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# Leukaemia in Nagasaki Atomic Bomb Survivors from 1945 through 1959 *

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*This review of the Nagasaki leukaemia experience during a period of 14 years after the detonation of the atomic bomb, together with comparisons with data from Hiroshima and from other series of post-radiation leukaemia cases, again demonstrates beyond reasonable doubt the leukaemogenic effect on man of ionizing radiation. An increased risk of leukaemia following doses probably as low as 100 rads (air-entry dose) of whole-body radiation is demonstrated on the basis of the available estimates of atomic bomb radiation doses. At doses above this level the increase in leukaemia incidence may be linearly related to the radiation dose. The data are too limited to allow of an evaluation of the risk represented by doses at the lower levels of radiation; but it seems clear that, if a threshold dose for leukaemia induction exists, it is lower than the threshold dose for the clinical expression of acute radiation syndrome.*

*The sex and age distribution of radiation-induced leukaemia and the types of leukaemia observed are also discussed.*

From time to time in the past sixteen years the results have been issued of surveys conducted on the rate of occurrence of leukaemia in survivors of the atomic bombings of Hiroshima and Nagasaki.[2] These interval reports on the studies in progress in Japan, along with studies on other irradiated populations, have established beyond reasonable doubt the leukaemogenic effect of exposure of human populations to large doses of ionizing radiation. A comparison of the data from these two cities with those from various other sources such as the British series of leukaemia cases following therapeutic irradiation, is desirable. In this report, I shall present the Nagasaki data in detail and compare these with Hiroshima data in some subjects.

## MATERIALS AND METHODS

### *Case-finding*

Leukaemia patients at the Nagasaki Medical School form the greater portion of the series. The staff of the haematological division in this school have continued to collect cases in close connexion with other hospitals and practising physicians in Nagasaki City and the US Atomic Bomb Casualty Commission since 1947. All deaths in Nagasaki from 1945 through 1959 were screened for conditions of haematological interest and in each case an attempt was made to confirm the diagnosis. The term " exposed " as used in this study means that the survivor was within 10 000 m of the hypocentre at the time of the explosion. It is a statement of location only, and does not necessarily imply that the survivor received detectable radiation.

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[2] Valentine, W. N. (1951) *Present status of the study of the incidence of leukemia among individuals surviving exposure to the atomic bomb in Hiroshima and Nagasaki* (unpublished technical report of the ABCC); Folly et al. (1952); Lange et al. (1954); Moloney & Lange (1954a, 1954b); Yamawaki (1954); Moloney & Kastenbaum (1955); Tomonaga et al. (1956); Watanabe & Ito (1956); Tomonaga (1957); Watanabe (1957a, 1957b); Wald (1958); Wald et al. (1958); Watanabe et al. (1958); Heyssel et al. (1960); Watanabe et al. (1960).

*Case review*

For each subject, an attempt has been made to obtain the material upon which the diagnosis was based. Clinical course, when known, was taken into consideration in arriving at the final diagnosis. Definitions of types of leukaemia are essentially those given by Amano (1948). By the end of 1959, 108 cases of leukaemia had been found among the Nagasaki exposed survivors with an additional three cases of leukaemoid reaction and 11 cases of aplastic anaemia. Of the 108 exposed leukaemia cases, 67 involved survivors resident in Nagasaki at onset of the disease and 23 involved survivors in the " Master Sample".[1]

*Analysis*

In an epidemiological study, knowledge of the population is of major importance. It is believed that in 1945, at the time of the detonation of the atomic bomb, there were approximately 174 000 people in the city of Nagasaki. The 1945 exposed population could not be reconstituted for this analysis, and therefore it is necessary to rely on samples defined on the basis of residence in Nagasaki at the time of the 1950 Japanese National Census. Data regarding the population of Nagasaki City were obtained from a publication compiled by the Department of General Affairs of the city and entitled "*A 65-year history of Nagasaki City*" (1956).

Since the exposed portion of the Master Sample is essentially complete it provides the basis for the most rigorous comparisons, but at the expense of much information. The Master Sample estimates will be used for the rigorous analyses, while the larger series will make possible a broader exploration. As results obtained by using the estimated population of the city have not differed greatly from those using only the Master Sample, the analyses will be based, whenever possible, upon the resident population of the city and exposed leukaemia patients and 40 non-exposed subjects who were resident in Nagasaki at onset of the disease. Analyses of the data on all 108 cases of leukaemia among the Nagasaki survivors will also be shown when estimates of incidence rates are not under discussion.

