Epidemiology of Leukemia

By GILCIN F. MEADORS, M.D.

MOST definitions of leukemia incorporate the concept that it is an "invariably fatal systemic disease of unknown etiology primarily involving the blood forming organs . . . characterized by widespread, rapid, and disorderly proliferation of the leukocytes and their precursors and by the presence, almost without exception, at some time during the course of the disease, of immature leukocytes in the blood often in very large numbers" (*1*).

Leukemia is a rare disease, but because of its fatal character it exceeds as a cause of death many of the acute communicable diseases such as diphtheria, smallpox, and poliomyelitis. In 1950, it was the stated cause of 8,845 deaths out of a total of 210,723 deaths from cancer and 1,452,454 deaths from all causes. The unknown nature of its causation, the fact that it occurs most frequently in the acute form in childhood, and its invariably fatal outcome contribute to making leukemia a matter of interest and concern to the layman and a challenge to the scientist, the clinician, and the epidemiologist somewhat out of proportion to its position in the list of causes of death.

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Clinical Characteristics

Leukemia occurs at all ages. It has been reported as present at birth (*2*) or as diagnosed during the neonatal period (*3*), and it has been recorded in one woman who was 102 years old (*4*). It may be fatal in a few weeks, as far as the clinical course is concerned, yet one patient was observed for 29 years with the disease in its chronic form (*5*).

Morphologically, leukemia is classified as myeloid, lymphoid, or monocytic, according to the type of leukocyte or precursor involved. It is further grouped into acute and subacute, or chronic, types, according to the relative frequency of the immature or blast forms appearing in the bone marrow or blood. The percentage of patients with an unclassified cell type of acute leukemia varies from hospital to hospital and ranges from nearly zero to 40 percent or more. Aleukemic forms of the disease, with normal or depressed total leukocyte counts in the circulating blood, have been described for most cell types.

Leukemia is related to other lymphomas, such as lymphosarcoma, which occasionally may first become manifest clinically as leukemia or which may have a transient or terminal leukemic phase (*2*). Leukemia also occurs terminally in 20 to 30 percent of the patients with polycythemia vera. Hemorrhage, anemia,

intercurrent infection and toxemia, and symptoms arising from enlargement of the liver and spleen are characteristic of the clinical disease. The rapidity of development and severity of symptoms, the number and duration of remissions, and the length of survival have classically distinguished the acute from the chronic clinical course. Degree of response to specific chemotherapeutic agents may provide an additional dimension for differentiation of subgroups.

The relative frequency of the acute and the chronic forms in both clinical and autopsy series suggests that the acute form is more common in children and youths, and the chronic form occurs more frequently in older persons. Frequency distributions from these and similar sources cannot be related to the population at risk. The apparent difference in age selection of acute leukemia, in particular, may be of a different order from that currently accepted.

Problems of Classification

As pointed out by Gilliam (*6*), the classification of leukemia in the sixth revision of the International Lists of Diseases and Causes of Death (1948) is probably as detailed as is realistic for routine recording of deaths. It provides for classification of leukemia by cell type, but no distinction is made between the acute and chronic forms of these entities. Until 1910, the International List included all leukemia under the general term of "anemia." From that date Hodgkin's disease was tabulated under "leukemia" until 1921, when the two entities were given separate rubrics. Between 1938 and 1948, the two forms "leukemia" and "aleukemia" were distinguished by the International List but with no indication of cell type or chronicity.

Sacks and Seeman (*7*) explored the sources of error in the reporting of leukemia as a cause of death. They came to the conclusion that the system of diagnosis and of classification, as established by the fifth revision of the International List (1938), led to an understatement of deaths from leukemia, but that joint cause selection had no significant effect. Congenital leukemia is known to be overlooked as a cause of neonatal death (*2*). Other diagnoses, which possibly have been overlooked, are leukemia occurring in elderly patients who have died presumably from other diseases of old age and in patients of all ages who have died of a fulminating infection relating to an undiagnosed acute leukemia. This latter category has probably decreased in importance because of the effectiveness of antibiotic therapy. Beneficial results from the use of cortisone and chemotherapeutic agents in addition to radiation and blood transfusions make it likely that in the future a larger proportion of patients with leukemia, or suspected leukemia, will be hospitalized at some time during the course of their illness. Increased specificity of diagnosis can be expected and should result in more accurate death certification, followed by less underrecording of leukemia as a cause of death.

