1961 and 1962 chronic lymphocytic leukemia and chronic myelocytic leukemia accounted for about the same number of deaths, but in 1963 a divergence began that resulted in a difference of 40 more chronic lymphocytic leukemia deaths than chronic myelocytic leukemia deaths in 1964. The difference was slightly less in 1965. The over-all trend, as noted in Figure 1, is an increase in the number of deaths from all types of leukemia. Most of this increase is attributable to acute leukemia and chronic lymphocytic leukemia.

Figure 3 and Table 2 show leukemia mortality by age groups and by year. The 5-44 age group has the lowest mortality. The 5-14, 15-24, 25-34, and 35-44 age groups have been combined to simplify the figure, since mortality is uniformly quite small in them. Though no clear trend is observed in these data, the 65-74 and 75 and over age groups both show rather sharp increases in 1965 over 1964. They appear to account for a large part of the mortality excess observed in 1965. Below 54 years of age the rates appear very stable.

Table 3 shows yearly mortality by sex and race. Examination of the upper part of the table shows that males contributed slightly more to the increases in mortality observed from 1961 to 1965 than did females. Both

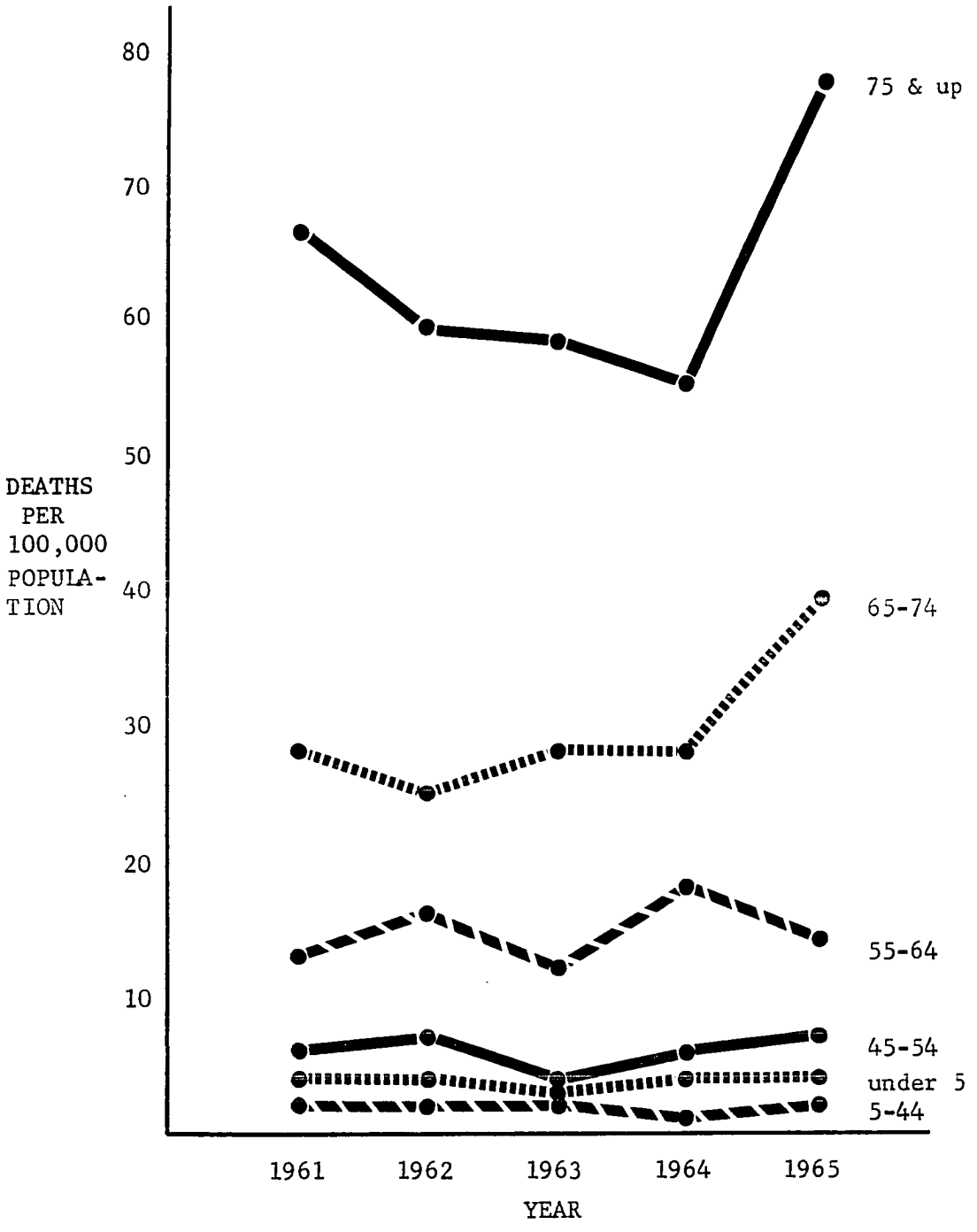

Fig. 3.--Leukemia mortality by age groups and by year in Oklahoma, 1961-1965.

TABLE 2

OKLAHOMA LEUKEMIA MORTALITY BY AGE GROUPS, 1961-1965

Age		1961	1962	1963	1964	1965	Total
Under 5	#	10	10	8	11	11	50
	Rate[a]	4.1	4.1	3.7	4.5	4.5	4.2[b]
5-14	#	10	13	22	12	14	71
	Rate	2.1	2.7	4.6	2.5	2.9	3.0
15-24	#	7	8	7	2	7	31
	Rate	2.1	2.4	2.1	.6	2.1	1.9
25-34	#	4	4	2	7	5	22
	Rate	1.4	1.4	.7	2.6	1.5	1.5
35-44	#	9	9	7	7	8	40
	Rate	3.4	3.1	2.4	2.4	2.8	2.8
45-54	#	14	16	12	19	20	81
	Rate	5.1	5.8	4.3	6.7	7.4	5.8
55-64	#	29	35	29	46	33	172
	Rate	3.5	16.0	12.7	19.4	14.0	15.1
65-74	#	45	42	48	46	56	237
	Rate	29.3	26.3	29.6	28.5	39.5	30.6
75 & up	#	56	58	58	54	80	306
	Rate	66.9	59.9	58.4	56.0	77.6	63.8

[a]Rates per 100,000.

[b]Five-year average rate.

TABLE 3

OKLAHOMA LEUKEMIA MORTALITY BY RACE, SEX, AND YEAR, 1961-1965[a]

RACE AND SEX	1961		1962		1963		1964		1965	
	Rate	#	Rate	#	Rate	#	Rate	#	Rate	#
All races	7.9	185	8.3	194	8.2	193	8.7	206	9.9	234
Male	9.1	105	10.2	118	10.8	125	10.7	125	11.9	139
Female	6.8	80	6.4	76	5.7	68	6.8	81	7.9	95
White	8.2	176	8.4	182	8.2	180	8.5	188[b]	9.6	216
Male	9.5	99	10.5	110	11.0	116	10.9	115	11.8	117
Female	7.2	77	6.7	72	5.9	64	6.7	73	8.4	91
Non-white	4.2	9	5.6	12	5.9	13	6.4	14	8.1	18
Male	5.6	6	7.4	8	8.3	9	9.2	10	12.8	14
Female	2.6	3	3.5	4	3.5	4	3.5	4	3.4	4
Sex ratio[c]										
All races	1.35		1.55		1.84		1.54		1.46	
White	1.26		1.53		1.81		1.58		1.37	
Non-white	2.00		2.00		2.25		2.50		3.50	

[a]Rates per 100,000.

[b]One case omitted for reason of race unknown.

[c]Ratio of male to female cases.

the whites and non-whites experienced consistent increases in mortality, although non-white rates increased slightly more than did white rates. Non-white males account for a small number of cases, but their rate more than doubles from 1961 to 1965.

Figure 4 shows age-specific mortality rates for the nine age groups. The small peak observed in the younger ages decreases with each older age group until reaching its lowest point in the 25-34 age group. The mortality rates then increase with each succeeding age group.

Leukemia mortality by age group and by type is illustrated in Figure 5. Acute leukemia makes up a large proportion of the cases in the first four age groups. It reaches its lowest point in the 25-34 age group and then begins an ascent that continues throughout life, with the possible exception of a slight downturn in the 75 and older age group. Mortality from chronic lymphocytic leukemia is low in the age groups under 45 but then begins an increase that becomes very sharp in the 45-54 age group. This increase continues thereafter. Chronic myelocytic leukemia mortality is about the same as that of chronic lymphocytic leukemia up to the 25-34 age group, but then exceeds mortality from all types (except acute leukemia) up to age group 55-64 where chronic lymphocytic leukemia becomes more common. Chronic myelocytic leukemia maintains

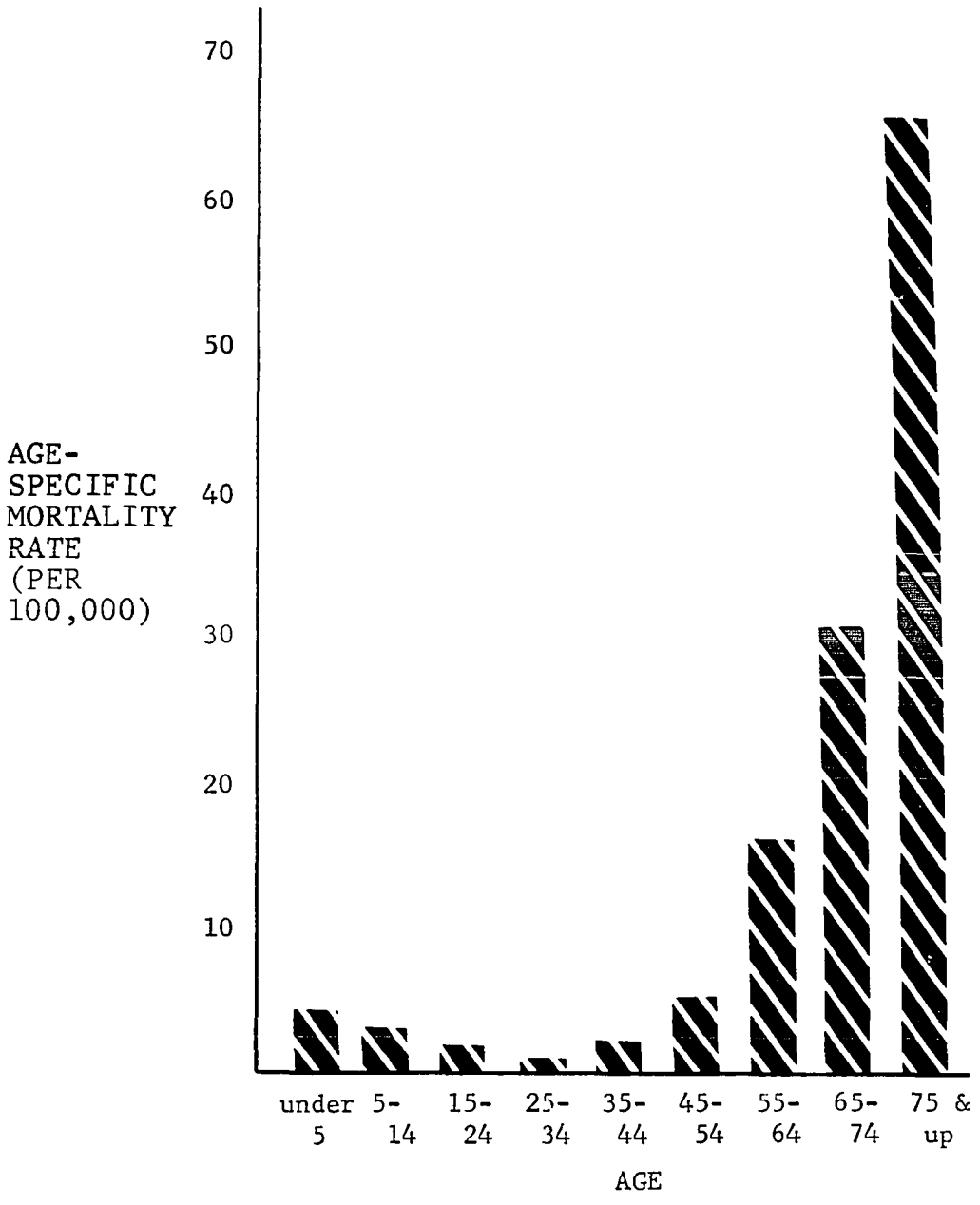

Fig. 4.--Age-specific leukemia mortality rates in Oklahoma, 1961-1965.

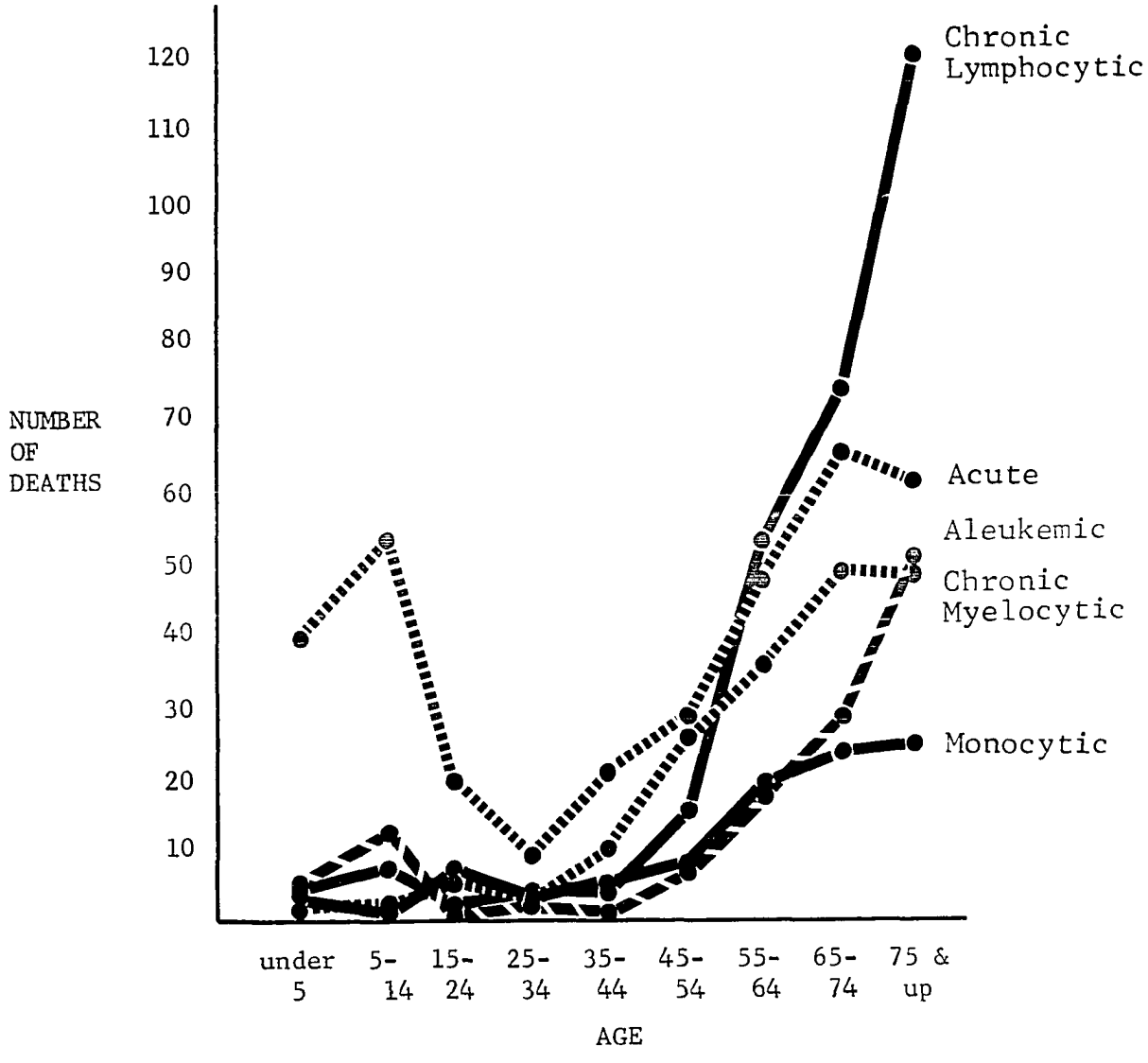

Fig. 5.--Leukemia mortality by age and by type in Oklahoma, 1961-1965.

a steady increase until the 75 and older age group where it levels off. Monocytic and monoblastic leukemia are relatively rare until age 45, showing rather sharp increases thereafter, and leveling off about the 65-74 age group. Atypical and aleukemic leukemia account for a peak of cases in the 5-14 age group and then another peak beginning in the 45-54 age group reaches its maximum height in the 75 and older age group. After 74 years of age, aleukemia and atypical leukemia account for more deaths than chronic myelocytic leukemia.

The classification of leukemia types used in mortality data differs from the system used for incidence data in the following section, requiring caution in point comparisons of the two sets of information. It is not known with certainty how many cases of acute aleukemic leukemia are placed in the "acute" versus "aleukemic" categories. Neither is it known how many cases of acute monocytic or monoblastic leukemia are placed in the "acute" versus "monocytic-monoblastic" categories. The most comparable items in the two sources of data are acute leukemia, chronic lymphocytic leukemia, and chronic myelocytic leukemia. Acute leukemia mortality and incidence are closely comparable between the ages of 15 and 44 since monocytic and monoblastic leukemia are so rare in these ages.

