Leukemia in Hiroshima Atomic Bomb Survivors

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A CAUSAL RELATION between radiation and leukemia has been well demonstrated.1-12 The reported cases of leukemia in people exposed to radium,13 thorotrast,14,15 occupational x-ray,16-18 therapeutic x-ray to the thyroid region in childhood19,20 and possibly in utero diagnostic x-ray,21 have been few in number. Estimates of the increased risk associated with exposure of man to radiation depend heavily upon studies of the survivors of the atomic bombing of Hiroshima and Nagasaki,1-11 and of patients with ankylosing spondylitis19 treated with high doses of x-radiation directed principally to the spinal marrow. Since the earlier reports from Hiroshima and Nagasaki established the increased incidence of leukemia in survivors, the number of cases has increased, and knowledge of population groups upon which to base analyses has improved. For the first time it is now possible to present analyses of incidence based on fixed samples of survivors. The present report summarizes the findings observed in the Hiroshima survivors from 1945 to 1958. A similar report is being prepared22 on the survivors of the Nagasaki atomic explosion.

MATERIALS AND METHODS

Immediately following the bombing, and intermittently for two years thereafter, teams of scientists entered Hiroshima to render assistance and to obtain information on the effects of radiation on humans. They, as well as members of the local medical community, were cognizant of the potential significance of hematologic findings resulting from irradiation. With improvement of local conditions and medical facilities, a systematic investigation became possible, and a routine hematologic survey was instituted.23 Since 1948, scientists of the Atomic Bomb Casualty Commission in cooperation with physicians in the community have made intensive efforts to detect hematologic and other abnormalities in both the exposed and the nonexposed segments of the population. To collect information on patients with hematologic abnormalities before 1950, lists of patients and any available slides and related materials were exchanged by the ABCC and local physicians and continuously reviewed. Since 1950 these efforts have been intensified, so that few if any leukemia cases among survivors remaining in Hiroshima or its immediate environs can have been missed. Even for the first four years after the bombing, the likelihood of missing cases of leukemia is probably small.


Submitted June 8, 1959; accepted for publication Aug. 12, 1959.
General Population Description

There are various estimates of the population of Hiroshima at the time of bombing. The best estimate suggests that of the 255,000 civilians initially located in the city, 64,600 were killed and 72,200 were injured. The population was dispersed widely, but in largest numbers to the immediate environs of Hiroshima. The lowest estimate of the exposed population remaining in Hiroshima (42,100) was obtained in November of 1945. In 1947 and 1949 the rate of return of exposed survivors to Hiroshima was so great that in 1949, according to a census conducted by ABCC, the population was found to have increased 100 per cent over the November 1945 estimate. The 1950 Atomic-Bomb Survivors Survey enumerated the exposed population at 90,000, which is the highest estimated point. Since 1950 the exposed resident population has been very slowly decreasing. Hiroshima is a commercial city which is growing continuously by virtue of a rapid influx of nonexposed persons. The nonexposed population being built up by births and migration is considerably younger than the exposed population.

Difficulties in medical follow-up of an ill-defined population, with problems of varying age composition as well as differential morbidity, migratory and mortality rates, led to the creation of a so-called Master Sample of exposed and nonexposed persons. The exposed survivors in the Master Sample are limited to those who were enumerated on the 1950 Atomic Bomb Survivors Survey. By 1958 97 per cent of the exposed people had been located, and additional information on exposure shielding factors, etc. had been obtained. The identification of the nonexposed portion of the sample is too incomplete for description at this time. The Master Sample is used for the majority of the calculations of leukemia incidence in this report. The rates thus obtained are minimum estimates of incidence since only confirmed cases are used. The only significant source of error lies in diagnoses that may have been missed.

The Leukemia Population

By December 31, 1957, the Atomic Bomb Casualty Commission had knowledge of 130 people exposed in Hiroshima who were said to have leukemia. An additional 19 were diagnosed as having aplastic anemia or a leukemia-related diagnosis exclusive of the lymphomas. For each of these diagnoses, confirmation was sought by review of blood and bone marrow smears and any other available material. The cases were subdivided by certainty of diagnoses into confirmed, probable and possible—depending upon the findings obtained on review. The probable cases are those in which the diagnosis was made in other hospitals based upon appropriate hematologic studies and although a summary of the findings was available the materials had never been reviewed by staff of the ABCC. The possible cases are those which are reported on death certificate alone and on whom no information could be reclaimed. The analyses in this report include only the 122 cases of leukemia confirmed by the Atomic Bomb Casualty Commission following review of hematologic material. All other supporting materials have been reviewed, and final classification determined by the authors of this report with no knowledge of exposure history. The borderlines are indistinct between leukemia, the lymphomas and so-called myeloproliferative syndromes. The lymphomas will be the subject of a later report. A tabular presentation of the numbers of patients with other diseases of myeloid tissue is shown separately in table 8.