In his search for clues to the etiology of leukemia, the epidemiologist must almost perforce be dependent on records designed and assembled for other specific purposes. Sources for clues to the epidemiology of leukemia include mortality records, cancer case registers and surveys, clinical and laboratory records, and results of studies of experimental leukemia. The characteristics of leukemia as determined from these sources are at times confusing, if not contradictory, and the question may be raised as to whether "the leukemias" is not a more appropriate term than "leukemia." The acute and chronic forms of leukemia exhibit such wide differences in the clinical course, response to therapy, age selection, and micropathology that they may be considered as different entities, with some manifestations common to both.

Vital and clinical records should not be neglected as sources of leads for more detailed and specific studies despite the problems involved in diagnosis and classification of individual cases of leukemia and questions that may be raised about the adequacy of such records. The trend in mortality from leukemia, as the stated cause of death in the United States registration area, has been reviewed by Sacks and Seeman (*7*), who reported an increase in the crude rate from 19 per 1 million population in 1900 to 37 per 1 million in 1940. Trends in mortality rates from leukemia, according to sex, are shown in figure 1 for 1933–50. This period is used because the United States death

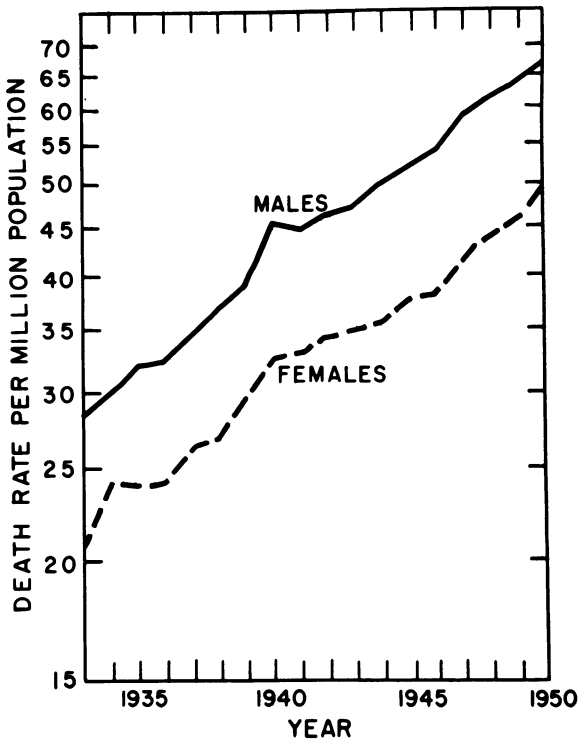
registration area, prior to 1933, did not include all of the States and the District of Columbia. The mortality rate has increased during nearly every one of those 18 years, and the rate of increase has remained nearly constant for the entire period. In 1950, the rate for all males was 67.4 and for females 49.8 per 1 million.

The question as to whether this observed increase is "real," that is, whether the risk of an individual developing leukemia is increasing or whether the risk is only "apparently" increasing, is the subject of considerable discussion. It is agreed that a portion of the increase is apparent and due to the changing composition of the population, with a relative increase in the numbers and proportion of older individuals who are known to have an increased risk for developing leukemia. This part of the apparent increase in rate may be estimated and an adjustment of rates made. Another part of the apparent increase is generally attributed to increased, improved, and more frequently used diagnostic services for leukemia, and to more public and professional interest in the disease. The influence of the latter factors has not been evaluated numerically, except for exceedingly crude estimation. And the amount of increase is dependent, to a great degree, on the convictions of the observer. Thus, when the question is restated, "Would you estimate that improved medical care and public and professional interest account for much or little of the increase in mortality from leukemia?" it is obvious that either less equivocal evidence or a direct method for estimating the real increase is required.

