Factors Influencing the Incidence of Leukemia: Special Consideration of the Role of Ionizing Radiation

By E. E. Schwartz and A. C. Upton

Since 1920 there has been a marked increase in the recorded incidence of leukemia and the lymphomas. At the same time, exposure to ionizing radiation has been shown to increase the frequency of these diseases. Consequently there is now mounting concern about the gradually rising level of background radiation in the environment.

In this paper, the incidence of leukemia and the lymphomas in different populations is analyzed. The importance of radiation as an etiologic factor in the occurrence of the different forms of these diseases is considered.

Incidence of Leukemia and Lymphomas

Increase in Rates

The recorded mortality rates from leukemia and the lymphomas have risen steadily since the earliest tabulations of these entities (fig. 1). However, owing to the limitations of death certificate data, changes in the classification of the leukemias and lymphomas, shift in the age of the population at risk, and improvement in case finding and diagnosis, the extent of any real increase in the prevalence of these diseases cannot be accurately gauged. Kaplan emphasized the relatively high frequency of these diseases, stressing that the crude death rate in the United States from leukemias and lymphomas in 1950 (5.9 per 100,000 population) exceeded that from primary tumors of the trachea, lung and bronchus, ranking fourth or fifth among the causes of death from all types of cancer.

Since the greatest increase in incidence has occurred in older people, it has been suggested that the rise can be explained by the progressively aging population. This probably is not the case, however, as indicated by the small differences between the crude death rates and the rates adjusted for the changing age of the population from 1921 to 1940. Also, tables of age-specific death rates from leukemia for England and Wales present evidence for an increasing number of cases at all ages, with the exception of the 20- to 34-year-old age group. Thus the rise in the total death rate...
from leukemia does not appear to be entirely attributable to increasing age of the population.

Since most previous surveys have not listed the distribution to the different hematologic types of leukemia, changes in the incidence of the various forms of the disease are difficult to follow and the data collected by different workers are not in agreement. Bethell called attention to a relative and absolute increase in the frequency of acute leukemias and a concomitant decrease in the lymphocytic forms among patients at his Michigan clinic. Gauld and co-workers, on the contrary, believe that the incidence of all types of leukemia has increased, especially the chronic lymphatic form. A shift in the distribution of acute leukemia toward older age groups was observed by Gunz and Hough and by Lea and Abbatt. Crude death rates for the
entire United States from all hematologic types of leukemia combined and from the lymphomas increased from 1949 to 1953; however, the rise in mortality rate from Hodgkin's disease was significantly less than that from leukemia (fig. 2), a difference that cannot be explained entirely by changes of classification in the International List of Causes of Death. On comparing the incidence of Hodgkin's disease in the United States in 1948-51 with that in 1923-27, Shimkin** found that, within each age bracket above 15 years, the rate had increased a relatively constant amount, whereas the increase in leukemia incidence was significantly greater in the older age groups.

**Variation in Leukemia Incidence with Age**

The highest death rates from leukemia occur in the aged, the next highest in the first 10 years of life. After the first decade, during which the acute

*Fig. 2.*—Crude death rates from leukemia and lymphomas in the United States, 1949 to 1953. The figures in parentheses are number of cases in 1949 and 1953. (By permission, Shimkin, M. B.: Proc. 3rd Natl. Cancer Conf., 1957.)
forms predominate, the incidence declines until the thirties or forties, after which it rises progressively with advancing age (fig. 3).

The prominent position of the leukemias in pediatric practice is illustrated by the Christie Hospital Series, in which lymphatic and hemopoietic tissue cancers accounted for 30 per cent of all malignancies in children and lymphatic leukemia was by far the principal type. Although the rarity of chronic leukemia in children is undisputed, opinions vary on the nature of the acute leukemias in childhood, perhaps because of the difficulty in classifying acute leukemia according to cellular type.

On the whole, owing to its predominance at the extremes of life, lymphatic leukemia is slightly more common than myelogenous leukemia among the

![Graph](image-url)
white population of the United States (1.5 to 1.0 among males and 1.2 to 1.0 among females). Between the ages of 20 and 50, however, myeloid leukemia exceeds lymphoid leukemia in frequency. In the nonwhite population, the rates of the two diseases are about the same.\(^8\)

The age pattern in other Western countries resembles that in the United States.\(^3\) Although comprehensive data on nonwhite populations are for the most part lacking, there is no reason to suspect, from the published experience of representative centers, that the age distribution differs greatly from race to race or in different locales.\(^1\)\(^,\)\(^7\)\(^,\)\(^8\)