Figure 6 shows age-, race-, and sex-specific mortality rates. Leukemia risk increases with age for both sexes in whites and non-whites. The increase is most noticeable in the last two age groups, particularly among white males. White females and non-white males occupy an intermediate position and encounter essentially identical risks of developing leukemia, whereas non-white females experience a relatively low risk.

Figure 7 shows Oklahoma leukemia mortality compared with leukemia incidence as determined by the study of hospital records, for 1961-1965. Incidence, as measured by the hospital records study, is 75.5% of the registered leukemia mortality for the same calendar period. The low incidence observed in 1962 will be discussed later. The five-year incidence trend does not demonstrate increases comparable to those observed for mortality during the same period.

Figure 8 shows the relative contribution of the different types of leukemia, acute, chronic lymphocytic, chronic myelocytic, and other and non-specified types. Acute leukemia shows a net increase and chronic myelocytic a net decrease over this period, but the other two types show no obvious trend. Acute leukemia is the most frequently observed type throughout the study period, chronic lymphocytic is second, chronic myelocytic third, and other and non-specified types are fourth. There is considerable

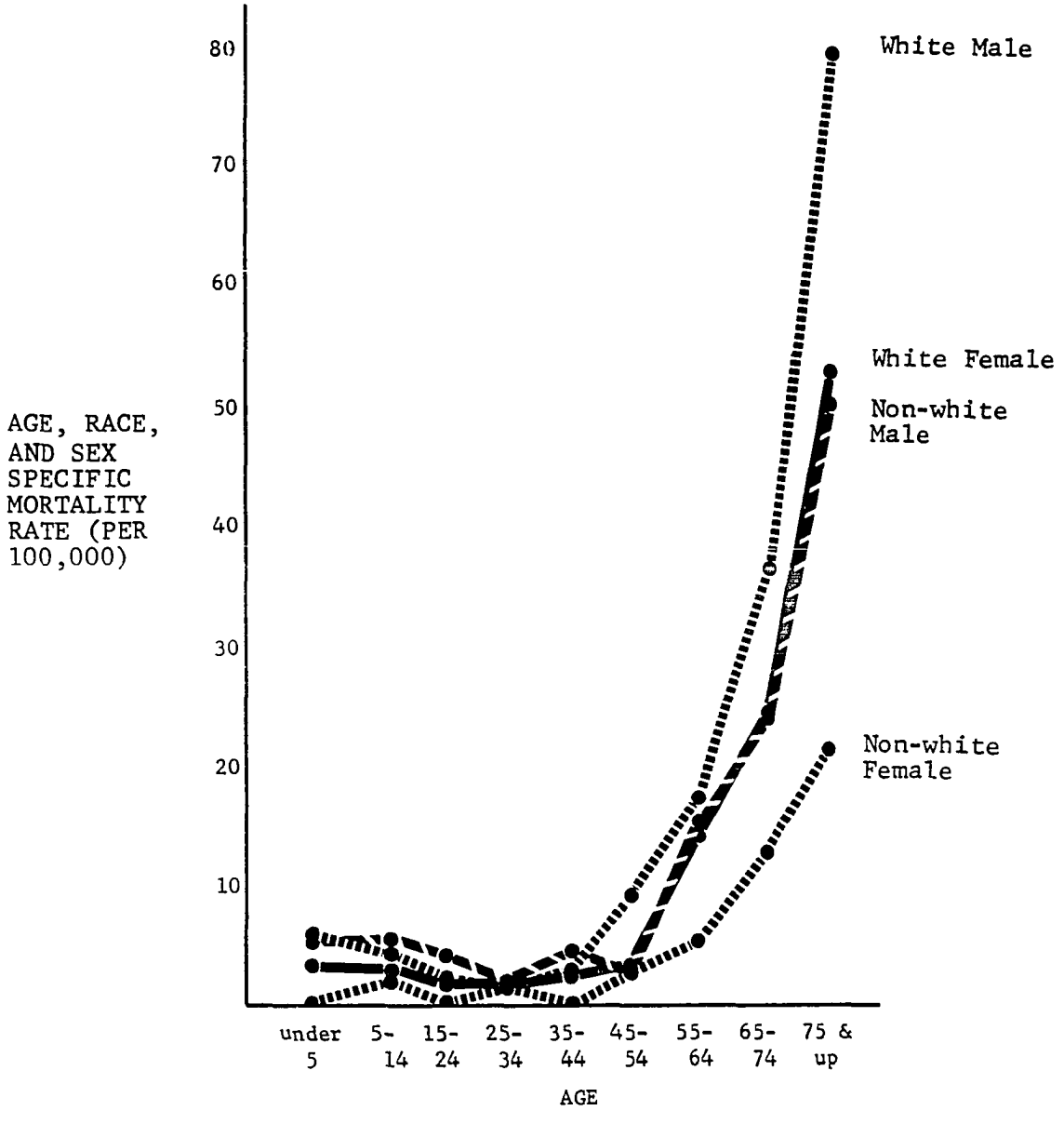

Fig. 6.--Leukemia mortality by age, race, and sex in Oklahoma, 1961-1965.

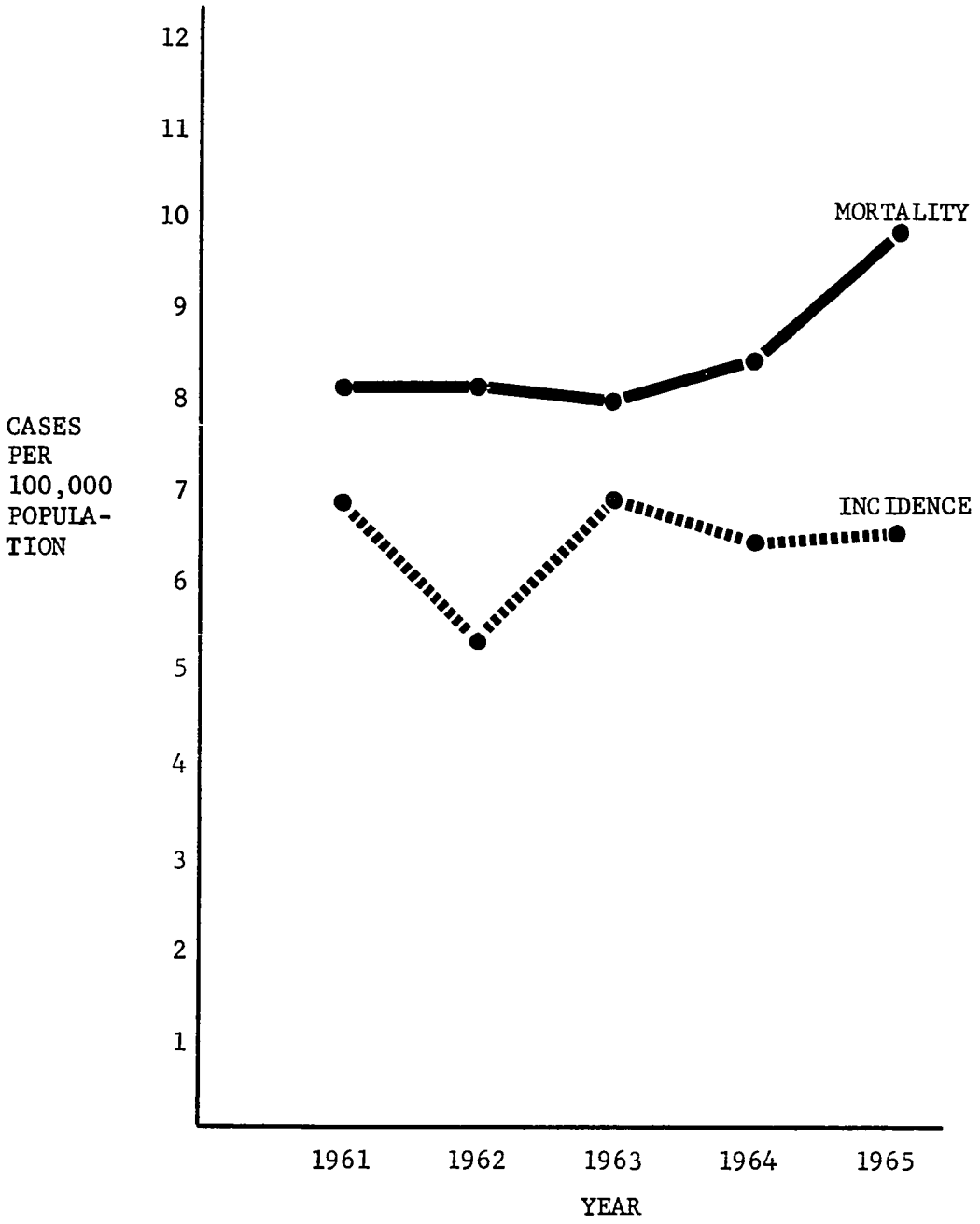

Fig. 7.--Comparison of Oklahoma mortality and incidence[a] from leukemia, 1961-1965.

[a]As determined by study of hospital records.

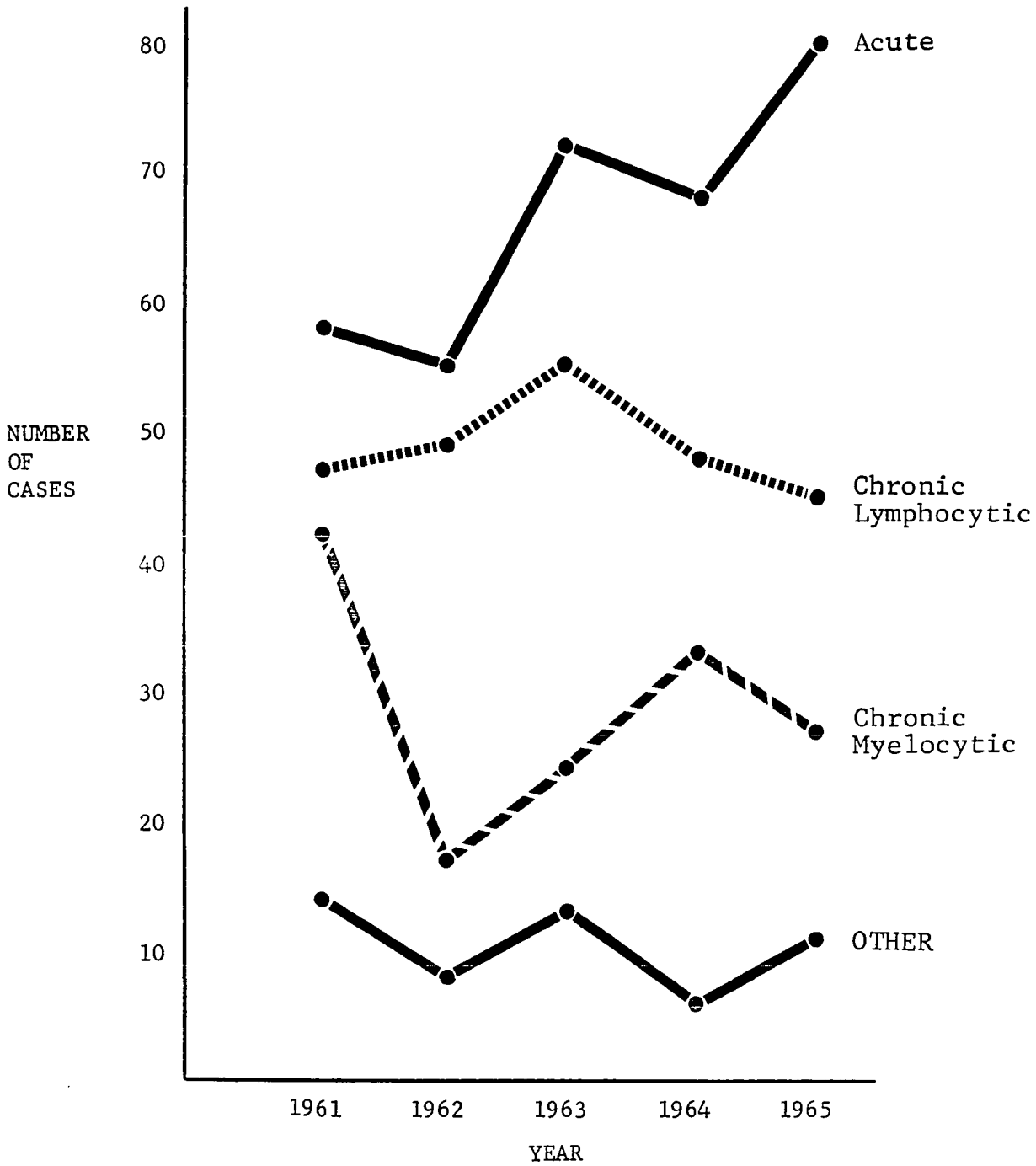

Fig. 8.--Leukemia incidence by year and by type in Oklahoma, 1961-1965.

variation in the proportion of each type from year to year, but the above order of frequency is consistent through the five-year period.

Regarding the small number of cases observed in 1962 in Figure 7, examination of Figure 9 shows sharp decreases in leukemia incidence in the 65-74 and 55-64 age groups and a slight decrease in the 45-54 age group in 1962. Examination of Figure 8 shows a sharp decrease in 1962 in chronic myelocytic leukemia, the most common type of leukemia in the 55-64 and 65-74 age groups (26). Figure 2 shows that this decrease is not reflected in chronic myelocytic leukemia mortality in 1962, but that substantial decreases in chronic myelocytic leukemia mortality did occur in 1963 and 1964. Figure 8 also shows smaller decreases for acute leukemia and for other non-specified types in 1962. The combination of decreases had a measurable effect upon the 1962 total. Figure 9 and Table 4 show that the age, sex, and race composition of the leukemia population in 1962 is not greatly different than in the other four years.

Figure 9 shows leukemia incidence by age groups throughout the study period. The highest incidence occurs in persons 75 years of age and older, and the lowest incidence in persons between 5 and 44.

Table 4 shows leukemia incidence by race and sex. The disease is more common among males according to these

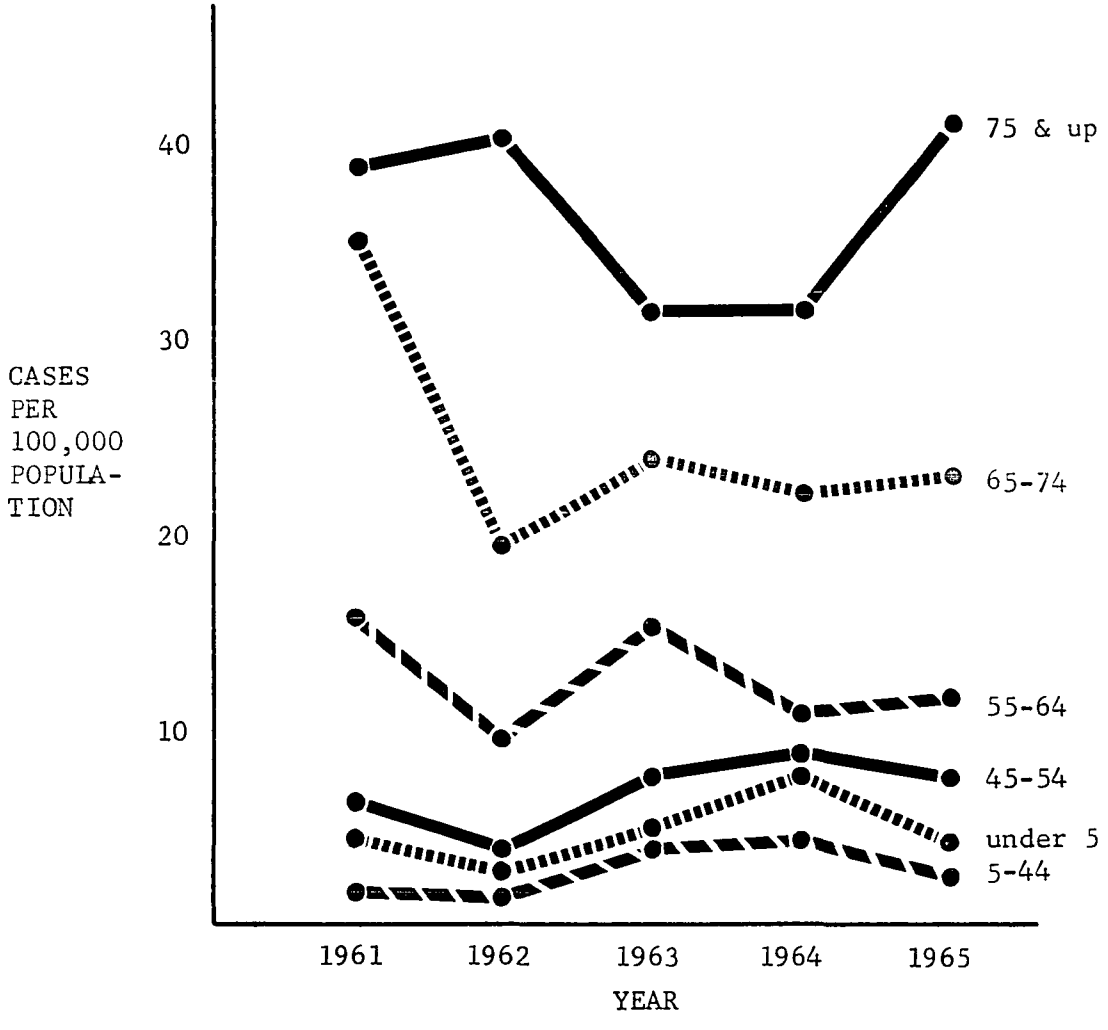

Fig. 9.--Leukemia incidence by year and by age in Oklahoma, 1961-1965.