Age, Race, and Sex Selection at Death

Gilliam (*6*) has recently published an analysis of leukemia deaths by age, race, and sex, based on United States mortality experience during 1949. He showed that the risk of death from lymphatic leukemia was higher during each of the first two decades of life than during the third and fourth decades combined. From the fifth decade on there is a marked increase of risk with longevity. The risk of death from myelocytic leukemia is less than that from lymphatic, and there is no secondary peak in risk during childhood. The risk of death

Figure 1. Annual death rate per million population for all forms of leukemia, by sex, United States, 1933–50.



from all forms of leukemia is higher for males than for females in both white and nonwhite races, the male to female ratio being 1.5 for each race. The ratio of white to nonwhite death rates for all forms of leukemia is 2.0 for males and 2.3 for females.

Urban-Rural Distribution

The reported mortality from all forms of leukemia and aleukemia during the years 1944–48 was examined for urban-rural differences in the United States. Average annual mortality rates, according to age and sex, were calculated for urban and rural residence (see table). Urban rates are almost consistently higher than corresponding rural rates for each age and sex group. In diseases for which the precision of diagnosis is dependent on more difficult or specialized procedures, this type of phenomenon is usually ascribed to the relative availability of medical care.

When these data are plotted on a semilogarithmic grid (fig. 2), a changing order of dif-

Average annual mortality rates from all forms of leukemia per 1 million white population for urban and rural residents, according to age and sex, United States, 1944–48.

Age in years	Male		Female	
	Urban	Rural	Urban	Rural
0–4	61. 56	50. 17	54. 81	40. 99
5–9	38. 30	25. 60	26. 84	19. 36
10–14	27. 43	15. 48	19. 93	14. 31
15–19	30. 61	21. 97	17. 10	12. 76
20–24	20. 29	21. 58	13. 96	12. 95
25–29	22. 50	17. 19	17. 26	12. 45
30–34	31. 26	20. 47	22. 65	15. 33
35–39	30. 20	20. 52	28. 06	18. 81
40–44	39. 43	29. 60	30. 28	23. 15
45–49	57. 28	37. 75	47. 05	32. 14
50–54	86. 00	59. 42	66. 17	42. 59
55–59	126. 32	89. 21	97. 85	63. 07
60–64	180. 08	115. 93	104. 74	86. 75
65–69	228. 45	144. 67	140. 30	102. 53
70–74	292. 71	200. 52	169. 89	127. 57
75 and over	318. 93	184. 13	174. 39	107. 14
Total	67. 35	45. 83	48. 39	32. 75

ference in rates at different ages becomes apparent. The greatest urban-rural differences in mortality rates for white males appear to be at ages 10–14 and 30–39; for white females at ages 10–19 and 25–39. The least urban-rural differences in rates for white male mortality appear to be at ages 20–24 and 0–9; for white females at ages 20–24 and 0–9. The white male experience was the largest in total number and was selected for statistical examination of the variability of urban to rural ratios. Analysis of variance techniques were applied, and the variation between age groups was significantly greater than could be accounted for by chance alone. This does not appear consistent with the hypothesis that urban-rural differences in leukemia mortality are attributable for the most part to urban-rural variation in the availability of medical care.

Clemmesen, Busk, and Nielsen (*8*) examined the topographical distribution of leukemia in Denmark and published diagrams showing the trend of rates of mortality attributed to all forms of leukemia for the years 1931–45, by sex and by density of population at place of residence. Age composition was not considered. Rates for residents of rural areas tended to be lower than for residents of the capital, with provincial towns somewhere in between. Annual fluctuations in the rates were wide, however, and the tendency in these data toward an urban-rural difference is not remarkable.

Socioeconomic Distribution of Deaths

From rather meager published data, the higher death rates for leukemia appear to occur more commonly in the more prosperous segments of the population. The two pieces of evidence cited display quite similar trends of increase in rates from lower to higher economic status.