**Sex Differences in Leukemia Incidence**

Leukemia is somewhat more common in males than in females, by a ratio of about 1.4 to 1.0. This sex ratio is remarkably uniform throughout the United States despite regional variation in the total leukemia death rate.\(^1\)\(^4\)\(^,\)\(^5\)\(^,\)\(^7\) Virtually the same sex ratio also exists elsewhere in the world (table 1). The sex difference becomes greater with age, as noted in respiratory and buccal cancer.\(^7\)

MacMahon and Clark,\(^5\) on reviewing leukemias diagnosed in Brooklyn from 1943 to 1952, found that the greater numbers of males afflicted late in life had mainly chronic lymphatic leukemia: the male-to-female ratio for chronic lymphatic leukemia was 2:1; for chronic myeloid leukemia, it was only slightly greater than 1:1. The sex ratio for all ages combined was lower for the myelogenous than for the lymphatic types and for the acute than for the chronic forms. Statistics from abroad also show a greater frequency of chronic lymphatic leukemia in males. A group of 674 leukemia patients, which was believed to include a large portion of all the leukemias

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### Table 1.—Mortality from Leukemia and Aleukemia in 1950–1952 in Different Areas of the World*  
**Mean Annual Rate per 100,000 Population**

<table>
<thead>
<tr>
<th>National Population</th>
<th>Sex</th>
<th>Death Rate, All Ages</th>
<th>Male:Female Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>U. S. white</td>
<td>M</td>
<td>7.5</td>
<td>1.4:1.0</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>U. S. nonwhite</td>
<td>M</td>
<td>3.9</td>
<td>1.4:1.0</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Japan†</td>
<td>M</td>
<td>2.0</td>
<td>1.3:1.0</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>M</td>
<td>4.8</td>
<td>1.4:1.0</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>M</td>
<td>4.0</td>
<td>1.4:1.0</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>M</td>
<td>5.9</td>
<td>1.3:1.0</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>M</td>
<td>5.1</td>
<td>1.2:1.0</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>M</td>
<td>6.8</td>
<td>1.4:1.0</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>5.0</td>
<td></td>
</tr>
</tbody>
</table>

* *Taken from reference 72.
†Average for the years 1951, 1952 and 1953.
occurring in the eastern half of Scotland from 1938 to 1951, contained 7 males for every 6 females; however, among these, 130 males but only 77 females had chronic lymphatic leukemia.25 There has also been a 2:1 male predominance in cases of chronic lymphatic leukemia at the clinics of the Akademiska Sjukescet, Uppsala, Sweden, but no significant difference between the sexes in the other leukemias.8

It is of interest that in Connecticut the sex ratio in both acute and chronic leukemia has shown little or no change with time within 3 successive 5-year periods (1935-51), despite a progressive rise in over-all leukemia incidence (table 2). Furthermore, the relation between the sex ratio and age has shown no significant change.27 This is in keeping with the stability in the sex ratio of leukemia incidence in the United States as a whole between 1925 and 1950.62,88

**Ethnic, Racial and Geographic Differences**

Although distributions of leukemia according to age and sex are fairly uniform throughout the civilized world (table 1), statistical surveys in the United States have shown a leukemia mortality rate for the white population twice that for the nonwhite. Socio-economic studies have provided a possible explanation for this difference and a reason for its apparent diminution.20,83,88 Sacks and Seeman55 classified persons afflicted with leukemia, in Baltimore, according to the sum they paid monthly for housing and found that the death rate was proportionate to the rental rate. Similarly, the listing of British decedents according to occupation revealed an increasing prevalence of leukemia with progression from unskilled to professional work.82 Also, the incidence in urban populations exceeds that in rural populations.62 These data, plus those on the relation between racial incidence and median income,27 lend support to the interpretation that the recorded higher leukemia rate in the white population is rather closely correlated with standard of living.66 Studies on the incidence of leukemia among the nonwhite population outside the United States are inconclusive on this subject.19,42,97

The white-to-nonwhite ratio of the incidence of lymphosarcoma, Hodgkin's disease, reticulum-cell sarcoma, and giant follicular lymphoma is lower than that of leukemia.14,26,88 Plasma-cell or multiple myeloma shows a greater frequency in the Negro population than in the white.17,56

The most pronounced ethnic selection of leukemia found in any population studied thus far is the twofold predominance of the disease in Jewish inhabitants of Brooklyn as compared to their white neighbors of other back-