The definitions followed are essentially those given by Wintrobe. Leukemia cases classed as “subacute” have been grouped with the acute leukemias. If the leukemic cells were too undifferentiated to permit any definite classification, patients with acute leukemia were classified as acute leukemia, type unspecified. The “Naegli” or “myelomonocytic” type of leukemia is included in the acute granulocytic group for purposes of analysis.

Results

Incidence of Leukemia

The incidence of leukemia has apparently been increasing throughout the world in recent years. Figure 1 compares annual death rates for Japan and the United States.
In both countries the incidence of leukemia has been rising for at least the past decade. In the United States the rise has persisted and has been documented for a longer period of time than in Japan. It is likely that the rate of increase seen in the United States was not operative in Japan for the same length of time. Differences in likelihood of diagnosis in the two countries over this time interval probably do not account for this finding.

Figure 2 compares age-specific incidence estimated for an American population center\textsuperscript{25} with that seen in Japan.\textsuperscript{26} The crude comparison of age-specific leukemia rates observed in Japan and the United States is of interest for several reasons. It shows that in young people the rates are comparable. In the older people, a much higher rate of leukemia is seen in the United States than in Japan. In Japan the recent increase in leukemia incidence is due primarily to an increase in acute granulocytic leukemia in the older age groups. The high incidence of chronic lymphocytic leukemia which occurs in the United States in older people is absent in Japan. This is the experience of the large medical centers\textsuperscript{26} as well as of the Atomic Bomb Casualty Commission during the last 12 years. This apparent discrepancy undoubtedly reflects an actual difference in the type incidence of leukemia in the Japanese. In the large cities the level of medical sophistication is comparable to that in the United States, especially in hematology, to which the Japanese have made important contributions. The occurrence of leukemia in areas away from large population centers is more difficult to assess.

**Exposed Population**

Estimated average annual incidence of leukemia is shown in table 1 by distance from the hypocenter of the bomb\textsuperscript{*} for survivors who were residents of Hiroshima at the time of onset of leukemia. The group of survivors exposed at less than a thousand meters received a heavy radiation dose, while the group exposed at distances greater than 2000 meters received a negligible dose (fig. 3). The incidence of leukemia estimated in the

\textsuperscript{*}The hypocenter is the point on the ground which was directly beneath the center of the explosion of the atomic bomb. All distances given are calculated from this point.
The innermost group (1460/million/year) is greatly in excess of that which is seen in the group exposed at 2000 to 10,000 meters which received negligible radiation (29/million/year). These figures do not differ remarkably from those reported in previous reviews derived from the same type of estimation.

Table 2 gives incidence estimates derived from the Master Sample. It will be noted that instead of the 69 cases used in table 1 the restrictions imposed by the Master Sample definitions reduce the group to 42 cases. The distribution of these cases by exposure distance is shown. The agreement between the leukemia incidence estimates based on the population of Hiroshima (shown in table 1) and those derived from the Master Sample (table 2) suggests that differential death and/or migration rates, if present at all, are not sufficient to distort the incidence estimates. It is of interest to note that the estimates of
incidence of leukemia in the most distant group (29/million/year) are in excellent agreement with recent estimates of leukemia incidence reported for the Japanese population as a whole (24/million/year).26

**Dose-Response Relation**

Early in 1958 air dose estimates were made available to the ABCC by Oak Ridge National Laboratory. More recently a discussion of these dose estimates, their derivation
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and comparability to previously published dose estimates for Hiroshima bomb appeared. Figure 3 illustrates the dose curves for neutron and gamma radiation as a function of horizontal distance in meters from the hypocenter. The two components are given separately in rads. The neutron contribution is calculated as a first collision dose. The figures for actual dose are not considered precise, as indicated by the assigned 50 per cent confidence limits. The slope of the curve, however, relating rad to distance (in meters from the hypocenter) is considered to be quite accurate.

