Leukemia in Atomic Bomb Survivors

I. General Observations

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tOKUSO YAMAWAKI, M.D.

LEUKEMOGENESIS induced by repeated exposures to x-ray and other
forms of radiation energy has long been recognized in man and in experi-
mental animals.1-3 The explosion of the atomic bombs in Japan exposed two
large human populations to single brief but massive doses of ionizing irradiation
and subsequently a marked increase in leukemia among survivors was
reported.4, 5 The present study consists of a review of all cases of leukemia re-
ferred to the Atomic Bomb Casualty Commission from 1948 to April 1952 to-
gether with thirty-nine new cases, bringing the total to seventy-five established
cases of leukemia occurring in atomic bomb survivors in Hiroshima and Nagasaki
up to January 1, 1953.

METHODS AND MATERIALS

In the five year period from 1948 through 1952, one hundred and fifty cases of leukemia
were investigated by the Atomic Bomb Casualty Commission. Of these, twenty-six cases
were excluded because of failure to meet the criteria of adequate clinical and radiation data
with blood smears, bone marrow smears, or autopsy material available for study by the
authors.

The sources of the leukemia cases were as follows:

1. Patients encountered during routine medical and hematologic surveys of atomic bomb
survivors. Ten such cases have been discovered: four during a hematologic survey of nine
hundred epilated Hiroshima survivors originally studied in 1947-1948 by Snell, Neel, and
Ishibashi, and by Yamasowa in 1949,6, 7 and six during the medical survey of two thousand
five hundred and eighty adult survivors in Hiroshima and Nagasaki.8

2. Patients referred to the Atomic Bomb Casualty Commission by local physicians or
visited by Commission doctors in Hiroshima and Nagasaki hospitals.

3. Cases discovered through death certificates. Only those cases in which there was ade-
quate clinical and radiation history with blood and bone marrow smears available for study
by the authors were included.

In all, one hundred and twenty-four cases of leukemia were studied, seventy-five among
exposed and forty-nine in nonexposed individuals. The term "exposed", as used in this
report, is applied to anyone present in the cities of Hiroshima and Nagasaki during the
atomic bombings. Exposure is further qualified by the factors of distance from the hypo-

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of Sciences-National Research Council, with funds supplied by the United States Atomic
Energy Commission.

The authors wish to acknowledge the fact that this study would not have been possible
without the assistance of many American and Japanese physicians in Hiroshima and Nagas-
ki, too numerous to list by name. We wish especially to mention Dr. William N. Valentine
of the University of California at Los Angeles who in his capacity as a consultant to the
Atomic Bomb Casualty Commission gave marked assistance in the earlier phase of this
study.

574
TABLE 1.—Cases of Leukemia in Hiroshima City and Prefecture by Age and Exposure Distance

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Combined

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center,* shielding, and a history of the presence or absence of complaints indicative of radiation sickness following the bombing.

The same methods of study were used for both the nonexposed and exposed groups. Information concerning the nonexposed cases is included in this report; however, the data are not used in a comparative analysis because of the differences in the two groups in regard to age and sex.

An estimation of the surviving population presents many difficulties mainly because movements of survivors to and from the cities makes the determination of the number of survivors conjectural. In 1949 the Commission carried out a radiation census in an attempt to determine the numbers, age, sex, and distance from the hypocenter of the survivors residing in the cities of Hiroshima and Nagasaki, from which it was determined that there were 98,265 survivors in Hiroshima and 96,962 survivors in Nagasaki. In 1950, during the

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* The hypocenter is that point on the ground immediately below the bomb burst.
Japanese National Census, a questionnaire was included concerning survivors and figures were obtained from this census as to the number of survivors not only in the cities and prefectures of Hiroshima and Nagasaki but also for survivors residing in other parts of Japan. Since the leukemia cases reported in this study were encountered not only in the cities of Hiroshima and Nagasaki but also in the prefectures, an attempt has been made to calculate the combined city-prefecture survivor population. Since the total number, age, and sex of survivors in the prefectures were known but not the distance from the hypocenter, the figures for the cities in each age and sex category were expanded to include the prefectural survivors (see tables 1 and 2). This calculation presupposes that survivors moved out of the city to the prefecture in the same relative proportions for age, sex, and distance, a supposition which, of course, may not be correct. However, until further and more accurate information is obtained, these population estimates are the only ones available.
Results of Studies

Sex

Of the seventy-five exposed cases of leukemia as shown in figures 1, 2, and 3, there were thirty-eight males and thirty-seven females; of the forty-nine non-exposed cases there were thirty-one males and eighteen females. As shown in tables 1 and 2, in certain age groups there were relatively marked differences in the numbers of males and females. However, a statistical analysis of the Hiroshima data showed no influence of sex on the occurrence of leukemia among the atomic bomb survivors of that city. This is of some importance since twenty of the twenty-four cases of leukemia following radiation exposure reported up until 1942 occurred in males. This was undoubtedly due to the increased occupational exposure of males since the present study shows no sex difference in the occurrence of leukemia following the exposure to radiation.