[1] From the 1950 Japanese National Census, the Atomic Bomb Casualty Commission (ABCC) has constituted the so-called " Master Sample ". The exposed portion of the Master Sample is a closed population composed of about 30 000 survivors who were living in Nagasaki on 1 October 1950. This Master Sample is still being compiled and was regarded as 99 % complete in April 1959.

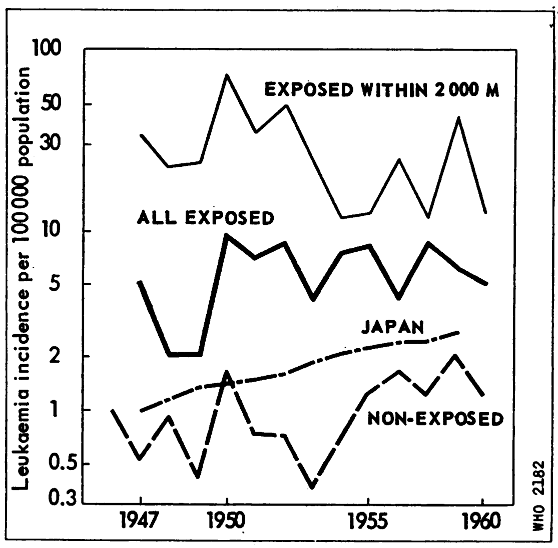
At present it is impossible to identify which of the cases were radiation-induced and which were spontaneous. To facilitate comparisons designed to identify possible differences, many of the analyses contrast the findings in survivors exposed under 1500 m with those in people who had been further away from the hypocentre. Since there were relatively few cases in persons between 1500 m and 2000 m (in particular, there was only one in the Master Sample), the more distant group used in these analyses (1500 m and over) probably contains few cases of radiation etiology. However, the distance groupings " under 2000 m " and " 2000 m and over " will be used when comparing the results in Nagasaki and in Hiroshima, because these were the groupings employed by Watanabe et al. (1960), whose data are quoted here for Hiroshima.

## RESULTS

*Incidence of leukaemia*

The annual incidence of leukaemia in the Nagasaki survivors and in Japan as a whole is shown in Fig. 1. There is considerable difficulty in specifying which were the very first cases of radiation-induced leukaemia. For survivors exposed under 2000 m the first case which came to our attention had its onset in October 1945 (Misao et al., 1960). It is very difficult to attribute this case to radiation. The

FIG. 1
ANNUAL INCIDENCE OF LEUKAEMIA IN NAGASAKI AND IN JAPAN AS A WHOLE



next cases noted had their onset in January and November 1947 in persons resident in the city at the time of onset, and the rate for that year is estimated at 3.63 per 100 000 population per year. The data suggest that the highest incidence was observed during 1950-52, and that it may subsequently have fallen. Although the numbers of cases are indeed small, the increased risk of developing leukaemia following radiation exposure is still greater than expected. Fig. 2 shows the number of cases by year of onset among persons exposed at under 2000 m in Nagasaki and Hiroshima.

The incidence of leukaemia is shown in Table 1, by distance from the hypocentre, for residents of the city during the period 1947-59. Of the total of 108 leukaemia cases among persons exposed to radiation in Nagasaki, 67 involved survivors still resident there at the onset of the disease. The rate of leukaemia in the most closely exposed survivors is 101.2 per 100 000 population per year. This rate is greatly in excess of the expectation for Japan (2-3 per 100 000 population per year). The rate decreases as the distance of exposure increases. The rate for the survivors located beyond 2000 m, where the estimated radiation dose was minimum (perhaps less than 20 rads), is 3.4 per 100 000 per year. This rate is greater than would be expected, and the increase is unexplained.