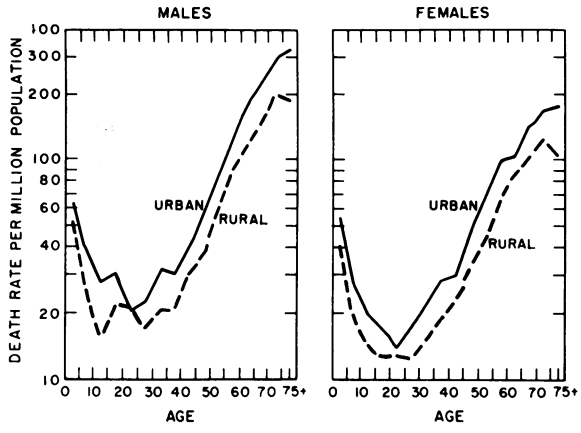
The older data are from the registrar general's report dealing with mortality in England and Wales during the years 1930–32 (*9*, *10*). Decedents were classified according to recorded occupation into five classes: class I, professional; class III, skilled artisan; class V, laborers and unskilled workers; classes II and IV, intermediate and mixed types of occupations or types not readily assignable to classes on either side. Deaths of men and married women only were considered in the analysis. The men were classified according to their own occupation and the women according to the occupation of their husbands. Standard mortality ratios for leukemia deaths in each class exhibited a progressive decrease from class I to class V. This trend is directly opposite to similar ratios computed for deaths from all forms of cancer.

More recently, Sacks and Seeman (*7*) grouped census tract populations into eight classes according to median monthly housing rental and computed average annual death rates from all forms of leukemia for the years 1939–43. Aside from an irregularity in the trend, probably arising from the small number of cases involved, the death rates from leukemia increased with corresponding increases in average rentals.

Other Etiological Factors

In 1938, Forkner (*1*) wrote that "in a minority of [human] 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, but in the majority of cases no such antecedent is demonstrable." Each year newly observed ante-

Figure 2. Average annual death rate for all forms of leukemia per million white population, according to age and sex, for urban and rural residents of the United States, 1944–48.



cedent events are reported, and the evidence, with regard to some, is mounting that they provide conditions "sufficient" to induce leukemia. Hueper (*11*) in his text on occupational tumors has provided the most exhaustive consideration of these factors.

Exposure to Radiation

Wynder (*12*), in a discussion of the practical aspects of cancer prevention, reviewed the evidence for the relationship between the development of leukemia and prior exposure to radiation or to chemicals suspected of having leukemogenic properties. His evaluation of present knowledge of these factors was that "no good evidence was at hand" except with respect to radiation and possibly with respect to benzol. Wynder's conclusion with regard to radiation was based, in part, on analyses by March and Ulrich of the mortality among radiologists from leukemia.

For a 20-year period ending in 1948, March (*13*) computed ratios of deaths from leukemia to all deaths for radiologists (4.68 percent) and for nonradiologist physicians (0.51 percent). He concluded that the risk of death from leukemia among radiologists was 9 or 10 times that of nonradiologist physicians. Dublin and Spiegelman (*14*) compared age-adjusted death rates from leukemia for male physicians (11.4 per 100,000) to the rate for the white male population (6.5) and found a ratio of 1.75. Later they found the number of deaths from leukemia among radiologists during 1938–42 was "several times the number expected on the basis of the mortality experience of all male physicians" (*15*).

Peller (*16*) cited age-standardized rates for mortality from cancer exclusive of leukemia and from leukemia for radiologists, all other physicians, and for all white American males of the same age. He concluded that the mortality from leukemia was 3.5 times greater for radiologists aged 35–74 than for other physicians, and 8.5 times that of all white males of similar age. These ratios are somewhat less than the estimates of March. It was his impression that part or all of the increase in the leukemia mortality took place at the expense of the total mortality from all cancer, including leukemia, though he was unable to confirm this from the data available.

The fact that all persons, with even more prolonged exposure to radiation or to chemicals, do not develop leukemia (for example, not all radiologists die of leukemia) suggests that for those who do not succumb, some condition or conditions "necessary" to leukemogenesis are not operative. It has been frequently suggested that presence or absence of a hereditary predisposition might explain some of the vagaries of the behavior of the disease in a human population, that is, that a "cancer diathesis" might be a necessary condition for leukemogenesis.

Genetic Predisposition

Videbaek (*17*) published in 1947 the results of a genealogical study in Denmark of the families of 209 leukemic probands selected from 310 leukemia patients on the basis of availability of sufficient family data. The study was controlled with the families of 200 nonleukemic persons. Leukemia was found to have been diagnosed in members of 17 of the 209 families of leukemic probands (8.1 percent), and in only 1 of the 200 families of controlled nonleukemics.