The ideal use of these dose curves would be to calculate the actual dose of radiation received by individual members of a large population sampled in a random fashion. Unfortunately, information dealing with the specific shielding circumstances of a randomly selected population is not available. An estimate of the general shape of the curve relating dose of radiation received to rate of occurrence of leukemia can be made, however, by utilizing the large portion of the Master Sample located in Japanese style wood frame houses at the time of exposure. The construction of this type of building is relatively uniform, and shielding for the group should be similar. The estimated amount of radiation received by individuals in Japanese style light wood frame houses is around 0.7 and 0.4 of the outside level for gamma rays and neutrons, respectively. Further tests must be done before the effect of orientation in the house of the survivors with regard to windows, doors, etc. on dose, can be made. This last is also true of the effect of neighboring houses. In Hiroshima there were only a few large concrete structures which could have shielded neighboring houses. Therefore, shielding by adjacent buildings other than those of comparable construction is probably not a factor of importance. Similarly, topography should have little effect because Hiroshima is located on a large flat river delta. The dosage estimate for groups of survivors located in succeeding 200 meter intervals from the hypocenter which were in Japanese style houses has been made by taking the dose in rad for the center of each distance interval and applying it to the group in question.

For estimating the total dose (gamma plus neutron) of radiation received by the survivors, we have arbitrarily selected an RBE (relative biological efficiency) of 1 for neutrons. There are no estimates presently available for the relative leukemogenic effect of neutrons in humans. Calculation of the effect of varying the RBE of neutrons from 0.1 to a factor of 5 or more indicates that between values of 0.1 to 2 the shape of the dose-response curve is not altered. When an RBE of 5 is used for neutrons a sigmoid-shaped dose-response curve is produced. The dose in rads, however, at an RBE of 5 stretches the limits of credibility. This is true even if the lower limits of dose (fig. 3) and the upper limits of attenuation of radiation by shielding are used for the calculation. Accordingly, it seems likely that the RBE for neutrons must be close to unity or, quite possibly, less. Another possibility is that tissue depth dose distribution is the most important consideration. The neutron dose here employed is calculated as a first collision dose rather than, as would be more appropriate for large mammals, a multiple collision dose. Therefore, any selected figure for dose of neutrons must be viewed with considerable skepticism.

Table 3 summarizes the findings for this group of survivors. Twenty-three cases of leukemia occurred in the population group under study at exposure distances for which radiation is a factor of importance. It should be stressed that the calculated dose has not been adjusted for attenuation of radiation by the shielding effect of houses, that the RBE for neutrons is unknown so that the arbitrary selection of unity may well be too high by an unknown factor and that the estimated dose in rads has wide limits of accuracy. Accordingly, the doses indicated are probably too high by at least a factor of 2 and perhaps more. This appears to be true on biologic grounds alone since survivors at a total body dose much in excess of 600 rad are unlikely. Eight person years at risk are assumed, and hence decrease in the population due to death or migration is not considered. There is no correction possible for deficiencies in case

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Table 3.—Japanese Style House Shielding—Master Sample:
Population Leukemia Incidence

<table>
<thead>
<tr>
<th>Distance from Hypocenter</th>
<th>(1) Estimated Dose (Center of interval) RAD.</th>
<th>Cases of Leukemia</th>
<th>Population</th>
<th>Incidence per 10^6 per year</th>
<th>(2) Estimated Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>000-699</td>
<td>-</td>
<td>0</td>
<td>27</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>700-899</td>
<td>2.620</td>
<td>3</td>
<td>210</td>
<td>1.790</td>
<td>1.020</td>
</tr>
<tr>
<td>900-1099</td>
<td>1.860</td>
<td>6</td>
<td>789</td>
<td>950</td>
<td>390</td>
</tr>
<tr>
<td>1100-1299</td>
<td>430</td>
<td>6</td>
<td>2,100</td>
<td>355</td>
<td>145</td>
</tr>
<tr>
<td>1300-1499</td>
<td>177</td>
<td>6</td>
<td>3,274</td>
<td>230</td>
<td>95</td>
</tr>
<tr>
<td>1500-1699</td>
<td>77</td>
<td>2</td>
<td>3,605</td>
<td>69</td>
<td>50</td>
</tr>
<tr>
<td>1700-1899</td>
<td>34</td>
<td>0</td>
<td>3,512</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>1900-1999</td>
<td>19</td>
<td>0</td>
<td>1,305</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2000-2499</td>
<td>&lt;0.1</td>
<td>9</td>
<td>342.279</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>2500-4999</td>
<td>&lt;0.1</td>
<td>9</td>
<td>342.279</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>5000-9999</td>
<td>&lt;0.0</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) Sum of gamma plus neutron (first collision dose) radiation. No correction for attenuation by shielding.
(2) The standard error is taken as Incidence x sqrt(L) where L is the number of leukemias.

finding. Such correction could only increase the estimated incidence figures. Figure 4 is a graphic representation of these results. The background incidence from which the curve starts is a population value subject to quite small sampling variation. The survivors exposed at less than 900 meters are few in number and both the dosage and incidence estimates for this group are subject to such large sampling error that they are not included in the figure. The rates of table 3 appear to be best represented by a linear relation between dose of radiation and leukemia incidence, throughout the region in which adequate information is available. A vertical bar indicating standard error of the incidence is given. No similar horizontal bar showing standard error of dose is indicated because of the problems related to actual radiation dose discussed earlier. Nevertheless, it must be emphasized that each “point” really ought to be represented as an oval area of which the perimeter is poorly defined.