TABLE 4

LEUKEMIA INCIDENCE BY RACE, SEX, AND YEAR, FOR OKLAHOMA, 1961-1965[a]

RACE AND SEX	1961		1962		1963		1964		1965	
	Rate	#	Rate	#	Rate	#	Rate	#	Rate	#
All races	6.5	154	5.5	132	6.7	162	6.3	155	6.5	162
Male	6.5	99	6.6	78	8.7	104	6.9	84	6.9	97
Female	4.6	55	4.4	54	4.7	58	5.7	71	5.1	65
White	6.7	144	5.8	125	7.1	156	6.7	149	7.1	159
Male	8.6	91	6.7	72	9.3	101	7.5	82	8.5	94
Female	4.9	53	4.8	53	4.9	55	5.9	67	5.7	65
Non-white	4.4	10	3.0	7	2.6	6	2.5	6	1.2	3
Male	7.3	8	5.4	6	2.7	3	1.7	2	2.6	3
Female	1.7	2	0.8	1	2.5	3	3.3	4	0.0	0
Sex ratio[b]										
All races	1.80		1.44		1.79		1.18		1.49	
White	1.72		1.36		1.84		1.22		1.45	
Non-white	4.00		6.00		1.00		0.50		....	

[a]Rates per 100,000.

[b]Male cases to female cases.

figures, and among males it is more common in whites. White females experience greater incidence on the average than non-white males, though the latter had higher rates in 1961 and 1962. Non-white females have the lowest rates of all. The sex ratios observed in the lower part of Table 4 illustrates the increased risk of leukemia in males of both races. The difference in rates for white males between 1962 and 1963 is significant at the .05 level.[a] The difference in rates for non-white males between 1961 and 1964 is also significant at the .05 level.[a]

Figure 10 illustrates age-specific incidence rates for 1961-1965 in Oklahoma. A bimodal distribution is observed here, although the peak in the under 5 age group is small.

Figure 11 shows leukemia incidence by type and by age. The peak noted in the younger ages is almost entirely the result of acute leukemia. Chronic leukemia makes up a very small proportion of cases up to age 45. In the middle age groups where the incidence of all leukemias is lowest, acute leukemia makes up about half of all

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[a]A significance test comparing the difference between two rates was utilized where the Standard Error was determined by the formula:

$$S.E. = \sqrt{\frac{r_1^2}{n_1} + \frac{r_2^2}{n_2}}$$

n_1 and n_2 refer to the numbers of cases of leukemia used in calculating rates r_1 and r_2.

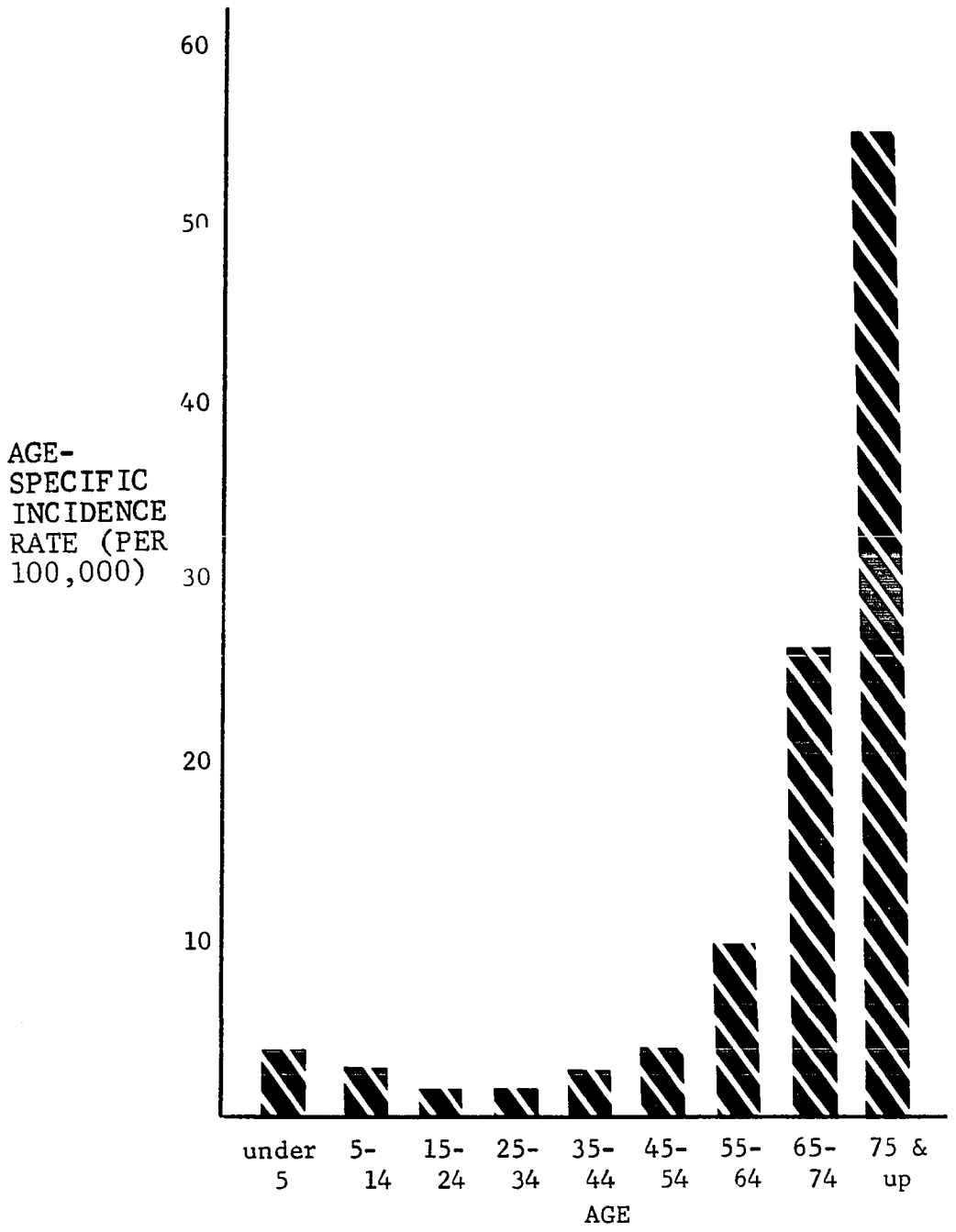

Fig. 10.--Age-specific leukemia incidence rates in Oklahoma, 1961-1965.

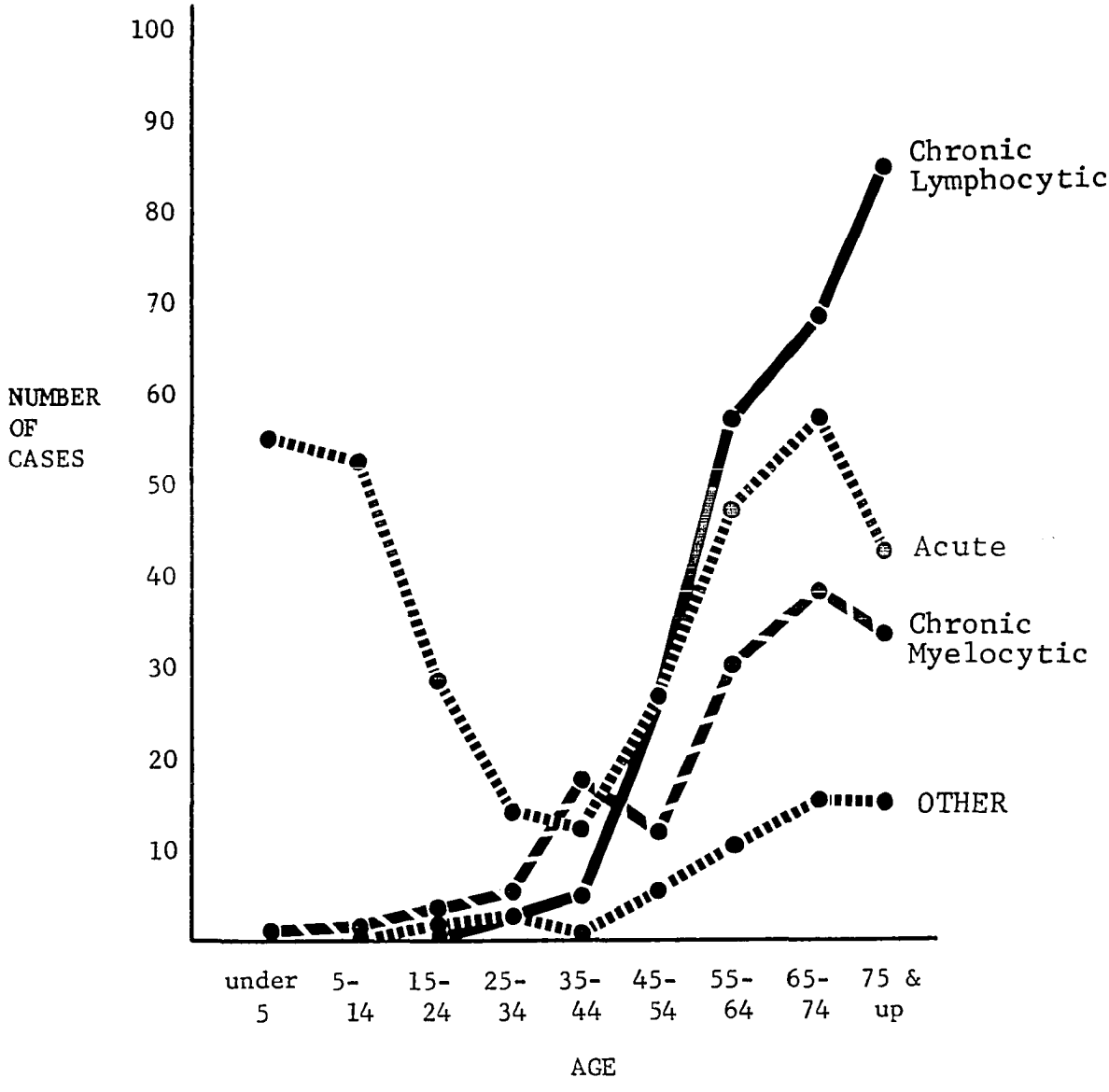

Fig. 11.--Leukemia incidence by age and by type in Oklahoma, 1961-1965.

cases. In the 45-54 age group chronic lymphocytic leukemia is approximately equal to acute leukemia and continues to increase with age, being the most prevalent type after age 54. All types increase with age up to about 70. During the 65-74 age group, acute leukemia and chronic myelocytic leukemia begin to show decreases in incidence, whereas chronic lymphocytic leukemia continues its steep increase. Chronic myelocytic and acute leukemia have very similar incidence in the 35-44 age groups. They separate shortly afterward with acute leukemia becoming the more common type on into old age.

Figure 12 illustrates age, race, and sex specific incidence rates for leukemia. White males have the highest incidence of leukemia from birth to death. White females are consistently lower throughout life, and non-white males and females are still lower. The unusual pattern noted in non-white females in the last two age groups is the result of a very small number of cases used in the construction of the rates. The white versus non-white difference is most marked in middle age.

Oklahoma leukemia mortality examined by Hill-Burton Regions exhibits the pattern seen in Figure 13 and Table 5. Complete descriptions of the Hill-Burton Regions are contained in Appendix C. Leukemia incidence for these regions appears in Figure 14 and Table 6. None of these regions has significantly higher leukemia incidence or

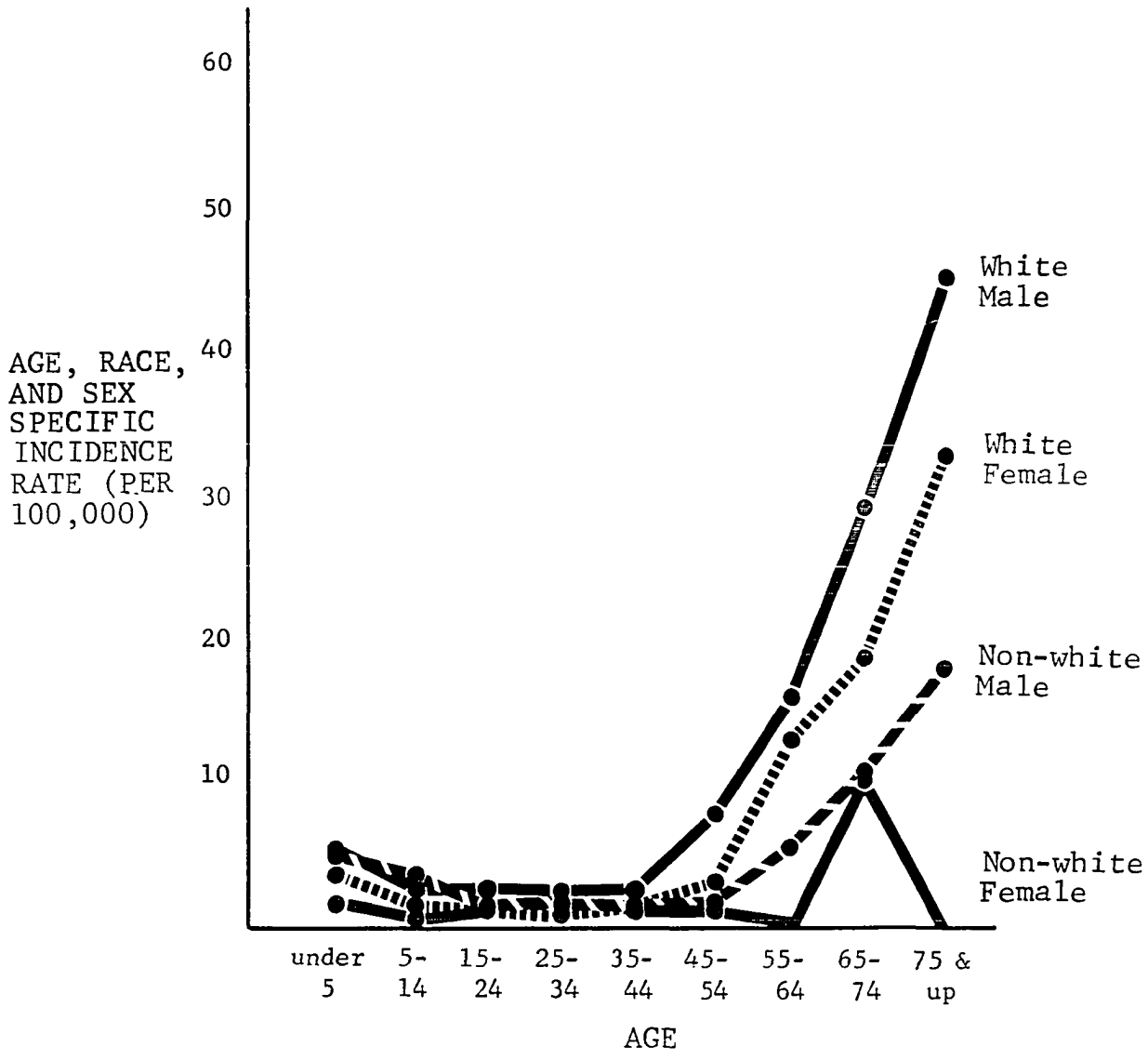

Fig. 12.--Leukemia incidence by age, race, and sex in Oklahoma, 1961-1965.