**Table 2.—Incidence of Leukemia in Connecticut**

<table>
<thead>
<tr>
<th>Period</th>
<th>Male</th>
<th>Female</th>
<th>Male:Female Ratio</th>
<th>Male</th>
<th>Female</th>
<th>Male:Female Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1935–40</td>
<td>1.1</td>
<td>1.1</td>
<td>1.0:1.0</td>
<td>1.5</td>
<td>1.2</td>
<td>1.25:1.0</td>
</tr>
<tr>
<td>1941–46</td>
<td>1.8</td>
<td>1.1</td>
<td>1.64:1.0</td>
<td>1.9</td>
<td>1.4</td>
<td>1.35:1.0</td>
</tr>
<tr>
<td>1947–51</td>
<td>2.5</td>
<td>1.5</td>
<td>1.67:1.0</td>
<td>2.8</td>
<td>2.1</td>
<td>1.32:1.0</td>
</tr>
</tbody>
</table>

*From data in Griswald et al.37
†Figures represent age-adjusted incidence per 100,000 population.
grounds. This difference in itself was sufficient to explain the white-to-non-white ratio in Brooklyn. The possibility that this greater incidence may also exist in other people of Mediterranean origin is suggested by the relatively high frequency of leukemia among patients treated at the University of Athens over a 10-year period. Since this frequency does not necessarily express the incidence in the general population, it can best be compared to clinically observed cross sections elsewhere (table 3); however, vital statistics indicated that the Italians (table 1) resemble other Caucasoids more closely than the Greeks.

Geographic and climatologic differences in leukemia incidence are difficult to interpret because of such variables as accuracy of reporting, disease classification, length of life and environmental factors. Hence, the lower crude death rates from leukemia and lymphomas in the southern part of the United States may not reflect real differences in susceptibility, as emphasized previously. Similarly, it is difficult to interpret the crude data indicating progressive increase from north to south in the leukemia incidence in England.

Although it is believed that leukemia (table 1), especially chronic lymphatic leukemia, is rarer in Japan than elsewhere, Steiner discovered practically no significant difference in the incidence of leukemia between the limited number of Japanese autopsied in Los Angeles and Caucasoids in the same area. The few data on this small sample of Japanese do not prove, however, any real indication of the relative frequency of lymphatic leukemia; hence, the possible influence of migration or of racial factors on the incidence of this disease is not clear.

In the Western world, the highest rates of mortality from leukemia prevail among the white population in the United States and Denmark. Rates in England, Wales and Scotland are lower by about 30 per cent, and those in Ireland are lower by about 40 per cent. As stressed earlier, however, the interpretation of these data is complicated by many variables, including differences in standard of living. Before the existing geographic and demographic data can be adequately evaluated, additional and more precise information must be secured.

Incidence of Leukemia as Affected by Radiation

An increased frequency of leukemia in people exposed to ionizing radiation has been noted repeatedly during the past 40 years. The Japanese atomic bomb survivors represent the most important single series of cases. This group comprises a large number in whom the incidence of leukemia

<table>
<thead>
<tr>
<th>Authors/Clinics</th>
<th>Period</th>
<th>Total Cases of Leukemia</th>
<th>Percentage of All Patients Seen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danopoulos et al.</td>
<td>1942-52</td>
<td>916</td>
<td>0.42</td>
</tr>
<tr>
<td>Best and Limarzi</td>
<td>1926-52</td>
<td>73</td>
<td>0.26</td>
</tr>
<tr>
<td>Nordenson and Asplund</td>
<td>All hospitals in Sweden combined</td>
<td>1933-53</td>
<td>1735</td>
</tr>
</tbody>
</table>
is clearly related to the distance from the explosion, or to the amount of radiation absorbed (table 4). Another notable series of cases is the collection of subjects previously irradiated for ankylosing spondylitis, in whom the incidence of leukemia, likewise, varies with the radiation dose (table 5).

How much radiation is required to increase the risk of leukemia and the precise relation between leukemia incidence and radiation dose are as yet unknown. From analysis of the incidence among A-bomb survivors according to their distance from the hypocenter, Lewis implied that the response was nearly linear with dose. His interpretation, however, rests on the assumptions that the doses received by victims equidistant from ground-zero in Nagasaki and in Hiroshima were identical in biologic effectiveness and that the dose distributions in the exposed groups were well known. Furthermore, his calculations are based on pooled incidence data, the statistical variation of which is relatively high. Nevertheless, a similar conclusion has been tentatively advanced by Court Brown and Doll, who report that the relation between leukemia incidence and radiation dose in patients treated for spondylitis approximates a simple linear proportion. Both these analyses suggest, therefore, that there may be no threshold dose of radiation required for the induction of leukemia. Reports suggesting that merely diagnostic irradiation in utero or later in life may enhance the risk of developing leukemia subsequently support this conclusion.