Considering the slope of the curve to be accurate and the actual dose received overestimated, it appears likely that a linear relation would hold over the dose ranges represented. In the lower dose range insufficient data preclude a prediction of the shape of the curve. This same material may be presented relating incidence of leukemia to distance rather than dose if a semi-log arithmetic plot is used giving incidence on the ordinate and distance from the hypocenter on the abscissa. Linearity exists in this example over the same regions as when “dose” is used. Inaccuracies in dose then do not appear falsely to have altered the relationship. The same reservations exist concerning the extremes of the curve at the nearest and greatest points from the hypocenter, i.e., at the highest and lowest dosage, when distance is used. The last point on the dose-response curve at which one can properly relate dose to incidence of leukemia is at a level of around 70 rads gamma plus 10 rads neutron. At this point the incidence of leukemia is elevated well above the background
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Fig. 4.—Incidence of leukemia—Master Sample: Japanese style house shielding.

incidence (fig. 4). A guess could be made on the basis of the 50 per cent confidence limits of the curve and on known factors of attenuation that linearity exists from a lower limit of dose of about 50 rad total body radiation. Below this lower limit of dose, uncertainty exists as to the shape of the curve.

These data, then, do not lend themselves readily to calculating a per rad risk for the development of leukemia, by reason of the uncertainties of actual dose received and the equal uncertainty of the shape of the curve in the lower dosage regions. It should be emphasized that the existence of a "threshold" effect is not disproved.

The Relation of the Acute Radiation Syndrome to Leukemia

Whether initial radiation signs and symptoms are a good index of the likelihood of subsequent leukemia must be considered. It is well known that there is a sigmoid relationship between incidence of acute radiation signs
LEUKEMIA IN HIROSHIMA ATOMIC BOMB SURVIVORS

Table 4.—Leukemia Incidence in Master Sample—Age and Sex

<table>
<thead>
<tr>
<th>AGE A.T.B.**</th>
<th>Distance from Hypocenter in Meters</th>
<th>0-999</th>
<th>1,000-1,999</th>
<th>2,000-10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Incidence</td>
<td>No. Incidence</td>
<td>No. Incidence</td>
<td></td>
</tr>
<tr>
<td>00-19</td>
<td>4</td>
<td>1.700</td>
<td>7</td>
<td>130</td>
</tr>
<tr>
<td>20-39</td>
<td>5</td>
<td>2.300</td>
<td>6</td>
<td>150</td>
</tr>
<tr>
<td>40+</td>
<td>2</td>
<td>1.100</td>
<td>8</td>
<td>160</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>3.000</td>
<td>10</td>
<td>170</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>800</td>
<td>11</td>
<td>130</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>1.700</td>
<td>21</td>
<td>150</td>
</tr>
</tbody>
</table>

* Per million Per Year. Years at Risk 1950-1957.
** A.T.B. is used to indicate age at time of bomb.

and symptoms and radiation dose in man.24 Of the 29 persons in the Master Sample who were exposed within 1500 meters, 20 had histories of severe acute radiation symptoms, while the remaining 9 had no severe manifestations. Most of the 9 who failed to show early signs of radiation sickness were located at the outer fringe of this distance interval. These 9 people unquestionably received a lower mean dose of radiation than did the 20 survivors who experienced acute radiation symptoms, and who were located closer to the hypocenter. The incidence for the group with severe radiation complaints is 870/million/year, while the estimate is 160/million/year for the group without severe initial radiation symptoms. The incidence estimated for each of these groups of survivors is significantly in excess of what would be expected. To learn the relative sensitivity of these two groups of survivors to leukemia induction, it would be necessary to know the actual radiation dose received by each individual. A comparison of the incidence estimate divided by the average dose received would be of great interest. These data are not available at present, but it is apparent that leukemia has developed in both groups, and that prior signs of severe acute radiation damage are not necessary for the subsequent development of radiation-induced leukemia.

Type of Leukemia

Table 4 shows the incidence of leukemia in different age groups of the Master Sample. As noted in an earlier report,25 the increase in incidence is seen in all of the age groups. The youngest age group (0 to 19), however, manifests the greatest susceptibility to radiation leukemogenesis in terms of degree of increase above the expected incidence for this age group, although the absolute incidence is higher in the group 20 to 39 years of age. From this table it is also apparent that the incidence in closely exposed males is considerably higher than in females.