Videbaek discussed genetic mechanisms which are consistent with the production of familial aggregates of disease of this order and came to the conclusion that human leukemia seemed to be generally dependent on, among other conditions, a nonspecific hereditary pre-

disposition to cancer. He estimated that this predisposition is present in at least 20 percent of the population and is partly dependent on one or several genes which determine, to some degree, the localization of the cancer.

There was no attempt in this study of genealogies to define the "other conditions" on which the occurrence of leukemia might be dependent. And since familial aggregates of similar order have also been observed for diseases of both infectious and environmental etiology no conclusions can be drawn with reference to the relative importance of genetic factors in the production of human leukemia.

Summary

1. Variations in age, sex, race, and socioeconomic selection of leukemia are reviewed and data on urban-rural distribution of deaths from leukemia in the United States are presented.

2. The finding that death rates from leukemia at certain ages are significantly higher in urban than rural populations of the United States, while at other ages they are of the same order, appears to be inconsistent with a hypothesis that the higher crude rates in urban population can be accounted for by superior diagnostic services in cities.

3. From the published data reviewed there is no evidence that hereditary influences or exposure to leukemogenic agents are mutually exclusive in the etiology of human leukemia nor that they may not be considered jointly as co-leukemogenic factors.

REFERENCES

(1) Forkner, C. E.: Leukemia and allied disorders. New York, Macmillan Co., 1938, 333 pp.

(2) Custer, R. P.: An atlas of the blood and bone marrow. Philadelphia, W. B. Saunders Co., 1949, 321 pp.

(3) Casilli, A. R., Rimsey, W. L., and Satulsky, E. M.; Acute neonatal myeloblastic leukemia. A. M. A. Am. J. Dis. Child. 83: 788 (1952).

(4) Cramer, R.: Mitoseverhaltnisse bei mit cortisen behandelten leukamien des kindesalters. Acta Hemat. 8: 209 (1952).

(5) Marlow, A. A., and Grant, R. B.: Survival for twenty-nine years in chronic lymphatic leukemia. J. A. M. A. 152: 1033–1035, July 11, 1953.

(6) Gilliam, A. G.: Age, sex and race selection at death from leukemia and the lymphomas. Blood 8: 693–701, August 1953.

(7) Sacks, M. S., and Seeman, B. S.: A statistical study of mortality from leukemia. Blood 2: 1–14, January 1947.

(8) Clemmesen, J., Busk, T., and Nielsen, A.: The topographical distribution of leukemia and Hodgkin's disease in Denmark 1942–46. Acta Radiol. 37: 223–230, March-April 1952.

(9) Great Britain, Registrar General: The registrar-general's decennial supplement, England and Wales, 1931. Part IIa. Occupational mortality. London, His Majesty's Stationery Office, 1938.

(10) Logan, W. P. D.: Social class variations in mortality. Pub. Health Rep. 69: 1217–1223, December 1954.

(11) Hueper, W. C.: Occupational tumors and allied diseases. Springfield, Ill., Charles C. Thomas, 1942, 896 pp.

(12) Wynder, E. L.: Some practical aspects of cancer prevention. New England J. Med. 246: 492–503, 538–546, and 573–582, March 27, April 3 and 10, 1953.

(13) March, H. C.: Leukemia in radiologists in a 20 year period. Am. J. Med. Sc. 220: 282–286, September 1950.

(14) Dublin, L. I., and Spiegelman, M.: The longevity and mortality of American physicians, 1938–1942. J. A. M. A. 134: 1211–1215, Aug. 9, 1947.

(15) Dublin, L. I., and Spiegelman, M.: Mortality of medical specialists, 1938–1942. J. A. M. A. 137: 1519–1524, Aug. 21, 1948.

(16) Peller, S.: Cancer in man. New York, International Universities Press, Inc., 1952, 556 pp.

(17) Videbaek, A.: Heredity in human leukemia and its relation to cancer: A genetic and clinical study of 209 probands. Copenhagen, Nyt Nordisk Forlag, Arnold Busck, 1947, 279 pp.