FIG. 2
LEUKAEMIA AMONG PERSONS EXPOSED AT UNDER 2000 M IN NAGASAKI AND HIROSHIMA, BY YEAR OF ONSET

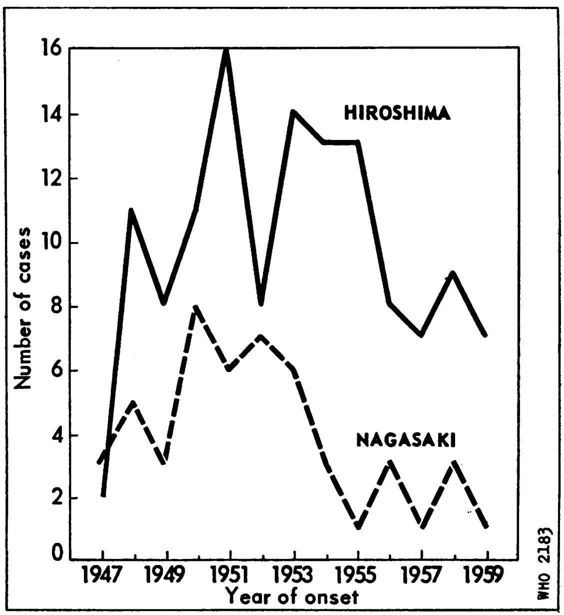



TABLE 1
INCIDENCE OF LEUKAEMIA IN RESIDENTS OF NAGASAKI AND HIROSHIMA, ACCORDING TO DISTANCE FROM HYPOCENTRE, 1947-59

| Exposure distance (m from hypocentre) | Nagasaki | | Hiroshima [a] | |
|---|---|---|---|---|
| | Cases | Rate [b] | Cases | Rate [b] |
| 0-999 | 6 | 100 | 20 | 100 |
| 1 000-1 499 | 22 | 54 | 40 | 27 |
| 1 500-1 999 | 5 | 10 | 19 | 7.1 |
| 2 000 and over | 34 | 3.4 | 18 | 1.8 |
| Total exposed | 67 | 6.0 | 97 | 7.0 |
| Non-exposed | 40 | 1.7 | 53 | 2.0 |
| Total exposed + non-exposed | 107 | 3.0 | 150 | 3.4 |
| Incidence for all Japan, 1947-58 | Cases = 20 305 | | Rate = 1.9 | |

[a] Hiroshima data from Watanabe et al. (1960).
[b] Rate per 100 000 population per year.

*Relation between leukaemia incidence and acute radiation syndrome*

Occasional statements have suggested that leukaemia developed at an increased rate almost exclusively in survivors who had suffered severe radiation exposure as manifested by a history of acute radiation syndrome. Among those of the Nagasaki survivors in the Master Sample who were exposed at under 1500 m and who developed leukaemia, seven had no history of acute radiation signs or symptoms, while eight had such a history. For the population so classified, the incidence estimates are 39 and 72 per 100 000 per year respectively, as shown in Table 2. These rates are not significantly different, but each is in excess of the expectation for Japan. Thus it must be recognized that if a threshold dose for leukaemia induction exists, it is lower than the threshold dose for the clinical expression of acute radiation syndrome.

*Relation between radiation dose and onset of leukaemia*

The difference in time of onset shown in Table 2 is of some interest. Since accurate dose information

TABLE 2

INCIDENCE OF LEUKAEMIA IN RELATION TO HISTORY OF ACUTE RADIATION SYNDROME FOR PERSONS IN ABCC MASTER SAMPLE EXPOSED IN NAGASAKI AT UNDER 1 500 METRES, 1950-58

| History of acute radiation syndrome | Number of cases | Man years at risk [a] | Rate [b] | Mean year of onset | Mean exposure distance (m) |
|---|---|---|---|---|---|
| Present | 8 | 11.070 | 72 | 1952.25 | 1 025 |
| Absent | 7 | 17.991 | 39 | 1954.00 | 1 171 |
| Total | 15 | 28.512 | 53 | 1953.06 | 1 093 |

[a] 1950 population multiplied by 9.
[b] Rate per 100 000 population per year.

for individual cases is not yet available, it is necessary to use an alternative approach in attempting to elucidate a relation between the radiation dose and the period of latency. The closely exposed Master Sample survivors who had histories of acute radiation syndrome had the onset of their disease 1.75 years earlier than did the leukaemia patients with no such history. Among the ten persons in the entire Master Sample with leukaemia who had been exposed at more than 1500 m, the mean year of onset was 1954.4. For the over-all sample irrespective of residence at the time of onset, there is a moderate but significant correlation between exposure distance and year of onset, as shown in Table 3. For these reasons, although the data are limited, it does seem likely that the interval between radiation exposure and the onset of leukaemia depends to some extent on the dose.