Table 5 shows the incidence of the various types of leukemia observed in the Master Sample. The granulocytic leukemias seem to be most increased following radiation exposure, with the chronic variety showing the greatest increase in incidence. The small number of cases makes generalization difficult, but it is likely that all forms of leukemia, with the possible exception of
Table 5.—Incidence of Leukemia by Type

<table>
<thead>
<tr>
<th>Type of Leukemia</th>
<th>Japanese Exposed Survivors *</th>
<th>&lt; 2,000 m</th>
<th>2,000-10,000 m</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Incidence</td>
<td>No.</td>
</tr>
<tr>
<td>Acute Granulocytic</td>
<td>12</td>
<td>80</td>
<td>7</td>
</tr>
<tr>
<td>Chronic Granulocytic</td>
<td>15</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>Acute Lymphatic</td>
<td>3</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Acute - Type Unspec.</td>
<td>2</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Chronic Lymphatic</td>
<td>0</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>


chronic lymphocytic and the Schilling type of monocytic leukemia, are increased following exposure to ionizing radiation. The increase in the chronic granulocytic leukemias, however, is most striking. Incidence estimates for the distally exposed survivors and the nonexposed agree very closely. In addition, the relative proportion of the various types of leukemia is the same in each of these latter two groups.

It is well known that specific types of leukemia are more common at certain ages. The type distribution in Japanese people has been studied and reveals some interesting findings (fig. 5). The usual predilection to chronic granulocytic leukemia in the middle years of life is seen in both the closely and distally exposed groups. The absolute incidence, however, is remarkably higher in the closely exposed. The closely exposed survivors who were over 60 at exposure show a remarkable increase in acute granulocytic leukemia, while at the younger ages (0 to 9) the increase is most marked in the acute leukemias other than the clearly differentiated granulocytic type.

Natural History of Leukemia in Exposed Survivors

The analyses to this point have been predicated upon the assumption that leukemia in the exposed survivors is no different in its behavior from the naturally occurring variety of the disease. It has been the general impression of the numerous physicians who have studied the patients clinically and reviewed pathologic materials that the mode of onset, clinical signs and symptoms, response to therapy, mode of death and laboratory and pathology findings are similar. More specialized studies have been done on occasion (e.g., alkaline phosphatase studies on white blood cells, serum vitamin B₁₂ studies, etc.). These specialized efforts have not been continuous, and the relatively small group of patients who have had such studies is too small to warrant general conclusions. The problems of changing availability and types of therapy and the lack of comparability of treatment make it extremely difficult to interpret the results of survival time analyses based upon this relatively small group of patients. No large portion of the group has been followed by
any one group of physicians throughout the course of their disease, and it is very difficult, if not impossible, to compare the exposed and nonexposed after an amalgamation of these series. No differences of a gross nature, however, have been noted.

Leukemia Expectation

It has been suggested that radiation causes tumors to appear earlier in the life of a population without actually increasing the total number of tumors in its entire life-span. An analysis of mean age at onset of leukemia by exposure distance reveals a trend toward a younger age at onset in the more closely exposed individuals. The proof of the hypothesis requires, however, that no over-all increase in the total number of cases of leukemia will have been experienced by the exposed survivors during their life-span. Table 6 shows the expected number of cases of leukemia in each age group of the Master Sample exposed under 1500 meters, based on the expected number of years of survival of the group. Approximately 10 people would be expected...
Table 6.—Leukemia Expectation in the Portion of the Master Sample Exposed at less than 1500 Meters

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Males</th>
<th>No. Leukemia Predicted</th>
<th>No. Leukemia Observed in Life (1954-56)</th>
<th>Male &amp; Female</th>
<th>No. Leukemia Predicted</th>
<th>No. Leukemia Observed in Life (1954-56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>62.23</td>
<td>638</td>
<td>39,703</td>
<td>129,452</td>
<td>3.04</td>
<td>15</td>
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<tr>
<td>10-19</td>
<td>55.73</td>
<td>603</td>
<td>31,778</td>
<td>20.6</td>
<td>.89</td>
<td>3</td>
</tr>
<tr>
<td>20-29</td>
<td>36.11</td>
<td>151</td>
<td>29,062</td>
<td>13.2</td>
<td>.65</td>
<td>1</td>
</tr>
<tr>
<td>30-39</td>
<td>29.25</td>
<td>2.154</td>
<td>24.513</td>
<td>10.0</td>
<td>.63</td>
<td>5</td>
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<td>40-49</td>
<td>22</td>
<td>262</td>
<td>1.300</td>
<td>6.77</td>
<td>.38</td>
<td>5</td>
</tr>
<tr>
<td>50-59</td>
<td>18.60</td>
<td>306</td>
<td>4.100</td>
<td>20.4</td>
<td>.24</td>
<td>9</td>
</tr>
<tr>
<td>Sub-Total</td>
<td></td>
<td></td>
<td></td>
<td>20.4,999</td>
<td>3.10</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>20.4,999</td>
<td>3.10</td>
<td>14</td>
</tr>
</tbody>
</table>

* Based on 1956 Abridged Life Table for Japan, weighted by the composition of the Master Sample for the various intervals.