Age

An analysis of the age influence on the leukemogenic effect of radiation has hitherto not been possible since all of the prior cases of leukemia, in which radiation has been implicated, have occurred in adults and were in the nature of an occupational hazard. The age at death or the present age of living individuals in this series is graphically shown in figure 4. (It should be noted that the age recorded here differs from that in tables 1 and 2, where the date of birth is re-
LEUKEMIA IN ATOMIC BOMB SURVIVORS. I

Fig. 2.—Distribution of leukemia cases by distance from the hypocenter compared to population of survivors in Nagasaki City and Prefecture.

corded.) In the exposed series there were ten cases of leukemia, 6 to 9 years of age; sixteen cases 10 to 19; fourteen cases 20 to 29; thirteen cases 30 to 39; nine cases 40 to 49; eight cases 50 to 59; and five cases occurring after the age of 60. By contrast, in the nonexposed series there were sixteen cases between the ages of 1 and 5 and six cases from 6 to 9. In the other age groups there were six cases in the 10 to 19 age group; five cases 20 to 29; four cases 30 to 39; four cases 40 to 49; five cases 50 to 59; and three cases beyond the age of 60. It is obvious from the disproportionate age groups and the sex differences that the nonexposed individuals in this series cannot serve as proper controls for the exposed groups in any discussion of comparative incidence or type of leukemia. Recent information indicates that most young infants were evacuated from the cities prior to the bombings. The lack of survivors in the lowest age group is shown in table 3. Another reason for the discrepancy in the age groups is apparent; because of the chaotic conditions and lack of medical facilities, no reliable information concerning leukemia is available before 1948 and therefore, no patient younger than 3 could have been included in this series. Actually the youngest patient reported in the exposed group was 6 years of age.

Experimental work indicates that young mice are more sensitive than older ones to the leukemogenic effects of radiation. In humans, prior experience with leukemia following radiation has been limited to adults. However, a statistical analysis of the Hiroshima data for exposed cases based on table 1 demonstrates that the leukemogenic effect of radiation is manifested in all age levels.
FIG. 3.—Combined data on cases of leukemia in Hiroshima and Nagasaki Cities and
Prefectures.

FIG. 4.—Distribution of exposed and nonexposed cases by age and sex.

represented in this series and, further, that there is no increased susceptibility
apparent in younger individuals, from the data collected thus far.

Type of Leukemia

The types of leukemia occurring in this series have been classified in the usually
accepted manner as myelogenous, lymphatic, monocytic, and reticulum cell. The
cases are further subdivided according to cell maturity and duration of the disease,
into acute, subacute, and chronic. In figure 5, which graphically portrays the
type of leukemia found in the exposed and nonexposed populations, the acute
and subacute leukemias are combined. In seven cases it was not possible definitely
to ascertain the cell type, and these were listed as acute leukemia, type un-
specified.

It may be seen from figure 5 that in the exposed group there are thirty-one
cases of chronic myelogenous, twenty cases of acute myelogenous, and twelve
cases of acute lymphatic leukemia. Of the remaining twelve cases, there were six
cases of acute leukemia, type unspecified, three cases of acute monocytic, two
cases of acute reticulum cell, and only a single case of chronic lymphatic leukemia.
In the nonexposed groups there were twenty-three cases of acute myelogenous
leukemia, fifteen cases of acute lymphatic leukemia, four cases each of chronic
myelogenous and acute monocytic, one case of acute leukemia, type unspecified,
and only two cases of chronic lymphatic leukemia.
The above observations are noteworthy in several respects. First, there is a marked difference in the types recorded for the exposed and unexposed groups, but this is no doubt related to the fact that the two groups are not matched by age. Secondly, myelogenous leukemia was the most frequent type reported in the exposed group and comprised fifty-one of the seventy-five cases. Thirdly, there has been only one case of chronic lymphatic leukemia in the exposed group. Some of the reasons for the lack of lymphatic leukemia in this series will be presented in the discussion. A fourth point of interest is that forty-three of the seventy-five cases in the exposed group were acute and thirty-two chronic, while in the non-exposed group forty-three of the forty-nine cases were acute and only six cases were chronic.

Incidence of Leukemia

The determination of the incidence of leukemia is complicated by the difficulties in the estimation of the number of survivors and the lack of information regarding the amount of radiation each survivor received. This has been partly overcome by the determination of the distance from the hypocenter, degree of shielding, and a careful evaluation of the radiation complaints occurring after the bombing.