As with other radiation-induced neoplasms, the induction period between irradiation and the clinical onset of leukemia is variable; it ranges from several months to more than a decade. Tabulations of annually diagnosed cases among survivors resident in Hiroshima provide no definite evidence that the incidence has yet begun to diminish in this irradiated population, especially among survivors beyond 2000 meters from ground-zero. It is, therefore, still too early to draw final conclusions from this series about the maximum rate of leukemia induction per unit dose.

### Table 4.—Incidence of Leukemia among Atomic Bomb Survivors of Hiroshima

<table>
<thead>
<tr>
<th>Distance from Hypocenter (m.)</th>
<th>Estimated Population of Survivors</th>
<th>Survivors with Leukemia</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–999</td>
<td>1,200</td>
<td>16</td>
<td>1.33</td>
</tr>
<tr>
<td>1000–1499</td>
<td>10,500</td>
<td>28</td>
<td>0.266</td>
</tr>
<tr>
<td>1500–1999</td>
<td>18,700</td>
<td>6</td>
<td>0.032</td>
</tr>
<tr>
<td>2000–over</td>
<td>67,700</td>
<td>10</td>
<td>0.015</td>
</tr>
</tbody>
</table>

*Modified from reference 9.

### Table 5.—Incidence of Leukemia among Patients Treated with X-rays for Ankylosing Spondylitis

<table>
<thead>
<tr>
<th>Total Dose to Spinal Marrow (r)</th>
<th>No. Men Treated</th>
<th>Men with Leukemia</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000 and over</td>
<td>379</td>
<td>8</td>
<td>2.111</td>
</tr>
<tr>
<td>1500–1999</td>
<td>805</td>
<td>4</td>
<td>0.497</td>
</tr>
<tr>
<td>1000–1499</td>
<td>3062</td>
<td>11</td>
<td>0.359</td>
</tr>
<tr>
<td>500–999</td>
<td>4180</td>
<td>10</td>
<td>0.239</td>
</tr>
<tr>
<td>0–499</td>
<td>2861</td>
<td>4</td>
<td>0.139</td>
</tr>
</tbody>
</table>

*From data of Court Brown and Doll (female patients excluded).*
LEUKEMIA INCIDENCE AND RADIATION

Since age and sex seem to have a marked influence on the evidence of leukemia in nonirradiated persons, their bearing on the incidence of the disease in irradiated people is of particular interest. In both the Japanese survivors and the spondylitis patients, the leukemia rate is higher thus far in males; however, the significance of the differences is doubtful. Whereas no definite age differences in susceptibility were initially apparent in the Japanese (table 6), it now appears that the induction rate may decrease with age (N. Wald, 1957, personal communication). In the spondylitis patients, on the other hand, the rate increases steadily with age, from 1.1 per 1000 persons less than 25 years old to 5.6 per 1000 aged 55 years and over. This increase with age may not, however, reflect solely an enhanced susceptibility of older people to the induction of leukemia by irradiation, since the age-specific rate of spontaneous leukemia rises correspondingly with age. Mole emphasized this and estimated from the data published by Court Brown and Doll that the age-specific incidence among spondylitis patients exposed to 55 r would be no higher than that prevailing in the nonirradiated population of England and Wales. Accordingly, the interpretation that there is no threshold dose for leukemia induction may be questioned.

In the hematologic classification of the leukemias induced by irradiation, the preponderant cell type in adults is myeloid. The incidence of other types also appears to be increased, however, as indicated by the following distribution of leukemias among patients treated for spondylitis:

- Myeloid leukemia: 9 deaths occurred; 1.49 were expected
- Lymphoid leukemia: 4 deaths occurred; 0.86 were expected
- Monocytic leukemia: 4 deaths occurred; 0.34 were expected
- Other and unspecified leukemias: 11 deaths occurred; 0.21 were expected.