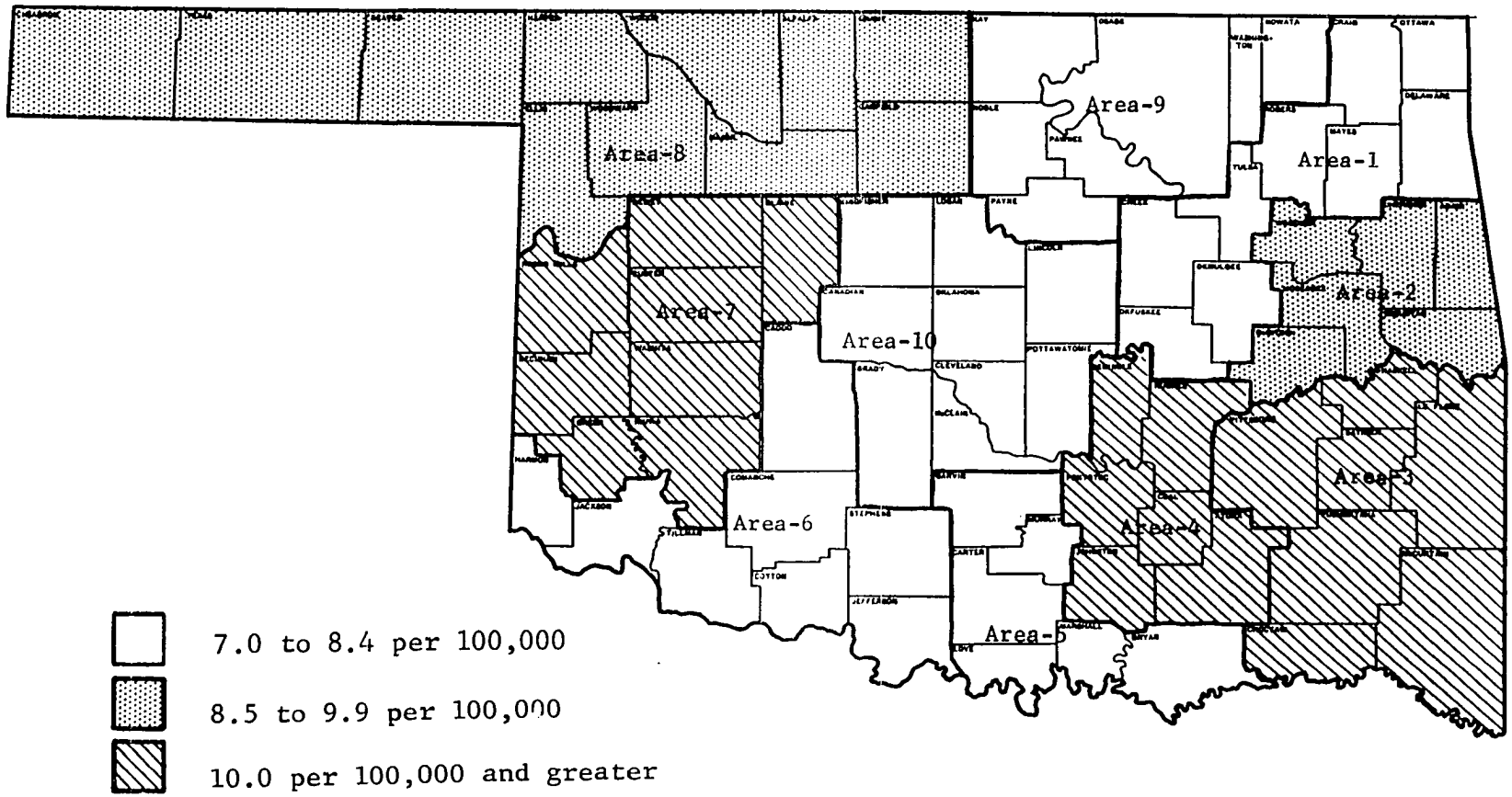

Fig. 13.--Geographic distribution of leukemia mortality in Oklahoma, 1961-1965.

TABLE 5

LEUKEMIA MORTALITY RATES FOR THE TEN HILL-BURTON REGIONS IN OKLAHOMA, 1961-1965[a]

Region	1961	1962	1963	1964	1965	Average Annual
1	8.6	7.3	6.3	9.5	10.4	8.4
2	11.4	6.4	12.7	10.5	4.8	9.2
3	11.3	10.7	8.7	13.2	14.8	11.7
4	6.1	12.3	13.2	5.1	13.9	10.1
5	7.8	7.8	7.7	6.8	6.8	7.4
6	6.0	8.3	7.8	5.7	9.2	7.4
7	6.6	14.6	9.1	13.6	10.7	10.9
8	10.6	8.1	10.5	6.9	6.8	8.6
9	3.9	7.9	9.8	8.3	10.7	8.1
10	7.4	7.7	7.4	7.1	8.9	7.7

[a]Deaths per 100,000 population.

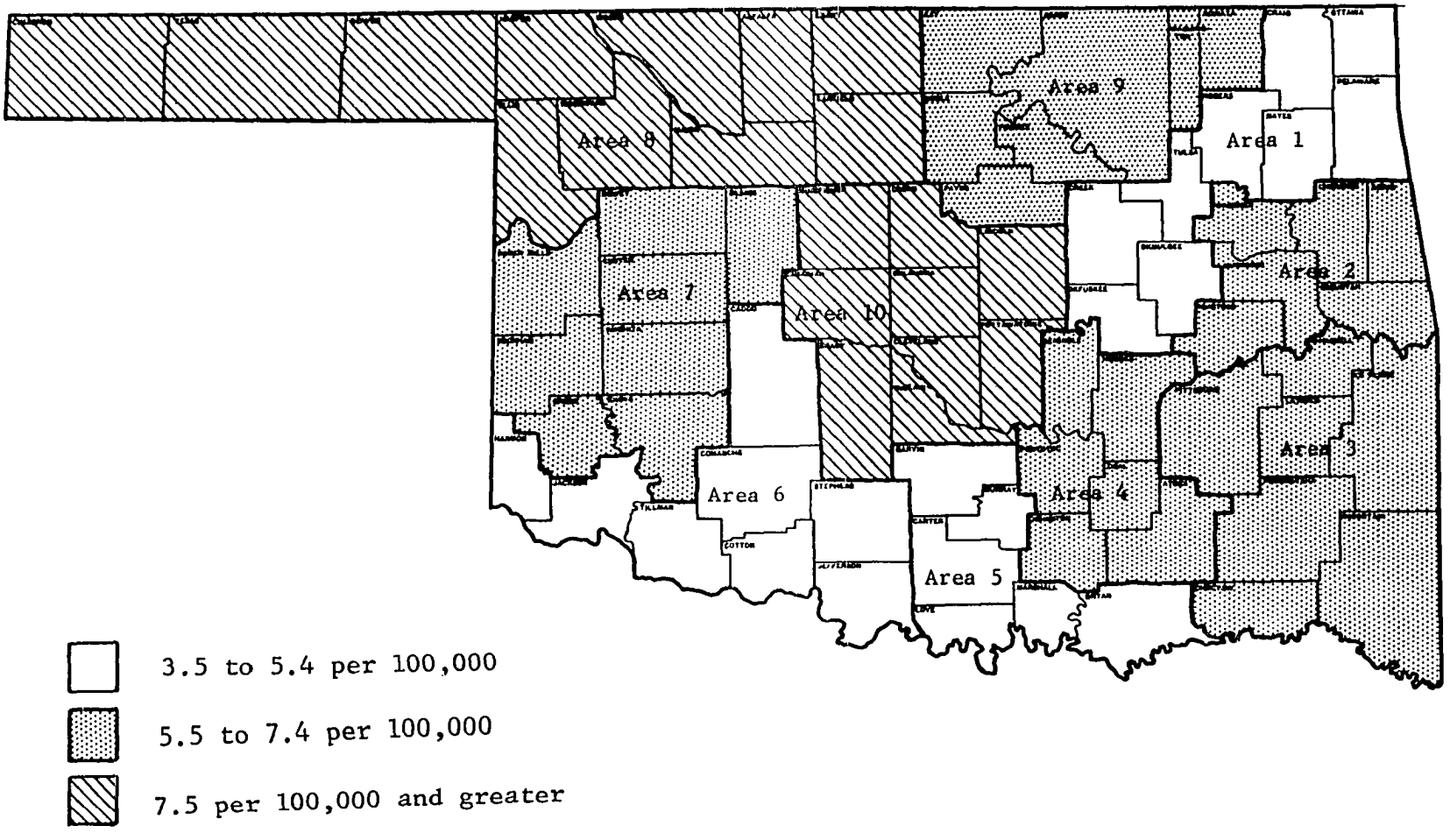

Fig. 14.--Geographic distribution of leukemia incidence in Oklahoma, 1961-1965.

TABLE 6

LEUKEMIA INCIDENCE RATES FOR THE TEN HILL-BURTON REGIONS IN OKLAHOMA, 1961-1965[a]

Region	1961	1962	1963	1964	1965	Average Annual
1	4.8	4.8	5.3	5.5	6.6	5.4
2	7.1	5.7	6.3	9.6	3.4	6.4
3	5.3	3.0	5.8	7.1	10.5	6.3
4	4.1	6.2	7.1	11.0	7.0	7.1
5	2.6	1.7	6.0	6.0	3.4	3.9
6	6.0	3.7	4.5	4.5	4.8	4.7
7	6.6	4.5	8.2	4.9	8.9	6.6
8	9.9	6.6	9.8	4.8	7.5	7.7
9	8.4	5.9	4.9	12.2	5.3	7.3
10	9.0	7.0	8.8	5.6	7.7	7.6

[a]Cases per 100,000 population.

mortality than the others although Regions 3, 4, and 7 show moderate mortality rate elevations (average annual rates greater than 10 per 100,000). Region 3 exhibited rates above state and national averages for all five years. Exceptionally high rates in 1964 and 1965 are responsible for this elevation. Region 4 experienced elevated mortality rates in 1962, 1963, and 1965. Though 1961 and 1964 rates were below average, the other three years were sufficiently elevated to produce a five-year average rate of greater than 10 deaths per 100,000. Region 7 experienced high mortality from leukemia in 1962 and again in 1964 of sufficient magnitude to result in a five-year average rate of greater than 10 per 100,000. The 1965 mortality rate in Hill-Burton Region 1 was significantly greater than the average annual rate for Region 1[a] (significant at 0.10). No other differences were significant. Leukemia incidence for the 10 Hill-Burton Regions is less remarkable, and little correlation can be observed between their mortality and morbidity experience. However, a difference significant at the

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[a]Significant differences were determined by constructing confidence limits for each year around the five-year average annual rate. The Standard Error was calculated by the formula:

$$S.E. = \sqrt{\frac{R}{n_i}}$$

where R equals the five-year average annual rate and n_i equals the number of leukemia deaths for the year under consideration.

0.05 level was observed between the 1965 incidence rate in Region 3 and the average annual rate for that Region.[a] A difference significant at the 0.10 level was observed between the 1964 incidence rate in Region 4 and the average annual rate for that Region.[a] A difference significant to the 0.05 level was observed between the 1964 incidence rate in Region 9 and the average annual rate for that Region.[a]

Age-adjusted rates were also computed for each county in the state, for each year, and for the five-year study period. Table 7 shows the incidence and mortality characteristics of the three counties which met or exceeded criteria established in chapter ii defining "cluster counties." Twenty-one cases of leukemia were diagnosed in Kay County during this time. Table 7 shows that 8 (31.8%) of these cases were diagnosed in 1962, resulting in an incidence rate of 15.7 cases per 100,000 population. Four of these 8 cases were acute leukemias in children and adolescents. Nineteen hundred sixty-one was also a high year with six cases and a rate of 11.7 per 100,000. The remaining

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[a]Significant differences were determined by constructing confidence limits for each year around the five-year average annual rate. The Standard Error was calculated by the formula:

$$S.E. = \sqrt{\frac{R}{n_i}}$$

where R equals the five-year average annual rate and n_i equals the number of leukemia deaths for the year under consideration.

TABLE 7

OKLAHOMA COUNTIES WITH SUSPECTED LEUKEMIA CLUSTERING,1961-1965

COUNTIES	1961	1962	1963	1964	1965	5 YEAR
KAY COUNTY						
Deaths	1	6	7	4	5	23[a]
Rate	1.9	11.8	13.6	7.8	9.6	8.9[b]
New Cases	6	8	3	2	2	21
Rate	11.7	15.7	5.8	3.9	3.8	8.2
STEPHENS CO.						
Deaths	4	8	8	2	6	28
Rate	10.5	21.0	20.9	5.2	15.6	14.6
New Cases	3	4	4	2	3	16
Rate	7.8	10.5	10.9	5.2	7.8	8.4
OTTAWA COUNTY						
Deaths	1	6	3	4	7	21
Rate	3.5	20.8	10.2	13.5	23.3	14.3
New Cases	0	6	2	8	1	17
Rate	0.0	20.8	6.8	27.0	3.3	11.60

[a]Total cases or deaths.

[b]Five-year average rate per 100,000.

three years were low. In 1963, the year after the 1962 incidence peak, a mortality excess appeared in Kay County. For the total period 1961-1965, 8 of the new cases occurred in persons less than 25 years of age, and 13 were 25 years and older. Of the 21 total new cases in the county, 10 were males and 11 were females. Twenty occurred in whites and only 1 (an Indian child) in non-whites. Of 21 cases, 10 were acute leukemia, 10 were chronic lymphocytic leukemia, and 1 was chronic myelocytic leukemia. The preponderance of older cases were females and the younger cases were mostly males.

The estimated 1965 population of Kay County is 51,108. Fourteen of the 21 new cases diagnosed from 1961 to 1965 resided in the county seat, Ponca City, a community of 24,411 (1965 estimate). Interestingly, 13 of these 14 new cases in Ponca City resided in the western half of the city as shown in Figure 15. A home address was not available for one case. This concentration of cases in one part of the city is not the result of non-uniform distribution of residential areas throughout the city. The aggregation of cases does lie immediately adjacent to refining facilities of two large petroleum companies located at the western and southwestern edges of the residential area of the city. Almost as striking as the aggregation of cases on the west side of the city is the absence of cases in other residential areas. Among

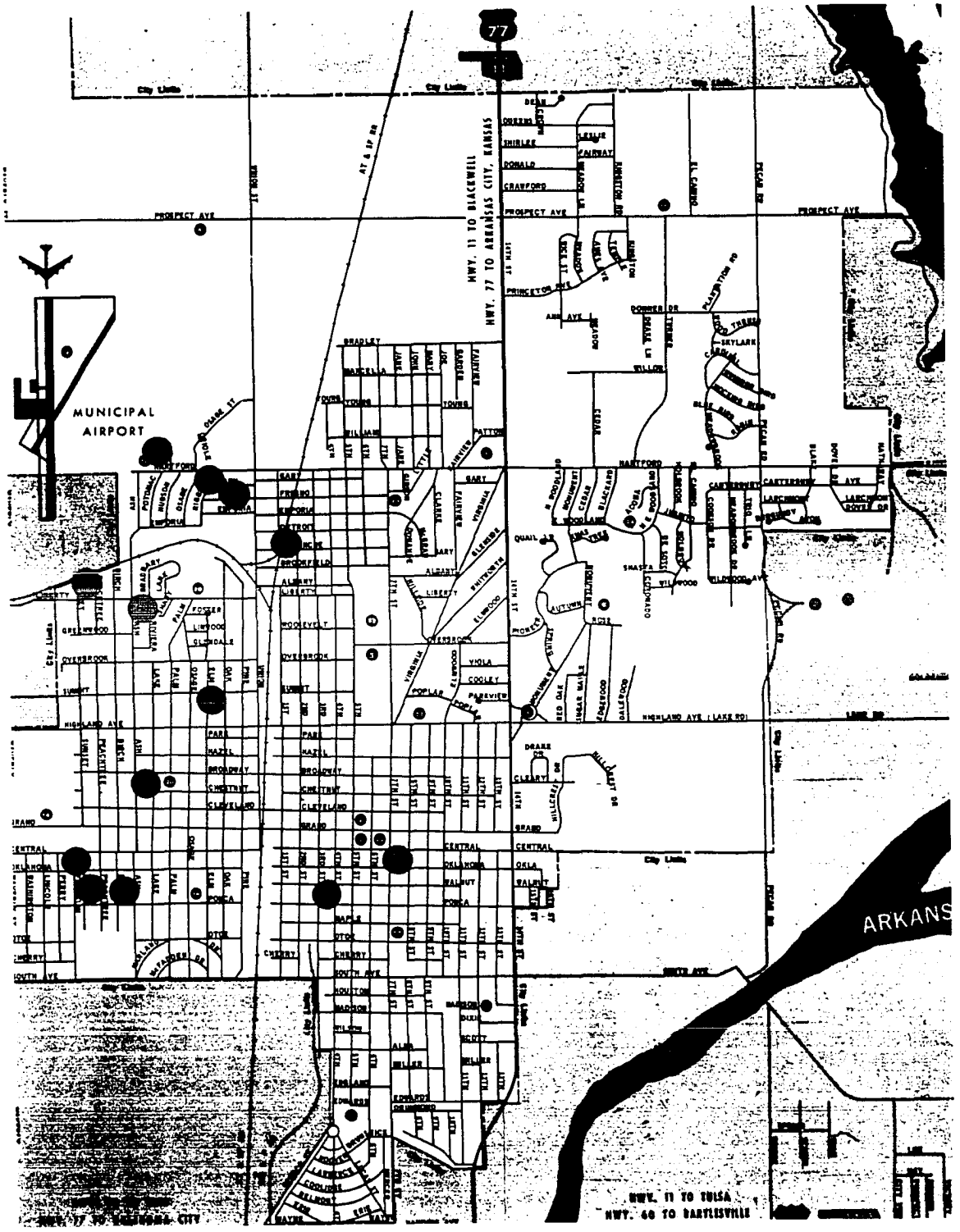

Fig. 15.--Places of residence of leukemia cases at onset in Ponca City, Oklahoma, 1961-1965.

the 14 cases diagnosed in Ponca City, 9 were acute leukemias, 4 were chronic lymphocytic leukemias, and 1 was a case of chronic myelocytic leukemia. Seven of the 14 were under 25 years of age at diagnosis, and only 4 were over 65. Six of the 14 were male and 8 were female. The 7 cases outside of Ponca City showed no tendency to aggregate. Kay County was recognized as a "cluster area" and further studies will be discussed later. A complete description of Kay County is contained in Appendix D.

