Epidemiology of Leukemia

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Demography

In studying etiology it is important to learn not only who is most susceptible but also who is least susceptible to certain forms of leukemia. Chronic lymphocytic leukemia (CLL) has a peculiarly low frequency in Chinese and Japanese, and is not induced by ionizing radiation [21]. CLL comprises only 1.5% of adult leukemias in Chinese and Japanese as compared with 30% in Europeans [10], and the frequency does not rise with migration to Hawaii [9]. These observations separate CLL etiologically from other forms of leukemia and indicate the extent to which inherent susceptibility may vary.

Acute lymphocytic leukemia (ALL) in childhood has a peak frequency at about 4 years in white children, but not in Blacks. The peak emerged in Great Britain in the 1920's, in the U.S. in the 1940's and in Japan in the 1960's [24], but not yet in the People's Republic of China [25]. Thus ALL appears to be related to "industrialization" or development of the nation, but Blacks seem not to be susceptible. In the United States the peak rose progressively until the late 1950's, when a decline set in before the era of chemotherapy (Fig. 1). Since 1972 the decline has steepened as new treatments have taken hold. Studies of cell surface markers indicate that the peak is due to ALL of the non-B non-T cell type [29].

Environmental Agents

Ionizing radiation: X-ray was the first environmental agent implicated in leukemogenesis. Case reports in the 1920's were followed by retrospective studies in the 1940's and a prospective study of atomic-bomb survivors in Japan since the 1950's [21]. Myelogenous leukemia, either acute or chronic, is the predominant type induced by radiation, but ALL was occasionally induced, usually when the age at exposure was under 20 years. An increased frequency of CML persisted until 1965, but the rates for acute leukemia continue to be elevated [4, 16]. Recently leukemia has been observed as a complication of radiotherapy for Wilms' tumor [28], indicating the need to seek a lower dose that would cure the original cancer without causing leukemia.

Emphasis is now being placed on the leukemogenic potential of low-dose radiation in the general population. The question is more likely to be resolved by understanding the biologic mechanisms involved than by argu-

ments about threshold and linearity of dose-response – at levels below which epidemiologic studies are impractical because of the large sample sizes required.

Beginning in 1956 Dr. Alice Stewart published data which seemed to indicate that each form of childhood cancer could be induced by small diagnostic x-ray exposures of the mother during pregnancy. The fullest presentation of her findings appeared in 1975 [3]. One by one she had dealt with the criticisms of her original study. The largest remaining puzzle was the constancy of the increase in relative risk (1.5-fold), regardless of the form of cancer, be it leukemia, lymphoma, Wilms' tumor, cerebral tumors, neuroblastoma or all other childhood cancer [21]. This finding seemed biologically implausible [21]. Recent studies have failed to duplicate her findings except possibly for the increased risk of leukemia [8,15,17]. A lingering doubt thus remains about the interpretation of her results.

Chemicals: Among chemicals known or suspected to be leukemogenic are benzene in persons occupationally exposed [1,31], and alkylating agents used for cancer chemotherapy [5]. Maternal exposure during pregnancy could conceivably induce leukemia in the offspring transplacentally. This possibility seems enhanced by a Swedish report that after occupational benzene exposure during pregnancy, an increased frequency of sister chromatid exchanges was observed in both mother and child [12] – a finding which needs to be confirmed elsewhere.