Table 6.—Leukemia in Persons Exposed within 1500 Meters of the Hypocenter

<table>
<thead>
<tr>
<th>Age (yr.)</th>
<th>Hiroshima Population in 1950</th>
<th>No. of Cases of Leukemia</th>
<th>Incidence Annual Rate per 100,000**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>0-9</td>
<td>839</td>
<td>878</td>
<td>6</td>
</tr>
<tr>
<td>10-19</td>
<td>955</td>
<td>1490</td>
<td>7</td>
</tr>
<tr>
<td>20-29</td>
<td>458</td>
<td>1352</td>
<td>3</td>
</tr>
<tr>
<td>30-39</td>
<td>713</td>
<td>1118</td>
<td>3</td>
</tr>
<tr>
<td>40-49</td>
<td>902</td>
<td>1016</td>
<td>3</td>
</tr>
<tr>
<td>50-59</td>
<td>606</td>
<td>572</td>
<td>1</td>
</tr>
<tr>
<td>60-69</td>
<td>236</td>
<td>278</td>
<td>—</td>
</tr>
</tbody>
</table>

*Modified from reference 9.
(Source: Estimated Number of Survivors in Hiroshima City in 1950; Preliminary Report, Death Certificate Survey.

$Source$: Listing of Leukemia Cases in Hiroshima and Nagasaki, September 1955. Cases are restricted to those in persons resident in Hiroshima at the time of diagnosis; they are described in the listing under the heading, "Diagnosis Acceptable;"

**95 per cent Poisson confidence intervals (in parentheses) calculated by M. A. Kastenbaum. Note that the small size of the samples involved results in extremely wide confidence limits; thus, any tendency to age selection is not statistically significant. The correct confidence intervals are probably much wider because of the extra-Poisson variation that is likely to be present.
It is noteworthy that only one case of chronic lymphatic leukemia was observed in this series and that, likewise, only a single case of this form was noted among the 92 instances of leukemia in Japanese A-bomb survivors reported by Moloney.\textsuperscript{70} Hence, despite the apparent rarity of this cell type in the general Japanese population,\textsuperscript{70} its incidence does not seem to be elevated by irradiation so markedly as other forms of the disease, if at all.

In contrast to the relative preponderance of myeloid leukemia in irradiated adults, at least 9 of the 21 Japanese survivors who developed leukemia before the age of 19 had the lymphatic type and only 7 the myeloid type;\textsuperscript{68} all but 5 of the 21 cases were acute, and one was subacute (N. Wald, personal communication). Although the classification of acute leukemias according to cell type may be questioned, cases of the lymphatic type also predominated among a series of 7 children who developed acute leukemia after irradiation of the mediastinum for thymic enlargement in infancy. Five of the 7 cases were lymphatic, and the other 2 were of stem-cell type.\textsuperscript{91} As to the relative distribution of acute and chronic types of leukemia, 50 of the 92 cases of leukemia in the Japanese survivors of all ages were acute,\textsuperscript{70} about one-half of which were classified as acute myelogenous. In the series reported by Court Brown and Doll,\textsuperscript{13} the acute form was present in 30 of 40 patients aged 17-69 years at the time of the first radiation treatment for ankylosing spondylitis; of these cases, 14 were classifiable as acute myeloid and only 2 as acute lymphatic. It therefore appears that the age of the person at the time of irradiation may influence the type of leukemia induced, as has been observed in experimental animals,\textsuperscript{99} myeloid leukemia of acute and chronic forms predominating in adults and acute leukemia of lymphatic type predominating in children. At all ages, a high correlation between the frequency of chronic myelogenous leukemia and irradiation has been noted in A-bomb survivors (N. Wald, 1957, personal communication). Induction of Hodgkin's disease and other lymphomas by irradiation has not been evident in man, although lymphomas are readily induced by irradiation in mice.\textsuperscript{99}

To assess the influence of environmental background radiation on the incidence of leukemia, one must weigh the effects of long-continued exposure to low radiation levels against the effects of intensive brief exposures. Although relatively little information is available on the leukemogenic effects of chronic irradiation, the higher mortality rate from leukemia among radiologists attests to the induction of the disease by prolonged low-level exposure.\textsuperscript{32,51,59,69,80,94,103} The downward trend in leukemia incidence among radiologists and the upward trend among nonradiologists may reflect greater safety precautions by the former and increasing use of radiologic apparatus by the latter (table 7). A causal relation for the leukemogenic influence of chronic irradiation from internally deposited radioisotopes has not been established; however, at least 5 cases of leukemia have been observed in patients given intravenous or intracavitary thorotrast, which is deposited in the reticuloendothelial system.\textsuperscript{52} Isolated deaths from leukemia have also occurred after administration of large amounts of I\textsuperscript{131}, 1.7.81,86 Very few cases of leukemia have been encountered among the many people who have received radium and its cogeners in therapy or as the result of occupational exposure, despite
TABLE 7.—Incidence of Leukemic Deaths Relative to Total Deaths among U. S. Physicians