TABLE 3

MEAN YEAR OF ONSET AND EXPOSURE DISTANCE IN ALL LEUKAEMIAS AMONG EXPOSED PERSONS IN NAGASAKI,[a] 1947-59

| Exposure distance (m) | Cases | Mean year of onset |
|---|---|---|
| 0-999 | 6 | 1950.8 |
| 1 000-1 499 | 38 | 1952.1 |
| 1 500-1 999 | 6 | 1950.3 |
| 2 000-2 999 | 11 | 1954.6 |
| 3 000 and over | 47 | 1954.9 |

[a] Not necessarily resident in Nagasaki at time of onset.

*Dose response*

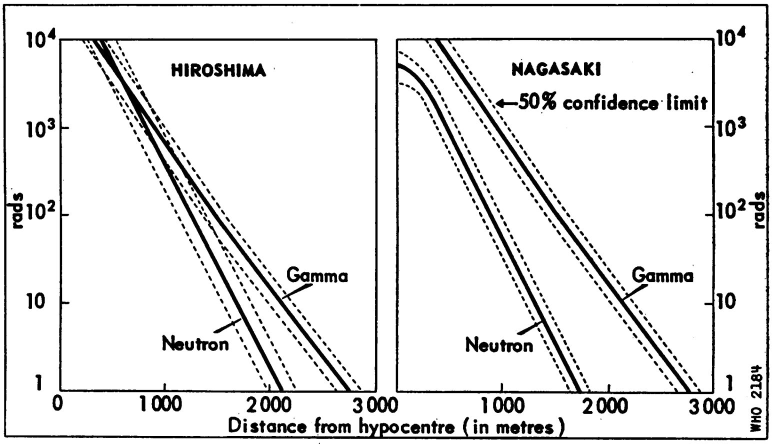
Dose response curves derived from experimental observations in plants and animals have been reported for various biological systems (Storer et al., 1957). The data for man are limited and the extrapolations to man of the results observed in lower animals are often challenged.

Recently the Oak Ridge National Laboratory has published curves (Fig. 3) showing the estimated air dose for neutrons and gamma rays at various distances from the hypocentre for the Hiroshima and Nagasaki bombs (Ritchie & Hurst, 1959). The figures are not considered precise, but it is felt that the slopes of the curves relating dose of radiation in air to distance are likely to be correct.

An accurate appraisal of the leukaemia risk following a given radiation dose requires knowledge of the number of leukaemia cases in a group receiving a known dose of radiation in a fixed time period. It would be essential to know the absorbed doses of radiation of the leukaemia-sensitive site and the neutron relative biological effectiveness (RBE). The necessary information is not yet available to permit this type of calculation for the Nagasaki material. A satisfactory alternative approach relies upon knowledge of distance and shielding of survivors located in the distance range where a significant air dose of radiation was present. Such knowledge is available for 25 persons in the Master Sample. For individuals who had been located in the open, no attenuation factor for passage through shielding material is applied. For those who were partly shielded, 15% attenuation of the air dose is assumed for the gamma-radiation and 25% for the neutrons. For persons who were inside houses of

FIG. 3

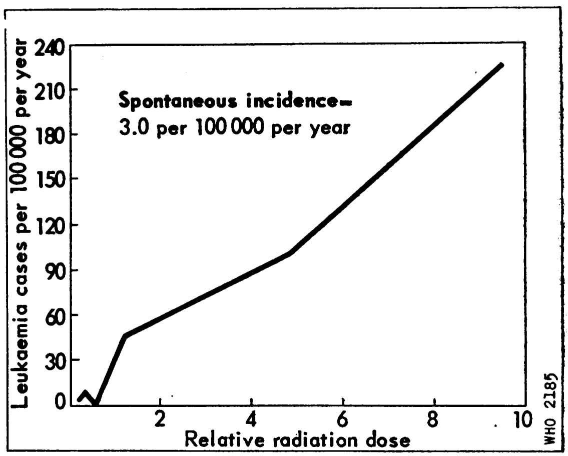
ESTIMATED AIR DOSE (NEUTRONS AND GAMMA RAYS) FOR HIROSHIMA AND NAGASAKI BOMBS, ACCORDING TO DISTANCE FROM HYPOCENTRE [a]




[a] After Ritchie & Hurst (1959).