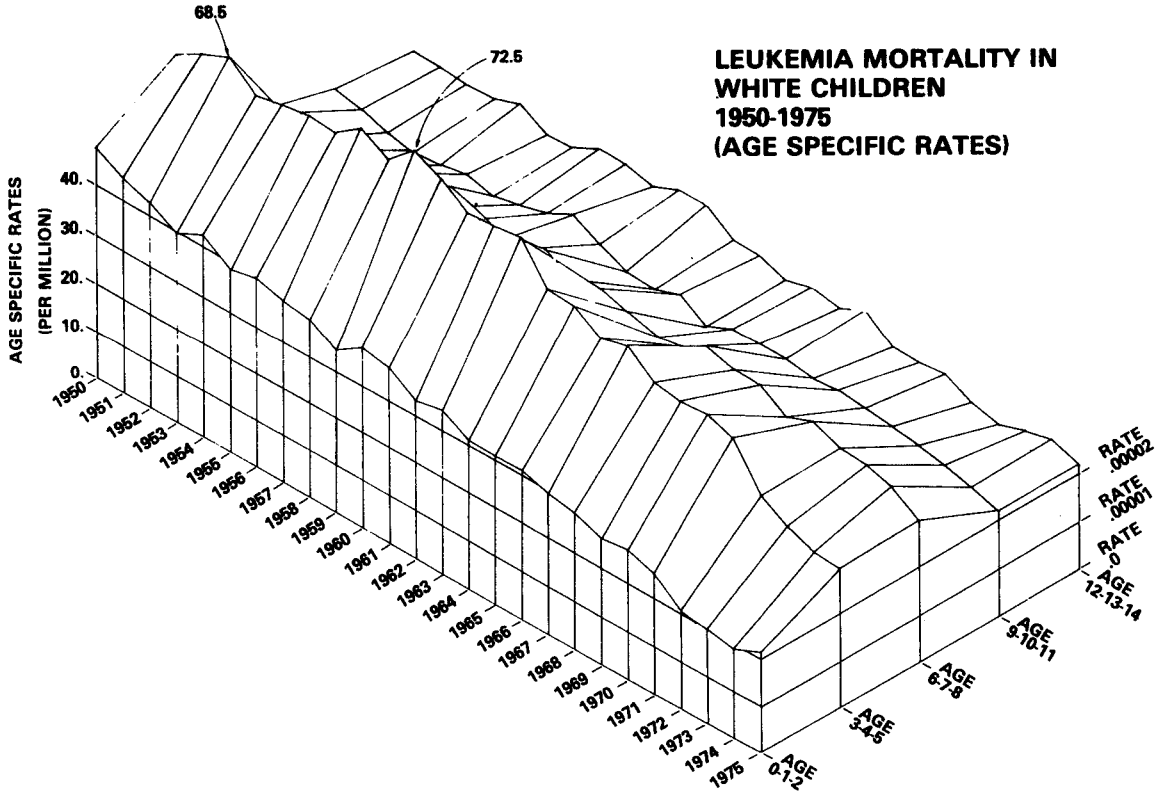

Fig. 1. Annual leukemia mortality rates for U.S. white children, 1950–1975, by 3-year age-intervals

In the treatment of multiple myeloma with melphalan, the predominant subtype of leukemia induced has been acute monomyelogenous (AMML) [19].

Leukemia Clusters: In the mid-1960's leukemia clusters were taken by virologists as evidence for horizontal transmission of the disease. Creative statisticians were stimulated to develop dispassionate procedures to determine if clustering of such rare events in time and space was attributable to chance. When applied to leukemia, these methods showed no striking excess of clusters suggestive of an infectious mode of transmission [6]. Individual clusters may nonetheless be environmentally induced, as by ionizing radiation in Hiroshima and Nagasaki [16], and by benzene in Italian shoemakers [31]. Clusters are more likely to be meaningful if they are of a particular subtype as in Ankara, Turkey, where AMML accounted for 40% of childhood leukemia [7] as contrasted with 4% in Boston [11].

Host Susceptibility

Inborn Chromosomal Abnormalities: It is now well known that leukemia, principally ALL, occurs excessively in Down's syndrome, but it is not well known that the childhood peak occurs three years earlier than in the general population [22]. An increased risk of leukemia might also exist in other autosomal trisomies, but may be less apparent because of the short lifespan. The risk of leukemia is markedly elevated in two recessively transmitted chromosomal fragility disorders, Bloom's syndrome [13] and Fanconi's anemia [26]. In Fanconi's anemia the cell type has almost invariably been AMML. It should be noted that this rare form of leukemia is the predominant form that occurs not only in this syndrome, but also after multiple myeloma treated with melphalan, and as a cluster in Ankara.

In ataxia-telangiectasia (AT) there is both chromosomal fragility and immunodeficiency, and a predisposition especially to lymphoma, but also to ALL [14]. Each of the foregoing constitutional disorders, as well as exposure to ionizing radiation or benzene, has as a feature in common chromosomal abnormality before the onset of leukemia [23]. With the development of banding techniques for the examination of chromosomes, leukemia in the general population is increasingly being associated with particular chromosomal aberrations (Rowley, this volume). The piecing together of clinical and epidemiological rarities has thus led to a more broadly applicable understanding of cytogenetics of leukemia in the general population. It now becomes a challenge to explain the exceptions in which no connection is yet known between leukemia and chromosomal abnormality. Among inborn diseases with a predisposition to leukemia but as yet without characteristic chromosomal abnormalities are Poland syndrome [32], Rubinstein-Taybi syndrome [18] and multiple neurofibromatosis, in which childhood leukemia is of the non-lymphocytic type [2].

A DNA Repair Defect in Familial AML?

The discovery of DNA repair defects in xeroderma pigmentosum and AT, two disorders with acute sensitivity to radiant energy, led us to seek such defects in disorders with sensitivity to a delayed effect of radiation; namely, neoplasia. An extension of this reasoning led us to studies of persons with multiple primary cancers or familial cancer of types that could be radiogenic, but in these cases were not. In one instance a boy with hereditary retinoblastoma and multicentric osteosarcoma of the limbs, not due to therapy, showed diminished survival of skin fibroblasts in culture after x-irradiation. Another such case is under study.

Study was also made of a family in which four siblings and three maternal relatives had acute myelogenous leukemia, and two other maternal relatives had malignant reticuloendotheliosis [30]. The occurrence of AML in the most recent sibling affected seemed to be predicted by increased transformation of skin fibroblasts in culture by SV40 seven years before the onset of leukemia [20]. This response was similar to that seen in Fanconi's anemia (FA) or in heterozygotes for the disease, but no stigmata of FA was observed in the family. The available skin fibroblasts, from two of the affected siblings and the mother, showed diminished cell survival, but those from healthy twin brothers and the father did not [27]. The cells are now being studied for DNA repair defects. These observations illustrate once again the importance of an interaction among epidemiology, clinical observations and laboratory research.

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