** Figures for the Kinki Region of Japan as reported at the Asian Hematology Society in April of 1958.

*** The Figures in parentheses represent the estimated number of leukaemias expected in the population’s lifetime based upon an incidence of 30/million/year, which is the maximum estimated for Japan.

to develop leukemia during the life-span of this group (based on an expected incidence of 30 cases of leukemia per million population per year, which is high for Japan). However, the number observed during seven years is 29.

Since the number of cases seen to date is even greater than the number expected in the entire lifetime of the group, it seems almost certain that ionizing radiation causes new occurrences of leukemia in humans rather than simply accelerating the appearance of leukemia in individuals who would have developed the disease at a later date.

The Changes with Time

The interval between exposure to radiation and the appearance of leukemia in humans is of great interest. The analyses so far presented here have involved over-all figures for the entire period of observation. The manner in which the findings change with time has many interesting facets, three of which will be considered separately:

1. The time at which the first detectable increase in the incidence of leukemia occurred.
2. The time at which the increase in incidence was maximal.
3. The length of time during which an increase is thought to persist.

The answer to the first question is beset by the complexity imposed by the possibility of inadequate case finding in the early years following the war. Thus, it is impossible to determine with certainty the minimum time for the development of radiation-induced leukemia. In the years prior to 1947 no case of leukemia was confirmed in a survivor who was resident of the city of Hiroshima at the time of onset of the disease. In 1947 to 1948, eight cases of leu-
Table 7.—Yearly Incidence of Leukemia—Master Sample

<table>
<thead>
<tr>
<th>YEAR OF ONSET</th>
<th>0-1500 (m)</th>
<th>No. Leuk.</th>
<th>Population</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>4</td>
<td>8,251</td>
<td>480</td>
<td></td>
</tr>
<tr>
<td>1951</td>
<td>5</td>
<td>8,087</td>
<td>620</td>
<td></td>
</tr>
<tr>
<td>1952</td>
<td>7</td>
<td>7,932</td>
<td>880</td>
<td></td>
</tr>
<tr>
<td>1953</td>
<td>3</td>
<td>7,774</td>
<td>390</td>
<td></td>
</tr>
<tr>
<td>1954</td>
<td>3</td>
<td>7,612</td>
<td>390</td>
<td></td>
</tr>
<tr>
<td>1955</td>
<td>2</td>
<td>7,456</td>
<td>270</td>
<td></td>
</tr>
<tr>
<td>1956</td>
<td>1</td>
<td>7,301</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>1957</td>
<td>4</td>
<td>7,171</td>
<td>560</td>
<td></td>
</tr>
</tbody>
</table>

Leukemia were confirmed, while in a nonexposed Japanese population of the same size, less than 5 cases would have been expected. It seems likely, therefore, that the minimum time from radiation to leukemia is less than 3 years.

Evidence bearing on the last two questions comes from three sources. These are the yearly incidence rates in the Master Sample, the way in which the morphologic type of leukemia changes from year to year, and the shift, with the passage of time, of the center of the leukemia population from the proximal to the distal segment. First, Table 7 distributes by year of onset of leukemia patients in the Master Sample exposed under 1500 meters. With the exception of the 1957 estimate, it appears that the incidence was maximal between 1950 and 1952, and subsequently fell. The baseline incidence expected in a nonexposed Japanese population has not yet been reached. Secondly, in the years in which the highest incidence was found, there was a more marked predominance of the chronic granulocytic form of the disease. As the incidence has waned, there has been a return toward the type distribution seen in a nonexposed Japanese population generally. Acute granulocytic leukemia is more common than chronic granulocytic leukemia in Japan. The ratio of chronic to acute leukemia in Japan is less than 1 (0.70—reference 28). Figure 6 shows the ratios of chronic to acute granulocytic leukemia plotted by year of onset in the exposed survivors.