The total number of cases of leukemia which have occurred in relation to the population are given in tables 1 and 2, and graphically represented in figures 1, 2, and 3. It is emphasized that the figures represent a five year compilation in a fixed exposed population which theoretically can only decrease through death but cannot increase its numbers as in a normal population. In the 2463 survivors...
exposed under 1000 meters, thus far eighteen cases of leukemia have been discovered. Among 17,508 survivors between 1000 and 1499 meters there were thirty-three cases and in the zone 1500 to 2499 there were 56,960 survivors and fourteen cases of leukemia. Thus, in the 76,891 survivors under 2500 meters sixty-five cases of leukemia have been found to date, while in the combined total of 159,285 people beyond 2500 meters who survived in both cities, there have been only ten cases.

Since no significant differences existed between the sexes or age groups in their susceptibility to the leukemogenic effect of radiation in a statistical analysis of the Hiroshima data, the exposed cases from both cities were combined and a highly significant difference in the incidence of leukemia among the four distance groups was found. In fact, the probability of obtaining so large a difference, granting that the groups are derived from a homogeneous population, is less than .001.

The significance attributed to distance from the hypocenter as a factor in exposure must be qualified by actual radiation absorption. Typical radiation complaints in an individual who was exposed to the atomic bomb, represent the best available evidence of a significant amount of radiation. However, owing to the questionable accuracy in history-taking, as well as to individual biologic variation, the value of such information may be equivocal. Moreover, LeRoy and others\textsuperscript{11, 12} have pointed out that bone marrow depression, as evidenced by leukopenia, occurred even in the absence of other symptoms of the acute radiation syndrome.

The presence of significant radiation complaints in the exposed individuals with leukemia has been analyzed and is shown in table 4. In all eighteen cases exposed under 1000 meters there were significant radiation complaints. Of the thirty-three patients exposed between 1000 and 1499 meters, twenty had significant radiation complaints, and of the fourteen patients between 1500 and 2499 meters, nine had significant radiation complaints. In contrast, none of the patients exposed beyond 2500 meters had significant radiation complaints.

An attempt was made to evaluate whether shielding at the time of the bombing was a factor in the eighteen asymptomatic patients exposed under 2500 meters. Of the eighteen, eleven were located in Japanese style houses which
TABLE 4.—Type of Leukemia Related to Distance from Hypocenter, Radiation Complaints, and Sex

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<td>M F M F</td>
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<tr>
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<tr>
<td>Total</td>
<td>- - 7 11</td>
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</table>

N R C No radiation complaints
S R C Significant radiation complaints

Fig. 6.—Distribution of exposed and nonexposed cases by year of onset. In two cases, the date of onset was not known.

would have offered a minimal amount of shielding. One individual was in a train but was shielded by the concrete station which probably offered protection from radiation. Another individual was in a steel frame workshop covered by galvanized metal. However, his exact position in the shop was unknown so the extent of the shielding factor cannot be determined. Only three people were said to have been in the open and therefore presumably completely unprotected. In two remaining cases, information on shielding was not available.

Date of Onset

In the cases of leukemia previously described among radiologists, it has been impossible to delineate a true latent period since the exposure consisted of small doses of radiation absorbed over a long period of time. It becomes of particular interest therefore to note the dates of onset of leukemia in this series, since these individuals had a brief single exposure to ionizing radiation in 1945. As shown in figure 6, five cases of leukemia dated the onset of their symptoms in 1947. In the following years there were twelve cases with the onset in 1948, seven cases in 1949, twenty-one cases in 1950, nineteen cases in 1951, and eleven cases in 1952.
In this series it is noteworthy that the largest number of cases had their onset in 1950, five years following exposure. Actually some cases have been seen in 1953, in which the onset of symptoms was in 1952, but these cases are not included since this report covers the material seen from 1948 through 1952. Cases of leukemia have been reported as occurring before 1947, but it has been impossible to authenticate these reports; therefore these cases are not included. It should be noted that owing to the attendant publicity and heightened interest, the diagnosis of leukemia has been made with increasing frequency among the non-exposed population in recent years (see fig. 6).

**DISCUSSION**

Recently Furth and Upton\(^\text{13, 14}\) pointed out the similarities between leukemia occurring in irradiated mice to leukemia in atomic bomb survivors. They state that in both there is ample evidence that a single massive exposure to irradiation was leukemogenic. In mice it was found that the leukemia-producing dose of irradiation was high (200 r). The observations on leukemia in survivors support the concept that gamma radiation of high energy was the chief leukemogenic agent and that a single massive dose produces leukemia in man. These data also support the premise that the leukemogenic dose of irradiation is high and that the incidence of leukemia is directly related to the amount of irradiation received. In experimental animals, leukemogenesis is influenced by age, and leukemia occurs more frequently in younger irradiated mice. However, in atomic bomb survivors, leukemia occurred in all age groups represented but it was pointed out that infants were evacuated from the cities prior to the bombings and few very young children were exposed to atomic radiation.