FIG. 4

LEUKAEMIA AMONG LIGHTLY SHIELDED PERSONS IN NAGASAKI MASTER SAMPLE, 1950-58




the light Japanese style of construction, an attenuation of 30% of the air dose is assumed for the gamma-radiation and of 50% for the neutrons. These figures are based upon the average attenuation factors observed during test explosions in the Nevada desert (Ritchie & Hurst, 1959). To obtain the total tentative dose the gamma and neutron estimates were added in a 1 : 1 ratio. Persons in other shielding categories, including air-raid shelters and concrete buildings, cannot be used since the corresponding attenuation factors are not known. The air dose as estimated at the centre of each of the distance intervals was assigned to each person exposed in that interval after reduction in accordance with the appropriate attenuation factor. These results are shown graphically in Fig. 4. In assuming nine years at risk for each exposed survivor, the decrease in the population due to death and migration is neglected, and hence the incidence estimates are minimum. There is no correction possible for deficiencies in case-finding. Correction for all of these factors could serve only to increase the calculated rates. To emphasize the uncertainty in dosimetry, the estimated doses are shown in Fig. 4 as relative radiation dose, which is the air dose following attenuation by shielding calculated in rads and divided by 100. The number of cases upon which to base an estimate of the shape of the dose-response curve is small, and hence there are potentially large sampling errors associated with each incidence estimate. Although the points appear to be compatible with a linear model, the errors are such that the data are consistent with a variety of mathematical forms. However, it is interesting that Heyssel et al. (1960) found a similar linear dose-response relation from the Hiroshima sample.

*Type of leukaemia*

In Table 4 is shown the distribution of the entire series by type of leukaemia and distance from the hypocentre. The total absence of cases of chronic

TABLE 4

DISTRIBUTION OF ALL LEUKAEMIA CASES AMONG SURVIVORS EXPOSED TO ATOMIC BOMB RADIATION AT NAGASAKI, BY TYPE AND DISTANCE FROM HYPOCENTRE, 1947-59

| Type of leukaemia [a] | Exposure distance (m) | | | | | Total |
|---|---|---|---|---|---|---|
| | 0-999 | 1 000-1 499 | 1 500-1 999 | 2 000-2 999 | 3 000 and over | |
| AGL | 3 | 17 | | 6 | 19 | 45 |
| AML | 1 | 6 | 1 | 2 | 11 | 21 |
| ALL | | 4 | 1 | 1 | 6 | 12 |
| AUL | | 2 | 1 | | 6 | 9 |
| CGL | 2 | 9 | 3 | 2 | 5 | 21 |
| CLL | | | | | | |
| Total | 6 | 38 | 6 | 11 | 47 | 108 |

[a] AGL: Acute granulocytic leukaemia;
AML: Acute monocytic leukaemia;
ALL: Acute lymphocytic leukaemia;
AUL: Acute leukaemia, type unspecified;
CGL: Chronic granulocytic leukaemia;
CLL: Chronic lymphocytic leukaemia.

lymphocytic leukaemia is immediately apparent. The chronic granulocytic leukaemias seem to be disproportionately clustered in the zone of exposure under 1500 m as compared with the acute leukaemias, although this difference is not statistically significant. Table 5 shows the incidence of the various types of leukaemia observed in survivors resident in Nagasaki at the onset of the disease. For persons exposed at under 1500 m the rate of each type of leukaemia is significantly greater than even the total leukaemia rate for all of Japan. Table 6 shows the ratio of acute leukaemia to chronic granulocytic leukaemia in Hiroshima and Nagasaki. In Hiroshima, there is a tendency to a higher incidence of chronic granulocytic leukaemia among those exposed at a short distance. In Nagasaki the ratio

TABLE 5

INCIDENCE OF LEUKAEMIA IN SURVIVORS RESIDENT IN NAGASAKI AT TIME OF ONSET BY TYPE AND DISTANCE FROM HYPOCENTRE, 1947-59

| Type of leukaemia [a] | Exposed persons | | | | | | Non-exposed persons | |
|---|---|---|---|---|---|---|---|---|
| | Distance (m) | | | | Total | | | |
| | 0-1 499 | | 1 500 and over | | | | | |
| | Cases | Rate [b] | Cases | Rate [b] | Cases | Rate [b] | Cases | Rate [b] |
| AGL | 12 | 26 | 16 | 1.6 | 28 | 2.5 | 21 | 0.9 |
| AML | 6 | 13 | 10 | 1.0 | 16 | 1.4 | 6 | 0.2 |
| ALL | 4 | 9 | 4 | 0.4 | 8 | 0.7 | 4 | 0.2 |
| AUL | 1 | 2 | 4 | 0.4 | 5 | 0.4 | 5 | 0.2 |
| CGL | 5 | 11 | 5 | 0.5 | 10 | 0.9 | 4 | 0.2 |
| Total | 28 | 60 | 39 | 3.9 | 67 | 6.0 | 40 | 1.7 |

[a] AGL: Acute granulocytic leukaemia;
AML: Acute monocytic leukaemia;
ALL: Acute lymphocytic leukaemia;
AUL: Acute leukaemia, type unspecified;
CGL: Chronic granulocytic leukaemia.