Finally, yearly rates for the closely exposed survivors suggest that the likelihood of radiation-induced leukemia has been decreasing since the peak incidence between 1950 and 1952. An additional analysis may further illustrate this point. Figure 7 shows the relation between exposure distance and year of onset of all of the confirmed leukemia cases. The curve drawn through the median values has a parabolic shape and reflects a highly significant correlation. If extrapolated back to 1945, the curve should lie in the region of the midpoint of the population distribution of the survivors. It would be expected that the time at which the curve returns to its original level would correspond to the time at which the leukemogenic effect of radiation is no longer significant. The patients with onset of leukemia between 1948 and 1953 had been most closely exposed to the bomb and hence had received the highest average doses of radiation.

Thus, it would seem likely that following exposure to sublethal single dose gamma plus neutron radiation there is less than a three year minimum
period prior to the development of radiation-induced leukemia. The risk increases during the next two years and is maximal between four and eight years following radiation exposure. The risk apparently continues to exist as late as 13 years following significant radiation exposure. The evidence indicates, however, a gradual approach to the normal incidence.

Other Disease of Myeloid Tissue in Exposed Survivors

The dividing line is not sharp between leukemia and related disorders such as lymphomas, myelofibrosis, aplastic anemia and polycythemia vera. The lymphomas observed among exposed survivors have been few and are to be the subject of a subsequent report. Table 8 distributes by exposure distance the number of cases observed in this entire group of diseases. The number of cases in each category is small. With the possible exception of myelofibrosis with myeloid metaplasia, no striking relation to exposure distance is seen. This last diagnostic category has not been included in the analysis of leukemia although the evidence for a more than casual relationship to chronic granulocytic leukemia is good. The cases of polycythemia vera have likewise been excluded from the analysis of leukemia. At this writing none of the cases of polycythemia has terminated in a frankly leukemic picture.

The last group, the pancytopenias (either hypoplastic or refractory anemias), are included primarily because without adequate blood and bone marrow study, and occasionally postmortem examination, it is impossible to exclude "aleukemic" leukemia. There are only four confirmed cases in this category. The remainder are death certificate diagnoses of aplastic anemia. These cases do not readily lend themselves to statistical analysis.

Discussion

The material presented in this report confirms the leukemogenic property of radiation. Survivors of the Hiroshima atomic bombing who had been exposed...
Fig. 7.—Exposure—time of onset relation.

Table 8.—Myeloproliferative Disorders—Summary

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Acceptability</th>
<th>0-999</th>
<th>1000-1499</th>
<th>1500-1999</th>
<th>2000-2499</th>
<th>2500-4999</th>
<th>5000-10,000</th>
<th>Total</th>
<th>Not Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelofibrosis</td>
<td>Confirmed</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic Pancytopenia</td>
<td>Confirmed</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>3 EE*</td>
</tr>
<tr>
<td></td>
<td>Possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycythemia Vera</td>
<td>Confirmed</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (of above)</td>
<td>Confirmed</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>14</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Possible</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

*EE Refers to Early Entrant. These individuals entered the city within 30 days of the atomic explosion.

posed to the higher doses of radiation had a significant increase in leukemia incidence in the years following exposure.

A preliminary dose-response curve, based upon the observed incidence of leukemia in a group of survivors with relatively uniform shielding, is shown in figure 4. The dose figures are uncorrected for attenuation by materials other than air, and hence are approximately two times too high. The magnitude of the error involved in each estimate is large. Nonetheless, it is of interest that the relation appears to be linear, for air doses in excess of approximately 50 rad. It must be re-emphasized that the dose estimate is subject to error
and cannot at this time be corrected for attenuation by shielding factors. The controversy as to the shape of the curve between the lowest dose at which an increase in leukemia is shown and the origin of the curve (the incidence among persons with exposure only to background radiation) is receiving wide attention.\textsuperscript{30,40} No data currently are available which on analysis satisfactorily answer this question. It would seem reasonable that a cautious attitude be maintained toward the use of even small amounts of radiation. The magnitude of the risk must be opposed to the possible gain in each specific problem under consideration.

The British patients irradiated for ankylosing spondylitis were found to have an increased leukemia incidence primarily of the acute granulocytic type.\textsuperscript{12} In Hiroshima the closely exposed survivors who were over age 60 in 1945 have had an increased incidence of both the acute and chronic granulocytic leukemias. The people who were in the middle years of life at the time of exposure had an increase primarily in the chronic granulocytic form of leukemia. In the youngest survivors (i.e., those under age 20 at the time of exposure), the acute leukemias other than the clearly differentiated granulocytic type were most increased. The irradiated spondylitis patients and the closely exposed Hiroshima survivors differ in certain important respects. The former received x-radiation primarily directed toward their vertebral marrow in fractionated doses, the whole body equivalent of which, if delivered in a single dose, would be in the supralethal range. The atomic bomb survivors in Hiroshima received in a single whole body radiation exposure consisting of neutrons and gamma rays. The differences between the findings in the two series may be due in part to leukemia cases which might have been seen in the atomic bomb survivors who had received comparable doses but who expired of acute effects following massive single dose exposure. Patients with spondylitis may be different from normal people in their response to radiation alone or in combination with the other agents used to treat this condition.\textsuperscript{41} On the other hand, the type-specific incidence of leukemia normally seen in Japan is considerably at variance with the experience in Europe and the U. S. A. This may reflect a difference in the host which could in part account for the lack of exact correspondence of the radiation-induced leukemia experience in the two parts of the world.