Stephens County in Hill-Burton Region 6 in south-central Oklahoma experienced elevated leukemia mortality in 1962, 1963, and 1965 (see Table 7). Twenty-eight leukemia deaths were reported from 1961 to 1965. Of the 28 deaths, 14 were male and 14 were female. Only 3 were under 25 years of age, and 11 were over 75. There were no non-white leukemia deaths recorded during this period. Sixteen new cases were diagnosed from 1961 to 1965. Of the 16, 11 were male and 5 were female. Ten of the 16 were acute leukemias, 2 were chronic lymphatic, 2 were chronic myelocytic, and 2 were not specified. Of the 16 new cases, 5 were in persons under 25 years of age, and only 1 was over 75. Three cases of acute leukemia were diagnosed in white males in age group 65-74. There were no new cases reported in non-whites during the study period. Stephens County population is 38,281 (1965 estimate). Ten of the 16 new cases diagnosed resided in

Duncan, the county seat and a community with a 1965 population estimate of 20,009. These cases tended to reside in the east and northeast part of the city. Figure 16 shows the locations of the residences of 9 of these cases. The tenth case gave only a nursing home address and is not represented. Two additional cases resided in the adjacent rural area just northeast of Duncan. The other 4 cases in the county showed no apparent tendency to cluster. Four of the 10 newly diagnosed cases in Duncan were in children, and 6 were in adults. Stephens County was included as a cluster area, and further studies will be discussed later.

Ottawa County in extreme northeast Oklahoma experienced 21 leukemia deaths from 1961 to 1965 (see Table 7). Six deaths produced a mortality rate of 20.8 per 100,000 population. Four deaths in 1964 and 7 in 1965 produced rates of 13.5 and 23.3 per 100,000 respectively. Twelve of the 21 deaths were in white males, and 5 of these were acute leukemias with onset prior to age 25. Ten of the 21 occurred in persons 75 years of age and older. Four of these 10 were white males and 6 were white females. There were no reported leukemia deaths in non-whites, nor were there any deaths reported in persons under the age of 5 years.

During the 1961-1965 time period 17 new cases of leukemia occurred in Ottawa County. Six of these were

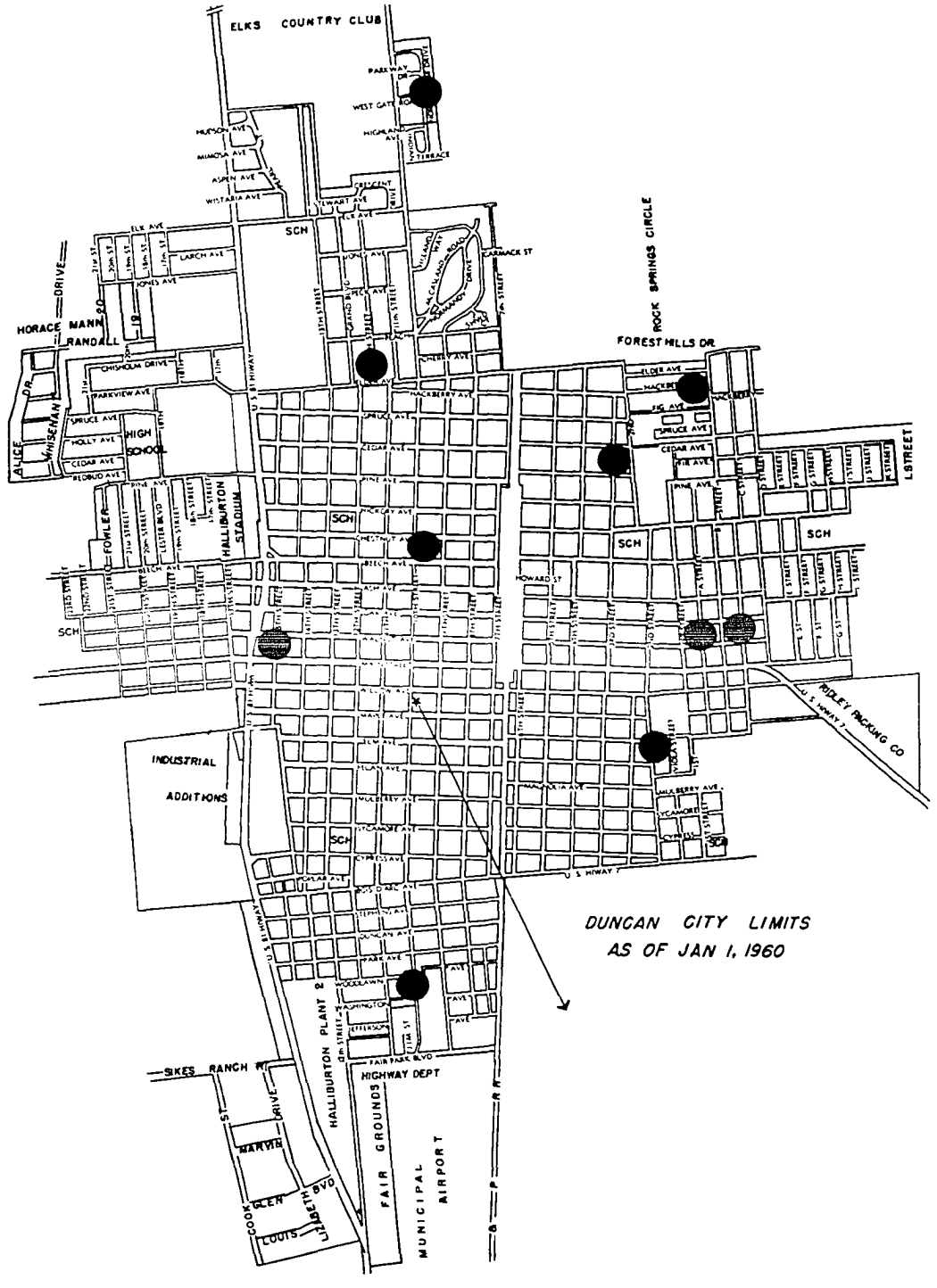

Fig. 16.--Places of residence of leukemia cases at onset in Duncan, Oklahoma, 1961-1965.

diagnosed in 1962 yielding a rate of 20.8 per 100,000, and 8 cases were diagnosed in 1964 yielding a rate of 27 cases per 100,000. There were no new cases diagnosed in 1961 and only 1 case in 1965. The average annual rate was 11.6 per 100,000. Of the 17 new cases, 9 were acute leukemias. Six of the acute cases occurred in persons under 35 years of age and 3 occurred in persons between 55 and 74 years of age. There were 8 new cases of chronic leukemia, 4 chronic lymphocytic and 4 myelocytic. Six of these occurred in persons over the age of 75. There was 1 non-white case, a 14 year-old Indian male.

Five of the 17 new cases diagnosed in Ottawa County have relatives or acquaintances with confirmed hematologic disturbances arising since the onset of leukemia in each index case. The severity of these cases ranges from anemia to suspect leukemia. They will be discussed later.

Ottawa County has an estimated 1965 population of 28,635. Miami, the county seat, has a population of 12,869 (1965 estimate). Seven of the 17 new cases diagnosed in Ottawa County occurred in residents of Miami. In Figure 17 the places of residence of these cases are seen. They are relatively uniformly distributed across the city. The 10 cases outside Miami are randomly distributed across the county. Ottawa County was considered a "cluster area" since the five year average mortality

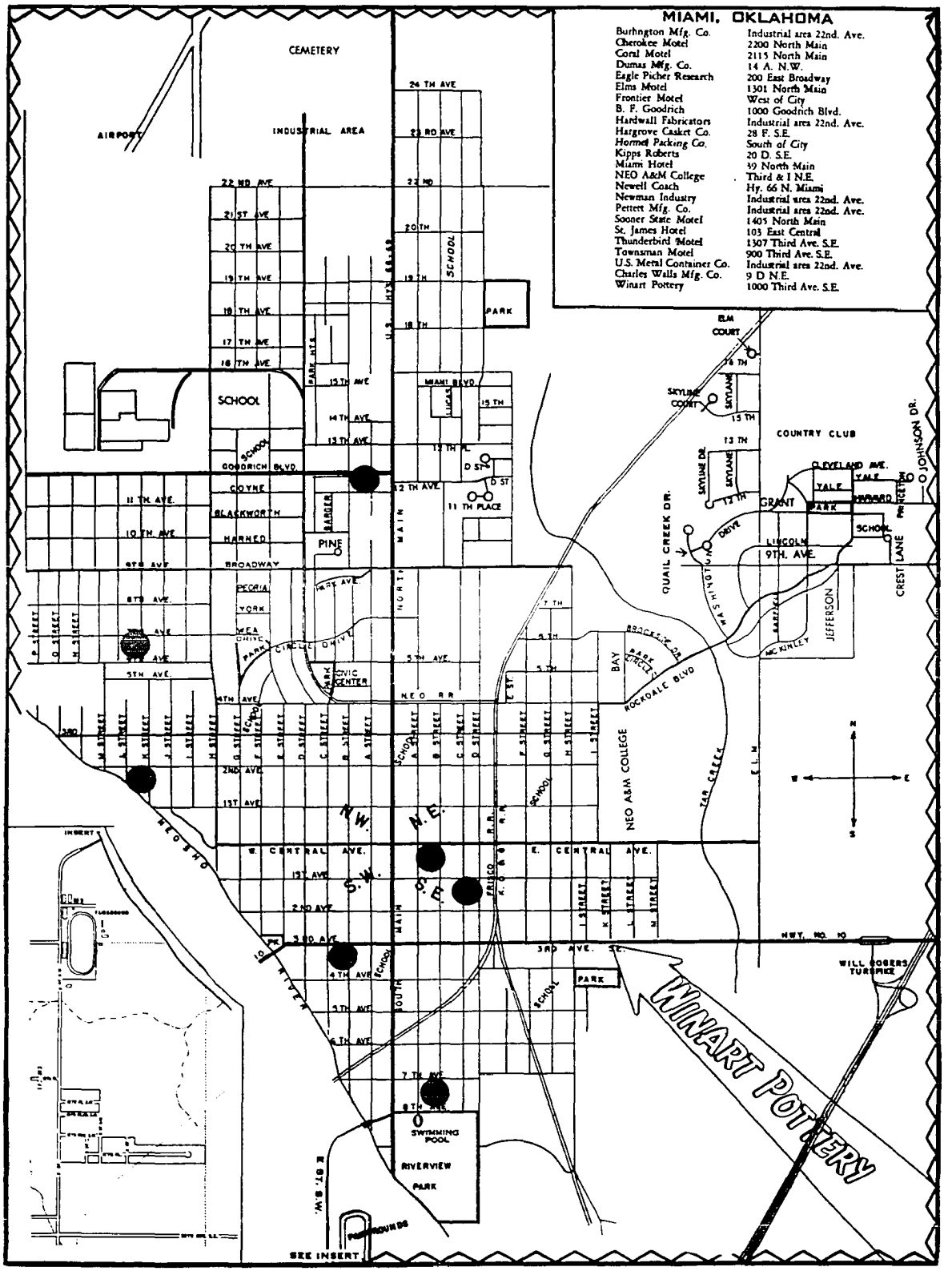

Fig. 17.--Places of residence of leukemia cases at onset in Miami, Oklahoma, 1961-1965.

was greater than twice the U.S. average mortality for the same period. Further studies will be discussed in the next section. A complete description of Ottawa County is contained in Appendix D.

Kay, Stephens, and Ottawa Counties in Oklahoma have been described as experiencing "excessive" leukemia incidence and/or mortality from 1961 to 1965. As outlined in chapter ii, leukemia cases from these counties have been pooled and each matched by age, race, and sex with a non-leukemic control residing in the same neighborhood as the case. Control counties were also selected for each of the cluster counties, and control subjects selected for leukemia cases in the control counties to allow for comparisons between cases and their controls within cluster and control counties, and for comparison of cases and controls between cluster and control counties. Complete descriptions of these three control counties are contained in Appendix D.

Figure 18 shows the locations of cluster and control counties. Thirty-nine of the 54 (72.2%) leukemia cases in the pooled cluster counties were interviewed, as were their 39 controls. Twenty-four of the 30 (80.0%) leukemia cases from the pooled control counties and their 24 controls were also interviewed. Table 8 shows a comparison of these four groups by sex, race, age, and type of leukemia. Within the cluster counties, the sex and

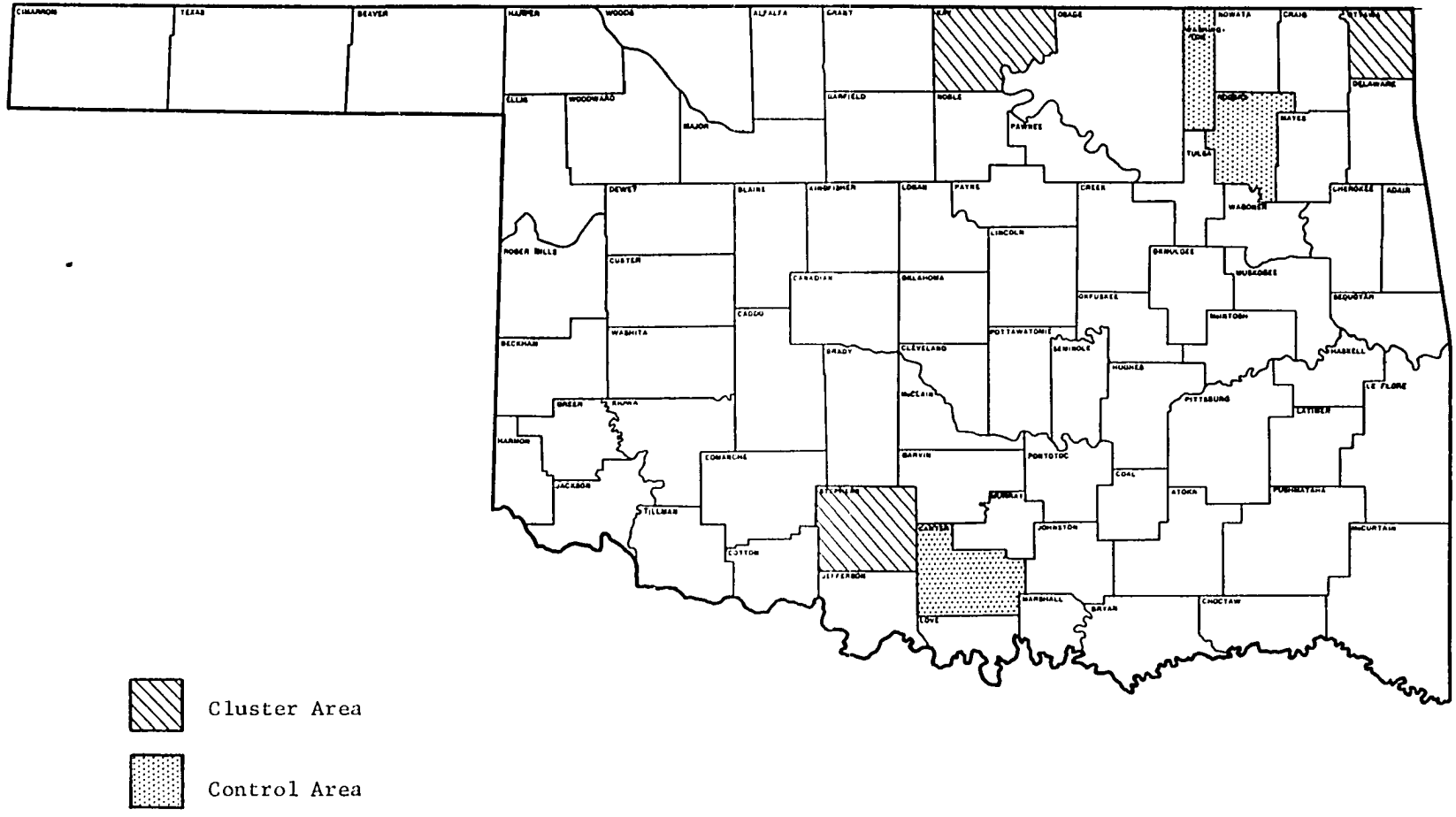

Fig. 18.--Location of cluster and control areas in Oklahoma, 1961-1965.

TABLE 8

CHARACTERISTICS OF LEUKEMIA CASES AND CONTROLS IN CLUSTER AND CONTROL COUNTIES IN OKLAHOMA, 1961-1965

	CLUSTER COUNTIES				CONTROL COUNTIES			
	Cases		Controls		Cases		Controls	
	No.	%	No.	%	No.	%	No.	%
Total	39	100	39	100	24	100	24	100
Male	25	64.1	25	64.1	18	75	18	75
Female	14	35.9	14	35.9	6	25	6	25
White	37	94.9	37	94.9	24	100	24	100
Non-white	2	5.1	2	5.1	..	...	..	...
Acute	28	71.8	..	...	8	33.3	..	...
Chronic Lympho-cytic	8	20.5	..	...	9	37.5	..	...
Chronic Myelo-cytic	2	5.1	..	...	6	25.0	..	...
Other	1	2.6	..	...	1	4.2	..	...
Mean age[a]	39.7 years		37.2 years		62.3 years		64.7 years	
Sex ratio[b]	1:1.77		1:1.77		1:3		1:3	

[a]Variability due to control selection from ten-year age interval.