The distribution of types of leukemia in this series was markedly dissimilar to the well established pattern occurring in Western populations. In two large series of cases recently published, one from the United States and the other from Scotland, chronic lymphatic leukemia was found to occur most commonly.\(^\text{15, 16}\) However, in leukemia occurring among atomic bomb survivors, chronic myelogenous leukemia was most frequently encountered (41 per cent), with acute myelogenous leukemia second in frequency (20 per cent). To date only one case of chronic lymphatic leukemia has been seen in the seventy-five exposed cases. In view of this myeloid preponderance, it would be tempting to postulate that the increase of myelogenous leukemia was due to the direct effect of radiation on the marrow. However, while the groups are not comparable, it was noted that chronic lymphatic leukemia was also infrequent in the nonexposed series. Inquiry made among Japanese hematologists confirmed the suspicion that chronic lymphatic leukemia is comparatively rare in Japan. In view of this fact, it seems unwarranted to ascribe a preferential myeloid leukemogenic activity to radiation. Nevertheless, these findings are certainly worthy of further investigation.

Although a greatly increased incidence of leukemia has been found, the number of cases presented in this paper are in reality minimum figures. Cases of leukemia have undoubtedly been missed and other cases have been omitted because of the lack of adequate material to confirm the diagnosis. Some cases of leukemia in the exposed group probably occurred before 1947, and cases are still appearing among the exposed population. Another obvious fact is that among the heavily irradiated population many potential cases of leukemia perished in the bombing
or subsequently died of other causes. Ancillary information concerning the incidence of leukemia has been obtained in the adult medical survey in Hiroshima and Nagasaki where a total of six cases of leukemia have been found in a sample of two thousand five hundred and eighty randomly selected adults exposed under 1500 meters. This is an incidence of roughly 1:400. There have been no cases in an equal number of nonexposed controls of the same age and sex. Similarly, from a hematologic survey of nine hundred epilated individuals in Hiroshima, there have been four cases of leukemia, an incidence of 1:225. The data on these survey cases, together with the method of choosing the samples, are presented in another report.8

Observations on the occurrence of leukemia following a single massive dose of ionizing irradiation presented a unique opportunity to estimate more accurately the latent period of radiation-induced leukemia in man. Moreover, routine blood examinations carried out on survivors resulted in the detection of very early cases of chronic myelogenous leukemia. The hematologic and biochemical studies in these preclinical cases will be reported in a subsequent communication.

SUMMARY AND CONCLUSIONS

1. Observations on seventy-five established cases of leukemia occurring in people exposed to atomic bomb radiation are presented.

2. These data indicate a great increase in the incidence of leukemia among atomic bomb survivors due to a single massive exposure to ionizing radiation.

3. The leukemogenic effects of radiation are manifested equally in both sexes and at all age levels represented in this series.

4. The striking preponderance of chronic myelogenous leukemia compared to chronic lymphatic leukemia has been noted in exposed individuals but it is pointed out that chronic lymphatic leukemia is comparatively rare among the Japanese.

5. Cases of leukemia are still appearing in atomic bomb survivors. However, since 1950 there has been a steady decline in the number of cases.

SUMMARIO IN INTERLINGUA

Le presente studio consiste de un revist-a del 36 casos establite de leucemia in superviventes del bombardamenti atomic de Hiroshima e Nagasaki le quales esseva reportate al Commission pro le Victimas de Bombas Atomic inter 1948 e april 1952 insimul con 39 casos additional que augmenta le numero tot-al a 75. Le observationes resultante del studio es:

1. Le exposition unic e non repetite a un massa de radiation ionisante ha resultate inter le superviventes del bombardamenti atomic de Hiroshima e Nagasaki in un grande augmentation del frequentia de leucemia.

2. Le effectos leucemiogene del radiation es equalmente manifeste in ambe sexos e a omne etates representate in iste serie.

3. Es notate un frappante preponderantia de leucemia myelogene chronic super leucemia lymphatic chronic, sed on debe rememorar se que leucemia lymphatic chronic es comparativamente rar in Japaneses.

4. Nove casos de leucemia continua revelar se inter le superviventes del bom-
barded atomic. Nonobstante, ab 1950 un continue decrescentia de lor numero ha essite notate.

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Leukemia in Atomic Bomb Survivors: I. General Observations

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