The Japanese material supports the British studies in that a peak incidence of leukemia in humans can be expected about four years following radiation exposure. The number of cases of leukemia observed in the Japanese population to date is in excess of the number expected in the entire life-time of the population under study. At least in the case of leukemia, then, radiation in humans appears to cause new occurrences of the disease rather than simply accelerate onset of the disease.\textsuperscript{36,37,42} Through the year 1957, the rate of leukemia in the survivors is still elevated, indicating that the maximum latent period is at least 13 years. The clinical characteristics of leukemia seen among the Japanese survivors do not seem to vary from those which occur in the general population.

Moloney\textsuperscript{43} has pointed out that one cannot be certain that a given case of leukemia is truly the result of radiation exposure. He has suggested that a case
should not be accepted as a result of radiation which occurs less than one year following exposure because of the well documented long “preleukemic phase” of human leukemia. The upper limits of time, or the maximum length of the latent period, are poorly defined but are certainly 12 years and perhaps as long as 20. The data from Japan support these observations. If a case of leukemia occurs in a member of a population which has received unusual radiation exposure, if it can be demonstrated that there is an increased rate of leukemia occurring in the population as a whole, and if the case falls into the proper temporal relationships, then radiation can be implicated as a causal agent. Causality is further strengthened when the cell type is of the granulocytic variety. Two points are worthy of emphasis. The first is that at present only a presumptive relation between radiation and a given case of leukemia can be made. Leukemia occurs in human population with or without radiation exposure. A case which occurs in a group with an increased rate of leukemia following radiation exposure may well have occurred irrespective of the radiation. The second point is perhaps of greater importance. With the possible exception of exposure to low doses of radiation in utero,21 the studies in humans which have established a definite relation between radiation and leukemia have without exception involved groups of people exposed to fairly large amounts of radiation. Since the evidence for the leukemogenic effect of radiation in humans at present is primarily statistical, studies which examine the relationship at low doses (below 50 to 100 rad) are necessary before leukemia occurring in individuals exposed to doses of radiation in these ranges can be evaluated with regard to radiation causality.

Summary

The incidence of leukemia is higher among those closely exposed than among those more remote from the hypocenter. This increase was first manifest approximately three years following exposure. It apparently reached its peak between the years 1950 and 1952. Thereafter, the incidence has been diminishing, but 13 years after exposure it is still higher than would be expected in the general population. The type of leukemia most increased in incidence is the chronic granulocytic variety. No apparent difference in the natural history of the specific types of leukemia in exposed and nonexposed Japanese has been observed. Preliminary analyses of the data show a linear relation between dose of radiation and incidence of leukemia above 50 to 100 rad. Below this dose, the shape of the curve is not certain.

Summario in Interlingua

Inter le superviventes del bombardamento atomic de Hiroshima, le incidence de leucemia es plus alte in le subjectos qui esseva proximemente exponite al effectos del explosion que inter illes qui se trovava plus distante ab le hypocentro. Iste augmento esseva primo manifeste approximativemente tres annos post le exposition. Illo apparentemente atingeva su culmine inter le annos 1950 e 1952. Depost, le incidentia se has reducite, sed 13 annos post le exposition illo es ancora plus alte que lo que on expectarea super le base de studios del population general. Le typo de leucemia que se
augmentava le plus marcatemente in su incidentia es le varietate granulocytic chronic. Nulle apparenre differentia ha essite notate inter exponite e non-exponite japoneses con respecto al historia natural del varie typos de leucemia. Analyses preliminari del datos revela un relation linear inter le dose del irradiation e le incidentia de leucemia al nivellos inter 50 e 100 rad. Infra iste valores, le conformation del curva remane incerte.

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Leukemia in Hiroshima Atomic Bomb Survivors

ROBERT HEYSSEL, A. BERTRAND BRILL, LOWELL A. WOODBURY, EDWIN T. NISHIMURA, TARUNENDU GHOSE, TAKASHI HOSHINO and MITSURU YAMASAKI