<table>
<thead>
<tr>
<th>Period</th>
<th>Percentage Radiologists</th>
<th>Percentage Nonradiologists</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1929–43 (Ref. 59)</td>
<td>4.57</td>
<td>0.44</td>
<td>10.3:1</td>
</tr>
<tr>
<td>1944–48 (Ref. 60)</td>
<td>4.84</td>
<td>0.72</td>
<td>6.7:1</td>
</tr>
<tr>
<td>1952–55*</td>
<td>3.57</td>
<td>1.0</td>
<td>3.6:1</td>
</tr>
</tbody>
</table>

*Compiled from obituaries in the J. A. M. A., 1952–55, by C. S. Melville, Jr. The relative incidence of leukemic deaths in 1950 in the general U. S. white male population was 0.65 per cent (see reference 75).

the occurrence of osseous tumors in such persons. This is presumably attributable to the tendency for radium to deposit in the skeleton in small areas of high focal concentration, with the result that the bone marrow is not diffusely irradiated.

**Etiology and Pathogenesis of Leukemia and the Lymphomas**

The mechanism of spontaneous development of leukemia and the lymphomas or of induction of these diseases by environmental agents is poorly understood, but the influence of many intrinsic and extrinsic factors is now recognized. A brief summary of our knowledge of modifying elements, derived largely from studies with experimental animals, will provide a means of better evaluating the role of radiation in causation of leukemia. (For a more complete discussion of this subject, see reference 99.)

**Genetic Factors**

Although the importance of genetic factors in man is still uncertain, despite the unusually frequent occurrence of leukemia in certain families and the simultaneous development of leukemia in twins, genetic background has a decisive influence on susceptibility to the spontaneous development and induction of the disease in mice. The genetic influence is complex, however, in that susceptibility to any given hematologic type of leukemia or to the inducing action of any particular leukemogenic agent may not be accompanied by susceptibility to other hematologic types or other agents. Furthermore, there is evidence that more than one gene is involved and that the pattern of inheritance of susceptibility is therefore not typically Mendelian. Unfortunately, much of the early work on genetic transmission of susceptibility to leukemia must be reevaluated in the light of the discovery that the frequency of leukemia in inbred mice of certain “high-leukemia” strains, formerly attributed exclusively to genetic factors, may be the result of an egg-borne agent of viral properties.

**Constitutional Factors**

As has been noted in man, the incidence of various types of leukemia and lymphomas in mice differs with age and sex, and also with other endocrine and nutritional factors (see reference 99). Depending on the strain of mouse, estrogenic and androgenic hormones enhance or inhibit spontaneous development and induction of leukemia. Cortisone and ACTH also inhibit formation of lymphoid neoplasms in mice and their growth after transplantation; they also hinder growth of chronic lymphatic leukemia in man. The reverse effect
Schwartz and Upton has been noted in mice after adrenalectomy. Paradoxically, however, the incidence of lymphomas may be enhanced in C57BL mice by prolonged administration of ACTH. Thyroid and anterior pituitary hormones have less-pronounced and variable effects on the development and growth of experimental leukemias. Another, possibly hormonal, factor has been reported to occur in normal thymus tissue and in the plasma of patients with lymphatic leukemia. Injection of this substance provokes a lymphocytosis in newborn mice of low-leukemia strains, but not in those of high-leukemia strains. The possibility that this is a thymic hormone, its potential role in leukemogenesis, and its possible relation to the "lymphokentric" substances noted previously in the urine of patients with leukemia remain to be explored.

The relatively high incidence of leukemia in Mongoloid children also points to the existence of constitutional factors influencing the development of the disease. These deserve further investigation.

Extrinsic Agents

Apart from ionizing radiation, the existence of other agents capable of inducing leukemia in man is not well documented. A few cases of leukemia have been attributed to chronic intoxication of the bone marrow by benzol; others have been reported to develop after an initial period of marrow hypoplasia or dysplasia resulting from drug toxicity or hypersensitivity (see reference 35).

Repeated attempts to demonstrate an infectious etiology in Hodgkin's disease and in other forms of the lymphomas and leukemias have failed thus far to provide conclusive evidence of a specific causative organism (see reference 35). Notable is the discovery that filterable agents may be recovered, from certain patients with leukemia, that greatly accelerate development of lymphomas in mice of a high-leukemia strain or give rise to a leukemia-like disease in mice of low-leukemia strains or in guinea pigs. Since leukemic mice also harbor filterable agents that induce the disease on injection into newborn mice of low-leukemia strains, the data strongly suggest that, in certain instances in mammals as in fowl, leukemia may be caused by viral agents. The possible leukemogenic action of nonspecific infections has long been cited, without statistical basis. However, epidemiologic studies now point toward an unusually high correlation between leukemia and previous chicken pox. The significance of this association remains to be disclosed.