[b]Ratio of females to males.

race of cases and controls are of course identical, and mean ages are very close since these groups have been matched. The same comparisons, of course, hold for the control counties because of the matching. Between the cluster and control counties however, some interesting differences are observed. A striking difference is noted in the mean age of the two groups. In agreement with this mean age difference is an equally striking disparity in the observed proportions of acute leukemia between the two groups. Thirdly, a considerable difference exists in the sex ratios although the numbers are small.

Table 9 shows comparisons of the four groups interviewed in relation to the factors at the left column of the table. Leukemia cases in cluster counties reported histories of major surgery significantly[a] more often than their controls in the cluster counties (significant at 0.10 level). Major surgery was defined as any surgery requiring general anesthesia. Cases in cluster counties reported histories of radiation exposure more often than their cluster county controls (radiation exposure was defined as ever having been treated with radiation). Cases in cluster counties reported family histories of fetal wastage more often than their cluster county controls (history of fetal wastage was defined as two or more

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[a]Significance was determined by the Fisher Exact Probability Test.

TABLE 9

LEUKEMIA CASE AND CONTROL PROFILE SUMMARIES FOR CLUSTER AND CONTROL COUNTIES IN OKLAHOMA, 1961-1965

HISTORY	CLUSTER COUNTIES				CONTROL COUNTIES			
	Cases		Controls		Cases		Controls	
	#	%	#	%	#	%	#	%
Major surgery	10	25.6	3	7.7	5	20.8	2	8.3
Major illness	15	38.5	8	23.1	11	45.8	7	29.2
Toxin exposure	12	30.8	5	15.4	11	45.8	3	12.5
Immunization reactions	2	5.1	0	0.0	1	4.2	0	0.0
Recurrent infection	15	38.5	6	17.9	11	45.8	7	29.2
Allergies	7	17.9	8	23.1	10	41.7	7	29.2
Radiation exposure	7	17.9	3	7.7	5	20.8	3	12.5
Birth defects	2	5.1	1	2.6	0	0.0	0	0.0
Familial cancer	13	33.3	9	25.6	10	41.7	7	29.2
Second malignancy	3	7.7	1	2.6	8	33.3	1	4.2
Fetal wastage	6	15.4	2	5.1	6	25.0	2	8.3
Family birth defects	3	7.7	0	0.0	0	0.0	0	0.0
Household pets	15	38.5	17	43.6	12	50.0	13	54.2
Ill pet exposure	7	17.9	2	5.1	3	12.5	1	4.2
Livestock exposure	9	23.1	13	33.3	5	20.8	6	25.0

stillbirths or abortions among first degree relatives). Cases in cluster counties reported more exposure to ill pets than did their cluster county controls. Cases in control counties reported a greater prevalence of malignant disease in addition to their leukemia. These differences were not significant.

No significant differences were observed between leukemia cases in control counties and their controls. However, the cases did report considerably more exposure to toxic chemicals, more histories of malignancies other than leukemia, and more family histories of fetal wastage, than their controls. Comparison of controls from cluster counties with controls from control counties reveals a very consistent pattern with respect to all factors.

Because of the difference observed in the proportion of acute leukemia cases between cluster counties and control counties, further examination of leukemia experience in cluster and control counties was made. Table 10 gives a breakdown of leukemia cases, within cluster and control counties, by acute and chronic types, and includes mean ages, numbers of males and females, and whites and non-whites for each type of leukemia. The mean ages of acute leukemias in cluster and control counties are clearly different. The difference between the mean ages of chronic leukemias is negligible.

TABLE 10

CHARACTERISTICS OF LEUKEMIA CASES AND CONTROLS
IN CLUSTER AND CONTROL COUNTIES
IN OKLAHOMA, 1961-1965

	MEAN AGE	MALE	FEMALE	WHITE	NON-WHITE
Cluster Counties					
Acute Leukemia	33.8 yrs.	18	10	27	1
Chronic Leukemia	64.1 yrs.	7	4	10	1
Control Counties					
Acute Leukemia	54.8 yrs.	7	1	8	0
Chronic Leukemia[a]	67.1 yrs.	11	5	16	0

[a] Includes one case of "unspecified" leukemia.

In Table 11 case profile summaries of acute and chronic leukemias in cluster and control counties are examined. It is observed that acute leukemias in the cluster counties reported significantly[a] more histories of persistent infections than did chronic leukemias in cluster counties (significant at the 0.0001 level). Table 11 shows that histories of major surgery, persistent infections, fetal wastage, exposure to ill pets, and family histories of birth defects, were more often reported by acute leukemias in cluster counties than by acute leukemias in control counties though the numbers are too small for meaningful testing.

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[a]Significance was determined by the Fisher Exact Probability Test.

TABLE 11

LEUKEMIA CASE PROFILE SUMMARIES FOR CLUSTER AND CONTROL COUNTIES IN OKLAHOMA, 1961-1965

HISTORY	CLUSTER COUNTIES				CONTROL COUNTIES [a]			
	Acute		Chronic		Acute		Chronic	
	#	%	#	%	#	%	#	%
Major surgery	9	32.2	1	10.0	3	38.6	2	12.5
Major illness	13	46.5	2	20.0	5	62.5	6	37.5
Toxin exposure	10	35.7	2	20.0	5	62.5	6	37.5
Immunization reactions	2	7.2	0	00.0	1	12.5	0	00.0
Recurrent infection	15	53.5	0	00.0	4	50.0	7	43.8
Allergies	6	21.4	1	10.0	3	38.6	7	43.8
Radiation exposure	6	21.4	1	10.0	2	25.0	3	18.5
Birth defects	2	7.2	0	00.0	0	00.0	0	00.0
Familial cancer	10	35.7	3	30.0	4	50.0	6	37.5
Second malignancy	2	7.2	1	10.0	2	25.0	6	37.5
Fetal wastage	6	21.4	0	00.0	3	38.6	3	18.5
Family birth defects	3	10.8	0	00.0	0	00.0	0	00.0
Household pets	13	46.5	2	20.0	5	62.5	7	43.8
Ill pet exposure	7	25.0	0	00.0	1	12.5	2	12.5
Livestock exposure	6	21.4	3	30.0	3	38.6	2	12.5

[a]One case of "type unspecified" leukemia was found in the control counties.

CHAPTER IV

DISCUSSION

Epidemiologic studies of leukemia are of great importance to many types of investigation concerning leukemia, in that they provide the firm descriptive base from which subsequent research of several kinds can grow.

The first logical step in the study of any disease involves defining and characterizing the disease process. This depends in part upon another step, i.e., describing the manner in which the disease process affects the human population. A descriptive epidemiologic study provides this essential information. It can also expose unexpected or unique aspects of the disease which serve as "clues" for further study. Application of epidemiologic methods in "controlled" studies can then yield more knowledge about the disease, allowing formulation of hypotheses regarding possible etiologic determinants. These broad-based descriptive studies, though carefully controlled, may produce information which may lend itself to several different interpretations. It is necessary to perform in-depth analytic studies, often dependent upon

sophisticated laboratory procedures, to determine the validity of the several possible interpretations.

Leukemia is relatively rare; only about seven cases per 100,000 population occur each year in the United States (1). As a result, epidemiologic studies are usually retrospective in nature. The cost of prospective studies of the size to produce a sufficient number of cases would be prohibitive. Only in very high risk populations, such as atomic bomb survivors in Japan (14, 19) and Mongoloids (92, 94, 130) have prospective techniques been extensively employed. With retrospective studies, large population bases must be effectively dealt with to reduce error and produce reliable incidence rates. As a result, most studies have utilized readily available and relatively complete mortality registers. Studies which utilize and compare different systems of data acquisition, e.g., mortality versus incidence data, show great promise in solving problems posed by inadequate, out-dated sources of information, and will make more refined, more powerful epidemiologic methods available to the study of chronic disease. These methods will necessarily be expensive, but the more direct inferences made possible by better quality data will justify this expense.

Several sources of error are inherent in any study of this nature; their presence and effect must be

realized and minimized by the institution of appropriate control measures whenever possible. Potential sources of error in this study have been noted by the author in the text of chapter ii. The most important of these are the failure of death registration data to accurately describe disease incidence in time and space, loss of cases due to dissimilar access to medical care services, under-reporting, out-of-state referral, non-response or inability to locate subject for interview, difficulty in standardization of interview technique, the questionable ability of relatives to provide requested information, and the lack of comparability in interviews between the relatives of leukemia cases and control subjects (relatives of cases were interviewed whereas control subjects were interviewed directly).

Greatly refined diagnostic methods have been largely responsible for the differentiation of the many types of leukemia now encountered in pathology and hematology texts. The exact relationship of these disorders is not fully known, though it is generally accepted that similar pathogenic mechanisms are involved (1). The variability observed in leukemia cases appears very much dependent upon age, race, and sex. Many experts feel that the variability observed in clinical and hematologic manifestations result from host factors and environmental differences, but that the initial event in the development

of the disease is similar, if not identical, in all cases (79, 84). Some workers feel that leukemia is a very generalized response to an entire spectrum of initiating factors (109, 110).

The findings of this study are largely compatible with similar work done by others (35, 36, 119). The sex, race, and age distribution of the cases have been within the ranges of normal variability. The geographic distribution of the disease, including the cluster counties identified in the study were not unexpected. Where the disease has been thoroughly studied, these aggregations have been found. It is felt by several authors (44, 64, 66) that these phenomena represent unusual events, peculiar to the time and place in which they occur, that they indicate abnormal amounts of etiologic factors, and as stated in chapter i, provide an unusual opportunity to identify these factors. The controlled studies within leukemia cluster sites also produced results generally in agreement with those of other investigators. Such factors as histories of unusual exposure to radiation, increased familial tendencies, congenital defects and fetal wastage, and histories of lymphatic tissue surgery (tonsillectomies and appendectomies) have been well documented (1, 19, 27, 29, 81). They provide starting points for more specific and sensitive studies.

In addition, unusual occurrences, seldom reported in studies of leukemia, have been observed. An unusual familial incidence of leukemia was noted in one community studied (136). The rare occurrence of monocytic leukemia in a man and his wife was noted. One additional finding observed in the study involved several cases of leukemia and other malignancies associated with a single wood-frame residence in southwestern Oklahoma. Miami, in Ottawa County, a cluster community, experienced a truly unusual incidence and mortality during the past several years, wherein several of the cases studied have surviving relatives with a broad spectrum of hematologic disorders, ranging from chronic, unexplained anemia to chronic relative lymphocytoses. These phenomena constitute complete studies in themselves and merit further study and discussion. They are excellent examples of the manner in which descriptive epidemiology can identify specific problems for further, more detailed examination.

Since the clustering phenomenon was first described (66) workers have pondered concerning the differences in conditions that might exist between these cluster communities and other communities, in addition to their leukemia experience. This study has indicated that such differences may in fact exist, namely that cluster areas experience not only a greater number of leukemias per unit population, but that an unusual proportion of

these cases are acute leukemias, occurring in younger persons. One interpretation of this finding is that the leukemia excess observed in cluster communities may be due almost entirely to acute leukemia, and thus suggests a high level of one or more etiologic determinants specific for the acute form of the disease. It may also be hypothesized that a high level of a non-specific leukemogen would tend to shift newly occurring cases toward the acute end of the severity spectrum, while at the same time producing an excess of acute or chronic leukemia that would otherwise not have occurred.

A number of investigators (95, 116, 121) have discussed the possible role of viruses in the etiology of leukemia. Others (3, 70) have noted the greater severity of many viral infections when initial exposure to the virus is postponed until later in life. Poliomyelitis is one example of a viral disease that is more severe with increasing age. Prior to the advent of polio vaccine the disease tended to occur in the paralytic form more often in upper-middle class communities where exposure to the polio virus may be delayed by modern sanitation measures until an older age. Acute leukemia is also more common among the upper-middle class (27), and a viral agent has long been suspect though not yet proven. If infection with a "leukemia virus" is delayed past the age when infection "generally" occurs, and an unusually severe

infection results, it is interesting to speculate as to what would be expected to occur in populations where exposure to the "virus" has been delayed by modern sanitation or other factors, resulting in perhaps large numbers of susceptible persons for later, potentially more severe, infection. Under these circumstances, clusters or "epidemics" of acute leukemia might occur when the virus is introduced. Variation in the latent period of the disease, unknown factors relating to host resistance and environment, and even the high mobility of modern society might make such outbreaks rarely observed phenomena.

A relatively large number of "cluster" areas have been described in the literature (29, 36, 45, 54, 64, 65, 66, 80, 85, 139). Though techniques for statistical evaluation of these phenomena are yet in their infancy, and though seroepidemiology has not contributed greatly to their understanding, sophistication of these and other tools can be expected to yield more sensitive appraisals of such time-space aggregations, and thus contribute considerably to the understanding of the disease. Greater insight into factors now felt to be important in the development of leukemia may make possible the selection of high-risk cohorts to be followed in longitudinal studies. Much information regarding essential sequences of events in the development of chronic and acute neoplastic disorders await such study methods.

In 1968 Assal (144) described the geographic and secular clustering of malignant disease mortality in Oklahoma, 1956-1965. He examined malignancies involving thirty-four sites. Among his observations were that leukemia is one of three malignancies accounting for increased mortality from cancer since 1930, and that leukemia mortality rates show considerable variability from county to county.

Mortality rates for leukemia in the United States averaged 7.1 per 100,000 population during the 1961-1965 period (138). No apparent yearly trend is observable in these rates although U.S. leukemia mortality rates have increased steadily since the early 1920's (52). In chapter iii it was mentioned that leukemia mortality rates in Oklahoma exceeded those of the U.S., and that was a pronounced increase in Oklahoma rates from 1961-1965. A review of Figure 1 shows this. The significance of the U.S.-Oklahoma difference is questionable since it could have resulted from the innate random variability in mortality patterns. The increase in Oklahoma mortality rates from 1961 to 1965 may also be due to random variability in mortality, although the further separation of the United States and Oklahoma curves in 1964 and 1965 may suggest the presence of additional factors.

Acute leukemia is the most common form of leukemia (44, 52). Figures 2 and 8 indicate that acute leukemia

was the most predominant form encountered in this study. A comparison of these two figures also reveals that each incidence peak is followed the next year by a mortality peak. The short average survival time of acute leukemia produces this pattern. Acute leukemia tends to be a disease of the extremes of life. Figures 5 and 11 show a definite bimodality in mortality and incidence. This distribution is classical for acute leukemia (44). It has been interpreted as meaning that acute leukemia in childhood may not be the same disease as that seen in adults. Others have suggested that the same initiating factors may be acting in both groups, but that environmental or certain host factors may be responsible for the differences in the age of expression of the disease (27). The age distribution of leukemia cases has also been correlated with changes in immunological competence that apparently occur with age (102). Specifically, it is hypothesized that immunological competence, or the ability of the body to recognize foreign or defective tissues or cells, decreases with age, allowing aberrant cell growths that were retarded before, to grow, i.e., the "forbidden clone" hyphothesis (116). Some feel that a similar alteration (inherent or induced) in immunological competence might occur in childhood, thereby initiating or predisposing to the leukemic process (17). Though the data presented are consistent with many "theories"

regarding the etiology of the disease, recent work in tumor immunology makes this an increasingly attractive one (113, 118).

A review of Figures 5 and 11 reveals an interesting difference in mortality and incidence from acute leukemia in the under five age group. At most points these two curves are very similar; however, in the under five age group mortality is considerably less than incidence. This could be interpreted in several ways. The possibilities range from under-reporting of acute leukemia deaths in this age group to greater survival experience in this age group.

Chronic leukemia shows unexpected variability within the mortality data and also within the incidence data. As mentioned in chapter iii, chronic lymphocytic leukemia and chronic myelocytic leukemia are usually observed in a rather constant ratio (119). Figure 2 shows anything but a constant relationship between these two types of leukemia. A similar pattern is seen in the incidence data in Figure 8. A poor correlation between incidence and mortality trends is not surprising considering the average time of survival in chronic leukemias, which is usually measured in years rather than in months as with acute leukemia.

The age distribution of cases included in the mortality and incidence segments of this study are consistent

with observed U.S. figures (44). Leukemia risk is great in the young, and decreases with increasing age until the forties where risk begins increasing with age. Leukemia risk is greatest in the eldest. This finding has been interpreted as being consistent with the "cumulative" radiation leukemogenesis hypothesis (14, 19, 28). Fraumeni (47) has observed in U.S. mortality statistics that a mortality peak has recently developed in three- and four-year-old whites, but not in non-whites, suggesting a possible delay in the exposure of non-whites to some environmental leukemogen. The same peak can be observed in Oklahoma mortality data, although involving numbers insufficient to warrant further comment.

In several instances in chapter iii it was observed that mortality and incidence curves often had a tendency to decrease in the 75 and older age group whereas the trend had been steep increases with increasing age prior to that point. This could result from increasing mortality from other causes, or might be the effect of under-reporting that results when older persons with long-standing leukemia die from other causes.

It has been well documented that definite sex and race differences exist with regard to leukemia (1, 44, 46, 69). Figures 6 and 12 in chapter iii show that both leukemia mortality and incidence show great sex and race differences. The white male is at greatest risk of

leukemia throughout life (44). White females, non-white males, and non-white females follow in that order. These differences have led some to believe that non-whites, particularly females, may possess some protective mechanism (46). Conversely it has been suggested that white males may encounter greater exposure to environmental factors of leukemogenic potential than either white females or non-white males or females, and at the same time have access to superior diagnostic facilities than non-whites in general (131). Differences in non-white males and non-white females may also be due to similar environmental differences that white males and females experience. The difference in whites and non-whites has been interpreted as a delayed exposure of the non-white population to some environmental leukemogen (119). Supervening death by race-specific causes and differences in accessibility to diagnostic facilities might tend to affect leukemia incidence in the same manner.