It is well known that methylcholanthrene and other carcinogenic chemicals are leukemogenic for mice and rats. Hence, certain of the coal tar derivatives to which man is occupationally exposed, e.g., aniline dyes, have been cited by Dameshek as deserving of careful investigation for leukemia-inducing potency in experimental animals.

The induction of leukemia and lymphomas by ionizing radiation has been studied extensively in mice, but the mechanism is still unexplained. In brief, it would appear that irradiation may cause leukemia through at least three conceivable mechanisms: (1) somatic mutation in hemopoietic cells, (2) activation of a latent virus infection, and (3) disturbance of growth-regulating mechanisms that control white blood cell production. The investigations of
Kaplan et al.39-41 and Law and Potter49 indicate that lymphomas may be induced in nonirradiated thymus tissue on implantation into irradiated recipients, revealing that under certain conditions radiation acts through systemic effects and not through direct action on potentially leukemic hemopoietic cells. This is further suggested by the marked inhibition of leukemia induction that occurs when a small volume of hemopoietic tissue is shielded from radiation during exposure of the remainder of the animal or when nonirradiated hemopoietic cells are implanted in the animal after it has been exposed (see reference 99). Although the results of these studies point to mechanisms other than radiation-induced somatic mutations in the induction of leukemia, the latter cannot be excluded as a leukemogenic factor in all instances, particularly under conditions of chronic irradiation at low dose rates.

Susceptibility to the induction of leukemia by x-rays is not limited to strains with a high spontaneous incidence of the disease.44 In the RF mouse, either lymphoid or myeloid leukemia may be induced, depending on the age of the animal at the time of irradiation99; lymphoma induction is maximal when the treatment is administered in the first month of life, and falls rapidly thereafter. The effectiveness of a given dose depends on the rate of irradiation, the incidence of lymphoma after alternate half-body exposures diminishing sharply when the interval between treatments is prolonged beyond 24 hours.38 Yet, well-timed, fractionated exposures of the whole body may be more leukemogenic than a single exposure.37 Relatively little experimental information is available on leukemia induction by chronic irradiation. In general, although the leukemogenic effectiveness of a given dose of radiation diminishes as the dose rate is reduced below a certain optimum intensity27 (A. C. Upton and J. A. Sproul, 1957, unpublished data), the incidence of reticular neoplasms is significantly raised in mice exposed throughout life to 0.1 r per day.53 Although the dose-response curve for leukemia induction in mice is not precisely known, owing to lack of experiments with low doses of radiation, there appears to be an effective threshold for lymphoid leukemias in the neighborhood of 100-200 r; for myeloid leukemia, however, the incidence is increased many-fold by 150 r (fig. 4). Further study is needed before we can determine more precisely whether a real threshold exists for the induction of either type of leukemia and to characterize the shape of the dose-response curves at levels below 100 r. The time required for the development of leukemia after irradiation varies inversely with the dose of radiation (table 8).

Conclusions

Although the recorded incidence of leukemia is rising, any increase in the actual risk of the disease that may have occurred cannot be accurately assessed.99 If it is assumed, however, that the increase is a real one, several possible causes may be postulated on the basis of existing data.

The possibility that growing amounts of man-made ionizing radiations have contributed to a rising incidence of leukemia is suggested by the knowledge that the disease is induced by radiation and by the fact that the amount of radiation in the environment has been steadily increased above natural levels.
Table 8.—Effects of Radiation Dose on Leukemia Induction Period

<table>
<thead>
<tr>
<th>X-Ray Dose (r)</th>
<th>No. of Mice</th>
<th>Mean Age at Death (mo.)</th>
<th>Myeloid Leukemia</th>
<th>Lymphoid Leukemia**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed</td>
<td></td>
<td>Incidence (%)</td>
<td>Mean Age at Death (mo.)</td>
</tr>
<tr>
<td>450</td>
<td>105</td>
<td>10.3</td>
<td>54</td>
<td>10.8</td>
</tr>
<tr>
<td>300</td>
<td>104</td>
<td>12.5</td>
<td>48</td>
<td>11.0</td>
</tr>
<tr>
<td>150</td>
<td>104</td>
<td>15.6</td>
<td>39</td>
<td>13.3</td>
</tr>
<tr>
<td>0</td>
<td>314</td>
<td>19.1</td>
<td>6</td>
<td>16.3</td>
</tr>
</tbody>
</table>


†Single exposure of males of the RF strain at 5-6 weeks of age to whole-body 250-kvp x-rays (hvl 0.44 mm of Cu), 80-100 r per min, with backscatter.