Figure 7 in chapter iii shows the comparison of leukemia incidence and mortality. Because of the comprehensive registration of leukemia deaths, mortality is a very accurate estimate of the number of cases occurring. Incidence data are desirable however since they are relatively free of the distortion resulting from the variable length of case survivals. Incidence measured by study of hospital records is 75.5% of registered mortality for the

same period. Comparison of Figures 5 and 7 shows that mortality and incidence from acute leukemia are almost identical, chronic myelocytic is also very close, but chronic lymphocytic leukemia is underestimated. Though the study of medical records does involve some loss of case coverage, takes more time and is more costly, the ability of this method to pinpoint spatial and temporal aggregation clearly justifies its use on a selective basis. The accuracy and timeliness of the data so obtained is required for more refined studies of time-space clustering.

Figure 7 shows that leukemia incidence was sharply decreased in 1962. The reasons for this decrease are not clear. Figure 8 shows substantial decreases occurring in chronic myelocytic leukemia in 1962, along with lesser decreases in acute leukemia, and other kinds of leukemia. Figure 2, however, shows increases in 1962 over 1961 in acute leukemia and in chronic lymphocytic and chronic myelocytic leukemia mortality. Most of the decrease is clearly in chronic myelocytic leukemia; however, there is no explanation for this.

Heath and Hasterlik (66) were among the first to document that leukemia cases cluster in time and space. They suggested that such clustering might indicate unusual distribution of some etiologic factor, providing a unique opportunity to identify that factor. The present study

has compared "cluster areas" with non-cluster areas for differences other than their leukemia experience, for differences in leukemia cases between them, and for differences between leukemia cases and matched controls within the cluster areas.

Three counties in Oklahoma were defined as "cluster counties" by arbitrarily established criteria (chapter ii). These three counties (Kay, Stephens, and Ottawa) experienced 54 new cases of leukemia from 1961-1965. Thirty-nine of these 54 (72.2%) were interviewed and case profiles were constructed for purposes of the comparison presented in chapter iii. Interviews could not be obtained in 15 cases. Each of the 39 cases was matched by age, race, and sex, with a control residing in the same community.

Three "control" counties were also selected, each one matching in size, population, location, and general socioeconomic and ecological characteristics, one of the three cluster counties. Rogers, Carter, and Washington Counties were chosen. These control counties experienced 30 cases of leukemia from 1961 to 1965. Interviews were obtained in 24 of the 30 (80.0%) and case profiles were constructed.

Kay County experienced an unusual aggregation of cases in the county seat, Ponca City. As observed in chapter iii this city is bordered on the south and

southwest by extensive petroleum refining facilities of two oil companies. The effluent of these facilities is carried into the neighboring residential areas in warm weather when winds are southerly, and away from the city when winds are northerly. The exact relationship of this effluent to the unusual leukemia incidence in the adjacent residential area is unknown but interesting. It is well documented that certain aromatic hydrocarbons are associated with the development of leukemia in man (32, 124, 128). It is interesting to speculate as to the exact relationship, if any, between the chronic exposure to the effluent in this community and the unique distribution of leukemia cases.

An additional observation of interest regarding the Stephens County cluster is the development of a case of lymphoma in a pet, a Siamese cat, in the home of one of the childhood cases, shortly after the death of the child. This cat gave birth to a litter of kittens shortly before death, all of which (except one) have since developed lymphomas and died. The one surviving animal is in the possession of the Oklahoma State University College of Veterinary Medicine, where the entire litter was taken after the death of the mother. Studies of these animals are still in progress but have not yielded relevant information concerning the possible relationship of hematopoietic disorders in man and animals.

Ottawa County experienced an unusual leukemia incidence from 1961 to 1965. In addition to this, hematologic disorders have been confirmed in close relatives (and one physician) of five of the deceased cases. These include two cases of unexplained, relatively severe anemias in first degree relatives, a single case of an unexplained relative and absolute lymphocytosis in the physician who treated several of the leukemia cases, one case of suspected leukemia in a first degree relative with prolonged household case exposure, and one case of an adolescent girl with persistent lymph node enlargement and fever during the course and after the death of a sib. None of these cases has developed leukemia as far as is known.

The comparison of cluster and control areas have shown some interesting differences. The mean age difference mentioned in chapter iii, along with the difference in the proportion of acute leukemias is an interesting observation. A difference also exists in the proportion of chronic myelocytic leukemia although the latter numbers are rather small.

The Profile summaries (Table 9) of cases and controls in the respective cluster and control counties show a number of interesting differences. These differences, though, should be cautiously interpreted because of the small numbers involved. The difference in the number of

cases and controls with histories of major surgery may indicate the tendency to infection that often precedes leukemia for months or years before the disease is diagnosed (Table 9). Most of the surgeries are appendectomies and tonsillectomies. These same findings have been interpreted by others as indicative that lymphoid tissues, e.g., tonsils and appendix, may play a role in defending the body against malignancies (113).

An interesting difference was observed between cases and controls in cluster areas regarding exposure to radiation. The association between ionizing radiation and acute and chronic myelocytic leukemia is well documented (14, 19, 24, 28, 51, 56, 60, 74, 78, 81, 95, 122, 125, 137). Radiation exposure is not associated with chronic lymphocytic leukemia (56, 74). An examination of Table 11 shows that of the seven cases of leukemia in cluster counties reporting a history of radiation exposure, six are acute leukemias, lending greater significance to the differences observed between the cases and controls in this instance.

The difference in reported fetal wastage, between cluster cases and their controls, noted in Table 9 has been documented by others (51). The percentages given are based upon small numbers, however the same difference is observed between leukemia cases and their controls in control counties.

Leukemia patients report exposure to ill household pets more often than controls (51). Table 9 supports this finding both in differences in cluster counties and in control counties.

In control counties exposure to toxic chemicals, a history of malignancy other than leukemia, and a history of fetal wastage are more common in cases than in controls.

Malignancies other than leukemia were more often reported by leukemia cases in control counties than by leukemia cases in cluster counties. This may be related to the difference in mean age observed between the two groups, in that older persons would be expected to have second malignancies more frequently than younger persons since frequency of malignancies increases with age.

Because of the difference observed in the mean ages and the increased proportion of acute leukemia in cluster versus control counties, cases within cluster and control areas were examined with regard to type of leukemia. Table 10 shows that most of the difference observed between mean ages in cluster county cases and control county cases was due to acute leukemia, as a striking difference is observed in mean age of acute leukemia cases in cluster counties and acute leukemia in control counties. As mentioned in chapter iii acute leukemias in cluster counties reported more major surgery, persistent

infections, fetal wastage, and exposure to ill pets. It is interesting to note that no such differences are observed between acute and chronic leukemias in control counties.

The information contained in Tables 8 and 11 indicates that leukemia cases occurring in clusters tend to differ from cases occurring outside clusters, in that a significantly greater proportion of cases in the former are acute. Furthermore, acute leukemia in cluster areas tends to occur in significantly younger persons than acute leukemia in non-cluster areas. This evidence may lend itself to several interpretations, one of which is that leukemia occurring in clusters tends to be basically "different" than leukemia occurring outside clusters, suggesting that environmental or other factors of etiologic consideration may also be different.

Although this study has revealed interesting differences in cases from one area to another, it has been unable to identify any environmental factors which might be associated with these differences. If such differences do exist, they might be difficult to measure. Supposing a viral etiology in acute leukemia, the immunity of the population to the infectious agent might vary greatly from place to place. Such information would have to come from a population survey of immune status. Perhaps work with the EB virus will lead to such capability (38 40).

Environmental factors of known leukemogenic potential, e.g., radiation, would be relatively easy to measure, but information concerning the levels of such factors in the past would generally not be available. Routine radiation surveillance is not presently of sufficient scope to facilitate such study.

A comprehensive environmental appraisal of leukemia cluster areas, and a comparison of these with non-cluster areas, could shed additional light on the cluster phenomenon and perhaps provide important clues to the etiology of human leukemia.

CHAPTER V

S U M M A R Y

A study was undertaken to determine mortality and incidence from leukemia in Oklahoma from 1961 through 1965, to describe salient epidemiologic features of the disease, to determine whether or not spatial-temporal clustering of cases occurred, and then to compare the leukemia experience of cluster and matched control areas.

Leukemia mortality data summarized from death registration certificates filed with the Oklahoma State Department of Health, for all leukemia deaths from 1961 through 1965, were obtained. In addition, leukemia incidence data were secured by examination of the hospital records of all persons hospitalized with leukemia in all fifty-two accredited hospitals in Oklahoma from 1961 to 1965.

These two sources of information were analyzed by age, race, sex, type of leukemia, date of onset (or death) and place of residence at onset (or death). Mortality and incidence rates were computed for each county, for each multi-county Hill-Burton region, and for the state, for

each year and for the five-year 1961-1965 period.

The age, race, and sex composition of the leukemia population was within expected ranges, with the disease demonstrating a characteristic bimodal age distribution with a peak in the very young and a second higher peak in the elderly. White males had the highest race-sex specific incidence and mortality rates. White females were second, non-white males third, and non-white females fourth.

The types of leukemia observed were essentially identical in the mortality and incidence data with the exception of an apparent underestimation of chronic lymphocytic leukemia incidence. Acute leukemia was the most common type observed in both mortality and incidence data. The proportion of acute leukemia decreased with age while chronic leukemia proportions (lymphocytic and myelocytic) increased.

The geographic distribution of leukemia incidence and mortality did not show significant differences in any of the Hill-Burton regions. The ten regions contributed almost equally to the net increase in Oklahoma leukemia mortality from 1961 through 1965. However, three Oklahoma counties experienced sufficient leukemia incidence and/or mortality to meet arbitrarily defined requirements for "leukemia cluster areas."

The three cluster counties were matched with three neighboring control counties of approximately equal size

and population, and with essentially normal leukemia experience. Leukemia cases within cluster counties were pooled as were those in the control counties, to facilitate comparisons of the two groups of leukemia cases. In addition, age-, race-, and sex-matched control subjects were selected for all leukemia cases in cluster and control counties.

Descriptive profiles were constructed for all subjects (cases and controls) consisting of information obtained in a personal interview with either the subject or a surviving relative. This information related to past medical history, family history, and exposure to known or suspected leukemogenic agents. The descriptive profiles of leukemia cases were then compared with those of their non-leukemic controls in cluster counties, and with those of leukemia cases in control counties.

These profile comparisons revealed some interesting differences. For example, a mean age of 39.7 years was observed in leukemia cases in cluster counties, whereas the mean age for cases in control counties was 62.3 years, reflecting a higher proportion of acute leukemia in younger persons that was observed in the cluster counties. Significantly more leukemia cases in cluster counties than their non-leukemic controls reported (1) histories of major surgery, (2) familial histories of fetal wastage, and (3) histories of exposure to ill household pets. A single significant difference was noted between cluster

county leukemia cases and control county leukemia cases (excepting the mean age difference mentioned above), and this was the more frequently reported history of second malignancies in control county cases.

These findings are thought to indicate that basic differences in leukemias in cluster versus control counties may exist, and that these differences may be related to identifiable environmental or host factors which predispose to leukemia in man.

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APPENDICES

APPENDIX A

(1-2) STATE

(3-6) NCDC #

MEDICAL RECORD. This form contains medical information the disclosure or release of which is restricted by 5 U.S.C. 552, (b) (6); 45 CFR Part 5.

LEUKEMIA – LYMPHOMA CASE RECORD

1. PATIENT'S NAME *first, middle, (7-13) LAST*

2. RESIDENCE *number and street*

(14-17) City | (18-20) County | (21-30) Address Coordinates *(NCDC Use Only)* (21-24) (25-27) (28-30)

3. (31) RACE
☐1 White ☐2 Negro ☐9 Not stated
Other, specify _____

4. (32) SEX
☐1 Male ☐2 Female ☐9 Not stated

5. (33-34) AGE AT DIAGNOSIS

6. DATE OF:
(35-38) Birth _____ mo. day yr.
(39-42) Onset _____ mo. yr.
(43-46) Diagnosis _____ mo. day yr.
(47-50) Death _____ mo. day yr.

7. NCDC USE

(51-52) o-dx	(53-54) o-d	(55-56) dx-d

8. (57) GENERAL DIAGNOSIS
☐1 Leukemia ☐2 Lymphoma
☐3 Leukemia & lymphoma
☐4 Other, specify _____

9. (58) TYPE OF LEUKEMIA
☐1 Acute ☐4 Subacute
☐2 Chronic ☐9 Not stated
☐3 Other, specify _____

10. (59) LEUKEMIC CELL TYPE

11. (60) TYPE OF LYMPHOMA
☐1 Hodgkin's ☐5 Multiple myeloma
☐2 Lymphosarcoma ☐9 Not stated
☐3 Reticulum cell sarcoma
☐4 Other, specify _____

12. (61) UNUSUAL FEATURES (See instructions)

13. (77-80) LLCS

Name of physician _____ Name of hospital _____

Address _____ Hospital # _____

Date of report _____ Death certificate # _____

WORK SHEET - DEVELOPMENTAL

APPENDIX A

Occupation _____ Home phone _____

Next of kin or
close contact _____

Present illness as recorded on: _____
mo. day yr.

Past history

Family history

Physical findings

spleen _____

liver _____

nodes _____

bruises _____

CBC: _____
mo. day yr.

Hct _____

Hgb _____

Plt _____

WBC _____

seg _____

band _____

lymph _____

mono _____

Marrow: _____
mo. day yr.

Biopsy

Autopsy

Comments:

Reviewed by _____ Date _____

WORK SHEET - DEVELOPMENTAL (BACK)

APPENDIX B

CLINICAL RECORD. This form contains clinical information, the disclosure or release of which is restricted by 5 U.S.C. 552, (b) (6); 45 CFR Part 5; and 42 CFR Part 1.

LEUKEMIA – LYMPHOMA
CASE INVESTIGATION

DATE OF INTERVIEW	
NAME OF INTERVIEWER	

NAME OF PATIENT		RACE	SEX
ADDRESS AT ONSET		DATE OF BIRTH	
		DATE OF ONSET	
PERSON INTERVIEWED (NAME AND ADDRESS)	RELATIONSHIP	DATE OF DIAGNOSIS	
	PHONE	DATE OF DEATH	
PRESENT ILLNESS			

MEDICAL HISTORY

MAJOR ILLNESSES, OPERATIONS		TOXINS, DRUGS
PERINATAL PLACE OF BIRTH RESIDENCE AT BIRTH		IMMUNIZATIONS
CONGENITAL DEFECTS	X-RAYS	INFECTIONS
		ALLERGIES

APPENDIX B

FAMILY HISTORY

NAME	SEX	AGE	BIRTH DATE	DEATH DATE	HEALTH
PARENTS					
SIBS					
SPOUSE					
CHILDREN					
FETAL DEATHS	OTHER (ESPECIALLY CANCER, LEUKEMIA, AND CONGENITAL DEFECTS)				
MULTIPLE BIRTHS					

ENVIRONMENTAL HISTORY

HOUSEHOLD AT ONSET			HOUSE AT ONSET
NAME	REL	OCCUPATION OR SCHOOL / GRADE	
PATIENT	–		

PAST RESIDENCE			SOCIAL CONTACTS
ADDRESS	FROM	TO	
			ANIMALS

PARENTS' BIRTHPLACE:	CHURCH ATTENDED:	TRAVEL
MOTHER FATHER		

APPENDIX C

DESCRIPTION OF TEN HILL-BURTON REGIONS

Region I is located in northeastern Oklahoma and consists of nine counties--Craig, Creek, Delaware, Mayes, Okfuskee, Okmulgee, Ottawa, Rogers and Tulsa--covering 6,216 square miles. The 1960 population of the region was 533,673 with 73.2% residing in urban areas. The area population is 10.3% non-white which includes 55,500 negroes and 17,500 American Indians. The ratio of licensed physicians to general population is 1:733; and of medical doctors to general population, the ratio is 1:1,321. Approximately 38% of the population is between 1 and 19 years of age, 52% between 20 and 64, and 10% is 65 or older. Median years of school completed by person 25 and older is 11.0. Approximately 21% had less than eight years of schooling, and 9% had four or more years of college. There are 141,493 families in the region. The median annual family income is $5,251 with 35,160 families having annual incomes of less than $3,000 and 32,391 having incomes in excess of $8,000 per year.

Region II is located in east central Oklahoma and consists of six counties--Adair, Cherokee, McIntosh, Muskogee, Sequoyah and Wagoner--covering 4,173 square miles. The 1960 population was 138,785, with 60.9% residing in rural areas. The population is 20.4% non-white which includes 20,937 negroes and 11,389 American Indians. The ratio of licensed physicians to general population is 1:971; and of medical doctors to general population, the ratio is 1:1,309. Approximately 40% of the population falls in ages 1 through 19, 47% in ages 20 through 64, and 13% is 65 and over. Median years of school completed by persons 25 and over is 8.7, 15.7% had less than 5 years of schooling, and 5.8% had four or more years of college. There are 35,515 families in the region. Median family income is $3,068 annually, with 17,461 families having incomes of less than $3,000 per year and 3,526 having annual incomes in excess of $8,000.