§Incidence adjusted to correct for intercurrent radiation mortality (see reference 43).

**Arising as lymphosarcoma of the thymus.

The extent to which this increase above background has occurred is variable and difficult to determine; yet it has been estimated that the average dose to the population has been elevated by 30 to 100 per cent in the United States and Great Britain through the widespread medical use of radiography, and to a lesser extent by miscellaneous sources such as watch dials, shoe-fitting machines and nuclear fall-out. Although the leukemogenic effects of this amount of radiation cannot be precisely reckoned, Lewis estimated that the background dose may conceivably account for 10-20 per cent of the spontaneous incidence of leukemia. His calculations and his assumption that the
incidence of leukemia is linear with radiation dose are, admittedly, subject to error, as emphasized previously. If, however, they constitute an approximation, the increase in radiation background is clearly not sufficient to account for the tremendous rise in the recorded incidence of leukemia that has taken place during the past 30 years (fig. 1). Before the effects of radiation on leukemia incidence can be assessed more accurately, better records of radiation dosage must be had, and further studies must be made on the possible influence of age at irradiation, sex, anatomic distribution of the radiation, and dose rate—all important factors in the experimental induction of leukemia. Similarly, more information is needed on the distribution of the various hematologic types of leukemia in irradiated subjects, particularly chronic lymphatic leukemia. It is noteworthy in this connection that the incidence of reticulum-cell sarcoma and of monocytic leukemia is not increased by irradiation in mice and that the dose-response curves for myeloid leukemia, lymphoid leukemia and lymphomas are significantly different from each other, neither one appearing to be linear over the dose range 0–1000 r.

The possible contribution of chemicals and other agents to the growing frequency of leukemia must not be overlooked. The relatively high incidence of leukemia among city dwellers, as compared with country dwellers, may well be related to the atmospheric pollution of urban areas by hydrocarbons and other carcinogenic industrial fumes (see reference 100). It is also conceivable that the growing use of drugs that are potentially toxic to the marrow has contributed to the more frequent development of leukemia.15

Lastly, the relatively greater incidence of leukemia among people of high socio-economic status may be the result of mechanisms, yet to be disclosed, that are related in some way to the rising standard of living.

SUMMARY

The recorded incidence of leukemia and lymphomas has markedly increased during the past 30 years. During the same interval the amount of ionizing radiation in the environment has been steadily increased by man-made additions to the natural background.

The possibility that radiation may account in part for an increasing incidence of leukemia is suggested by the more frequent development of the disease in those exposed to large amounts of radiation.

Although the extent of increase in the risk of leukemia cannot be determined accurately from the recorded rates and the relation between leukemia incidence and radiation dose cannot be estimated precisely, it appears probable that radiation is only one of many environmental agents influencing the occurrence of the disease.

Other factors associated with the changing standard of living, such as the increasing use of marrow-depressing drugs and the growing contamination of the atmosphere with chemical pollutants, deserve further investigation as leukemogenic influences.

SUMMARIO IN INTERLINGUA

Le reportate incidencia de leucemia e de lymphomas ha crescite marcamente in le curso del passate 30 annos. Durante le mesme intervallo, le nivello
del radiation ionisante in le ambiente ha cresce constantemente in conseguenza di addiziones artefactive al fundo natural.

Le possibilitate que le radiation explica in parte le augmentate incidentia leucemia es sugerite per le facto que le morbo se disveloppa plus frequemente in subjectos exposite a alte nivellos de radiation.

Ben que le grado del augmento in le riso de leucemia non pote esser determinate accuratemente super le base del datos cognoscite e ben que le relation inter le incidentia de leucemia e le dosage de radiation ionisante non pote esser estimate precisemente, il es probable que le radiation es solmente un inter plure agentes ambiental que influentia le occurrentia del morbo.

Altere factores associate con le evolution del standard de vita—le augmentate uso de drogas que deprime le medulla, le crescente contamination del atmosfera con substantias chimic, etc.—merita esser investigate additionalmente in lor possibile potentialitate leucemiogene.

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LEUKEMIA INCIDENCE AND RADIATION


Factors Influencing the Incidence of Leukemia: Special Consideration of the Role of Ionizing Radiation

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