Region III is located in southeastern Oklahoma and consists of seven counties--Choctaw, Haskell, Latimer, LeFlore, McCurtain, Pittsburg, and Pushmataha--covering 8,346 square miles. The 1960 population was 130,901 with 73.3% residing in rural areas. The population is 13.6% non-white which includes 13,388 negroes and 6,270 American Indians. The ratio of licensed physicians to general population is 1:1,309; and of medical doctors to population, the ratio is 1:1,870. Approximately 38% of the population

is between 1 and 19 years of age, 47.7% is 20 through 64, and 14.5% is 65 and over. The population 25 years of age and older has 8.4 median years of schooling, 18.9% has less than five years, and 4.4% has completed four or more years of college. The 33,972 families in the region have a median income of $2,601. Of these, 19,428 have annual incomes of less than $3,000, and 2,353 have annual incomes of $8,000 or more.

Region IV is located in the southeast-central part of Oklahoma and is comprised of six counties--Atoka, Coal, Hughes, Johnston, Pontotoc, and Seminole--covering 4,312 square miles. The 1960 population was 95,714 with 57.8% residing in rural areas. The population is 12.1 non-white, which includes 7,045 negroes and 6,126 Indians. The ratio of licensed physicians to general population is 1:1,100; and of medical doctors, the ratio is 1:1,490. Approximately 37% of the population is between 1 and 19 years of age, 49.9% is between 20 and 64, and 13.9% is 65 and over. The population 25 years of age and over has 8.7 median years of schooling. Only 15.3% have less than 5 years of schooling, and 5.4% have four or more years of college. The 25,940 families in the region have a median income of $3,060. Of these, 12,199 have annual incomes of less than $3,000, while 2,572 have $8,000 or more yearly income.

Region V is located in south-central Oklahoma and consists of six counties--Bryan, Carter, Garvin, Love,

Marshall, and Murray--covering 3,810 square miles. The 1960 population was 115,333, with approximately 52.3% residing in rural areas. The population is 6.9% non-white, which includes 7,281 negroes and 2,204 Indians. The ratio of licensed physicians to general population is 1:1,031; and of medical doctors to general population, the ratio is 1:1,480. Approximately 37% of the population falls in the 1 through 19 year group, 49.9% is 20 through 64, and 13.3% is 65 and over. The median years of schooling for the population 25 years of age and older is 9.1. Only 12.2% of the population have less than five years of schooling, and 5.6% have four or more years of college. The 31,207 families in the region have a median annual income of $3,721. Of these, 12,906 have an annual income of less than $3,000, and 3,534 have incomes of more than $8,000 per year.

Region VI is located in southwestern Oklahoma and consists of seven counties--Caddo, Comanche, Cotton, Harmon, Jefferson, Jackson and Stephens--covering 6,813 square miles. The 1960 population was 223,879, with approximately 56% residing in urban communities. The population is 9.4% non-white which includes 21,500 negroes and 7,500 Indians. The ratio of licensed physicians to the general population is 1:1,420; and of medical doctors to the general population, the ratio is 1:1,829. Approximately 39% of the population falls in ages 1 through 19

years, 52% in ages 20 through 64, and 9% is 65 and older. The median school years completed by persons 25 and over is 10.6 years. Only 7.6% have less than five years schooling, and 6.5% have four or more years of college. The 56,075 families of this region have a median income of $4,221 annually, with 18,341 having annual incomes of less than $3,000, and 7,323 having incomes of $8,000 or more a year.

Region VII is located in the west-central part of Oklahoma and consists of Beckham, Blaine, Custer, Dewey, Greer, Kiowa, Roger Mills, and Washita Counties, covering 7,587 square miles. The 1960 population was 103,863, with 60.4% residing in rural communities. The population is 2.7% non-white which is made up of 4,438 negroes and 3,291 Indians. The ratio of licensed physicians to general population is 1:1,125; and of medical doctors to population, the ratio is 1:1,533. Approximately 36% of the population is age 1 through 19, 51.1% is 20 through 64, and 13.4% is 65 and over. Median school years of education for the population of 25 years of age and over is 9.8. Only 7.2% had less than five years schooling, and 5.1% had four or more years of college. Of the 28,326 families in the region, the median annual income is $3,789, with 10,686 families having an annual income of less than $3,000, and 3,731 having annual incomes of $8,000 or more.

Region VIII is located in northwestern Oklahoma and consists of eleven counties--Alfalfa, Beaver, Cimarron, Ellis, Garfield, Grant, Harper, Major, Texas, Woods, and Woodward--covering 14,251 square miles. The 1960 population was 140,238, with 58.2% residing in rural areas. The population is 1.5% non-white which consists of 2,300 negroes and 400 American Indians. The ratio of licensed physicians to general population is 1:801; and of medical doctors, is 1:1,240. Approximately 36% of the population falls in ages 1 through 19, 51.8% is 20 through 64, and 12.3% is 65 and over. The median school years completed by those 25 and over is 10.8, whereas 5.5% had less than 5 years of schooling, and 6.9% had four or more years of college. The 37,776 families of the area earn a median annual income of $4,739, with 10,286 families having annual incomes of less than $3,000, and 6,596 families having incomes of $8,000 or more.

Region IX is located in north-central Oklahoma and consists of seven counties--Kay, Noble, Nowata, Osage, Pawnee, Payne, and Washington--covering 6,266 square miles. The 1960 population was 202,169, with 62.7% residing in urban communities. The population is 5.3% non-white which consists of 5,000 negroes and 5,600 American Indians. The ratio of licensed physicians to general population is 1:899; and of medical doctors to general population, the ratio is 1:1,321. Approximately 38% of

the population is ages 1 through 19, 51.7% is 20 through 64, and 10.8% is 65 and older. The population of 25 years and over has completed a median of school years of 11.0, whereas 6.0% has less than five years of schooling, and 10.3% has four or more years of college. The 53,549 families in the region earn a median annual income of $5,072, with 12,914 families having annual incomes of less than $3,000, and 10,791 having annual incomes of $8,000 or more.

Region X is located in central Oklahoma and consists of nine counties--Canadian, Cleveland, Grady, Kingfisher, Lincoln, McClain, Oklahoma, and Pottawatomie--covering 7,203 square miles. The 1960 population was 643,729, with 84% residing in urban areas. The population is 9.2% non-white which consists of 79,500 negroes and 13,000 American Indians. The ratio of licensed physicians to general population is 1:543; and of medical doctors to general population, the ratio is 1:673. Approximately 38% of the population falls in ages 1 through 19, 52.8% is 20 through 64, and 9.2% is 65 and over. The median school years completed by persons 25 years of age and older is 11.4, whereas 6% have less than 5 years of schooling, and 9.6% have four or more years of college. The 168,857 families in the region earn an annual median income of $5,285, with 38,443 families having annual incomes of less than $3,000, and 38,035 having annual incomes of $8,000 or more.

APPENDIX C--Continued

DESCRIPTION OF TEN HILL-BURTON REGIONS

Region	Location	Area (Sq. miles)	1960 Population	% Non-white	% Rural	Physician Ratio	Median Years School	Median Family Income
I	Northeast	6,216	533,673	10.3	26.8	1:733	11.0	$ 5251
II	East-Central	4,173	138,785	20.4	60.9	1:971	8.7	3068
III	Southeast	8,346	130,901	13.6	73.3	1:1309	8.4	2601
IV	Southeast-Central	4,312	95,714	12.1	57.8	1:1100	8.7	3060
V	South-Central	3,810	115,333	6.9	52.3	1:1031	9.1	3721
VI	Southwest	6,813	223,879	9.4	44.0	1:1420	10.6	4221
VII	West-Central	7,587	103,863	2.7	60.4	1:1125	9.8	3789
VIII	Northwest	14,251	140,238	1.5	58.2	1:801	10.8	4739
IX	North-Central	6,266	202,169	5.3	37.3	1:899	11.0	5072
X	Central	7,203	643,729	9.2	16.0	1:543	11.4	5285

APPENDIX D

DESCRIPTIONS OF CLUSTER AND CONTROL COUNTIES

Kay County is located in northern Oklahoma approximately 100 miles north of Oklahoma City. The county has an area of 944 square miles and had a 1960 population of 51,042 (1965 estimate: 52,020), 48,588 of which were white, and 2,484 non-white. The median age of the white population was 34.6 years, and that of the non-white was 21.9 years. The two major population centers of the county are Ponca City, with 24,000 residents, and Blackwell with 9,580. Remaining population is distributed between several smaller communities and the rural areas of the county. The economy of the area is strongly dependent upon two large oil companies having refining facilities near Ponca City. Agriculture and small private business essentially comprise the remaining economy.

According to the Oklahoma Geological Survey, Kay County lies entirely within a major area of oil and gas production. The county is characterized by surface rock strata of the Quaternary and Lower Permian, the latter

lying principally along streams. The topography is described as essentially Central Red-bed Plains in the western two-thirds of the county and Northern Limestone Cuesta plains in the eastern third. The area is not characterized by significant mineral deposits, exclusive of fuels. Small deposits of limestone and dolomite are located near Ponca City. None of these features are known to be associated with increased levels of background radioactivity or other items of carcinogenic potential. Vegetation is primarily tall grass, prairie type with Black Jack forest along rivers.

There are two accredited hospitals in Kay County, one in Ponca City and one in Blackwell, as well as a number of nonaccredited hospitals. As of January, 1966, there were 44 practicing physicians in the county, 5 of whom were in practice outside of the two major population centers. A health department employing a full-time director is in existence.

Washington County is located in northern Oklahoma, about 150 miles north of Oklahoma City. The county has an area of 425 square miles and had a 1960 population of 42,348 (1965 estimate: 43,033), 40,348 of which were white, and 2,000 non-white. The median age of the white population was 29.9 years and that of the non-white population was 26.7 years. The one major population center of the county is Bartlesville, a city of 30,000. The

remainder of the population is fairly uniformly distributed among several small communities and the surrounding rural area. The economy of the area is quite dependent upon the petroleum industry, although there are no large refineries in the immediate area. There is a large cement plant and a zinc smelter in the Bartlesville area. The economy is also supported by agricultural activity.

Vegetation in the western half of the county is Post Oak-Black Jack forest; in the eastern half it is tall grass, prairie type. The county lies entirely within a major oil and gas producing area. It is characterized by surface rock strata of the Upper Pennsylvanian. The topography is described principally as Claremore Cuesta Plains, with eastern Sandstone Cuesta Plains in the extreme west. The area is not characterized by great mineral deposits, excepting fuels. A belt of limestone and dolomite crosses the county running from southwest to northeast near Bartlesville. None of these geological features is thought to be associated with elevated background radioactivity or other items of carcinogenic potential.

There are two accredited hospitals in the county, both located in Bartlesville. There are a small number of nonaccredited facilities. In January, 1966, there were 51 physicians in practice in the county, 3 practicing outside of Bartlesville. There was no health department in

existence in Washington County.

Ottawa County is located in extreme northeast Oklahoma, 190 miles from Oklahoma City. The county has an area of 461 square miles and had a 1960 population of 28,301 (1965 estimate: 30,901), consisting of 27,079 whites and 1,222 non-whites. The median age of the white population was 32.6 years and that of the non-white, 27.4 years. Miami, a city of 12,869, is the major population center. The remaining population resides in a number of small communities and the surrounding rural areas. The economy of the county is dependent upon extensive mining and ore processing operations, and upon agriculture.

Ottawa County is characterized by vegetation of the tall grass, prairie type, with the eastern third predominated by oak-hickory forest type. The county is characterized by rock strata of the Mississippian and Middle Pennsylvanian. The topography is described mostly as Neosho Lowland, with a small area of Ozark Plateau in the southeastern part. The area is characterized by extensive deposits of limestone and dolomite, but is not underlain by fossil fuels. There are extensive deposits of lead and zinc in the northern third of the county. Certain of these features, namely the metallic deposits, have been associated with excessive mortality from

malignant diseases; but they have seldom been found to be associated with increased levels of radioactivity.

One accredited hospital in Miami, and a few small, nonaccredited hospitals serve this county. In 1966 there were 14 physicians in practice in the county, three of whom were located outside of Miami. The county has a local health department in full-time operation.

Rogers County is located in northeast Oklahoma about 125 miles northeast of Oklahoma City. The county has an area of 732 square miles and had a 1960 population of 20,614 (1965 estimate: 21,682), 19,398 of whom were white, and 1,216 non-white. The median age of the white population was 30.8 years, and that of the non-white population was 26.9 years. The one major population center is Claremore, a city of 6,639. The remainder of the population is essentially rural or semi-rural. The economy of the area is primarily agricultural with some petroleum and coal mining.

The Oklahoma Geological Survey indicates Rogers County lies almost entirely within a belt of coal and oil that runs north and south in northeastern Oklahoma. The county is characterized by surface rock strata of the Middle Pennsylvanian. A small area of Upper Pennsylvanian is found in the extreme northwest, and an even smaller area of Quaternary is located in the southern section. The topography is described as Claremore Cuesta

Plains, except for the extreme southeast corner which is Neosho Lowland. The area is also characterized by a large vein of limestone and dolomite running from southwest to northeast across the northwestern part of the county. No other mineral deposits, exclusive of fossil fuels, are noted. None of these features are thought to be associated with increased levels of background radioactivity, or other features having carcinogenic potential. Vegetation is the tall grass, prairie type, with belts of Post Oak-Black Jack forest.

There is one accredited hospital in Rogers County, located in Claremore. As of January 1, 1966, there were six physicians in practice in the county; five of these were practicing in Claremore. A health department in full-time operation is located in the county.

Stephens County is located in south-central Oklahoma, about 85 miles south-southwest of Oklahoma City. The county has an area of 890 square miles and had a 1960 population of 37,990 (1965 estimate: 38,401), 36,985 of whom were white, and 1,005 non-white. The median age of the white population was 31.2 years, and the non-white, 23.1 years. The major population center is Duncan, a city of 20,009. The remaining population is distributed throughout the surrounding smaller communities and rural areas. The economy of the area is greatly dependent upon agriculture with supplements from the petroleum industry

and light manufacturing.

Much of Stephens County lies within an area of oil and gas production. The county is characterized by surface rock strata of the Middle and Lower Permian. The topography is described as Central Red-bed Plains, with a small area of Western Sandstone Hills in the extreme northern part of the county. The area is not characterized by significant mineral deposits, exclusive of fuels. None of the above features are known to be associated with increased levels of background radioactivity or other characteristics of carcinogenic potential. Vegetation is half tall grass, prairie type, and half Post Oak-Black Jack forest.

There are two accredited hospitals in Stephens County, both in Duncan. There is also a smaller non-accredited hospital in Duncan. As of January 1, 1965, there were 17 physicians in practice in Stephens County. A full-time health department is in operation in the county.

Carter County is located in southern Oklahoma, immediately adjacent to Stephens County, and about 100 miles south of Oklahoma City. The county has an area of 829 square miles and had a 1960 population of 39,044 (1965 estimate: 38,288), 35,010 white, and 4,034 non-white. The median age of the white population was 33.1 years, the non-white, 25.2 years. The major population center is

Ardmore, a city of 20,184. The remainder of the population is fairly uniformly distributed throughout neighboring small communities and the surrounding rural area. The economy of the area is a combination of agriculture, rock asphalt mining, petroleum, and light manufacturing.

Carter County lies astride a belt of oil and gas bearing strata that extends southeast to the Red River. The county is characterized by surface rock strata of the Lower Permian in the west, Lower Cretaceous in the south and southeast, and a complex of Lower, Middle and Upper Pennsylvanian, Mississippian, Ordovician, Devonian and Silvanian, and Cambrian stretching across the hilly northern part of the county. The topography is described as Central Red-bed Plains in the west, Dissected Coastal Plain in the extreme south and southeast, Ardmore Basin in the east central part of the county, and Arbuckle Hills in the extreme north. The area is not characterized by great mineral deposits, excluding fuels, but does possess a small vein of limestone and dolomite in the south and far north, and some glass sand in the hills in the north. None of these features have been solidly associated with increased levels of radioactivity or other characteristics of carcinogenic potential. Vegetation is two-thirds Post Oak-Black Jack forest and one-third tall grass, prairie type.

There is one accredited hospital in Carter County, located in Ardmore. There are two smaller, as yet

un-accredited, facilities there. As of January 1, 1965, there were 38 physicians in practice in the county; 35 of these were in practice in Ardmore. There is a full-time health department in operation in Carter County.

APPENDIX D--Continued

DESCRIPTIONS OF CLUSTER AND CONTROL COUNTIES

County	Status	Area (Sq. miles)	1960 White Population	1960 Non-white Population	Accredited Hospitals	No. of Physicians	Economy
Kay	Cluster	944	48,588	2484	2	44	Petroleum-Farming
Washington	Control	425	40,348	2000	2	51	Petroleum-Farming
Ottawa	Cluster	461	27,079	1222	1	14	Mining-Farming
Rogers	Control	732	19,398	1216	1	6	Mining-Farming
Stephens	Cluster	890	36,985	1005	2	17	Petroleum-Farming
Carter	Control	829	35,010	4034	1	38	Petroleum-Farming