[b] Rate per 100 000 population per year.

TABLE 6

RATIO OF ACUTE LEUKAEMIA (AL) TO CHRONIC GRANULOCYTIC LEUKAEMIA (CGL)

| Exposure distance (m) | Year | Nagasaki | | | Hiroshima | | Japan 1947-57 [c] |
|---|---|---|---|---|---|---|---|
| | | Cases | | AL/CGL | AL/CGL [a] | AGL/CGL [b] | |
| | | AL | CGL | | | | |
| Under 2 000 | 1947-48 | 6 | 2 | 3.0 | 1.1 | 0.4 | |
| | 1949-50 | 9 | 2 | 4.5 | 0.9 | 0.4 | |
| | 1951-52 | 9 | 4 | 2.2 | 1.2 | 0.4 | |
| | 1953-54 | 5 | 4 | 1.2 | 1.4 | 1.2 | |
| | 1955-56 | 2 | 2 | 1.0 | 0.3 | 1.7 | |
| | 1957-58 | 4 | 0 | — | 1.3 | | |
| | 1959 | 1 | 0 | — | 2.5 | | |
| | Total | 36 | 14 | 2.6 | 1.0 | 0.9 | |
| Over 2 000 | 1947-59 | 51 | 7 | 7.3 | 2.1 | | |
| Non-exposed | 1946-59 | 36 | 4 | 9.0 | 5.8 | | 2.3 |

[a] Data from Watanabe et al. (1960).

[b] Data from Heyssel et al. (1960), showing ratio of acute granulocytic leukaemia to chronic granulocytic leukaemia.

[c] Data from Komiya (1960).

among those exposed at a short distance is almost the same as that in Japan as a whole, but remarkably lower than in those exposed at a great distance and in the non-exposed.

*Relation between age at exposure and leukaemia incidence and type*

Table 7 shows incidence estimates for acute leukaemia and chronic granulocytic leukaemia by

TABLE 7

INCIDENCE OF LEUKAEMIA IN RESIDENTS OF NAGASAKI AT TIME OF ONSET BY AGE, DISTANCE FROM HYPOCENTRE AND TYPE, 1947-59

| Type of leukaemia | Age at time of bomb (years) | Distance from hypocentre | | | | | |
|---|---|---|---|---|---|---|---|
| | | Under 1 500 m | | | 1 500 m and over | | |
| | | Cases | Population [a] | Rate [b] | Cases | Population [a] | Rate [b] |
| Acute leukaemia | 0-19 | 16 | 24 450 | 65.3 | 13 | 499 212 | 2.6 |
| | 20-39 | 4 | 12 933 | 30.9 | 8 | 248 044 | 3.2 |
| | 40-59 | 3 | 8 088 | 37.1 | 13 | 244 716 | 5.3 |
| | 60 and over | 0 | 1 068 | — | 0 | 55 455 | — |
| Chronic granulocytic leukaemia | 0-19 | 4 | 24 450 | 17.8 | 2 | 499 212 | 0.4 |
| | 20-39 | 0 | 12 933 | — | 3 | 248 044 | 1.2 |
| | 40-59 | 1 | 8 088 | 12.4 | 0 | 244 716 | — |
| | 60 and over | 0 | 1 068 | — | 0 | 55 455 | — |

[a] Estimated Nagasaki City resident population; sum of person-years at risk, 1947-59.

[b] Rate per 100 000 population per year.

TABLE 8
RATIO OF MALE TO FEMALE LEUKAEMIA CASES IN NAGASAKI AND HIROSHIMA

| Type of exposure | Nagasaki | | | Hiroshima | | |
|---|---|---|---|---|---|---|
| | Males | Females | Ratio | Males | Females | Ratio |
| All exposed persons | 69 | 39 | 1.8 | 79 | 76 | 1.0 |
| Persons exposed at under 2 000 m | 31 | 19 | 1.6 | 68 | 61 | 1.1 |
| Non-exposed persons [a] | 37 | 21 | 1.8 | 43 | 29 | 1.5 |
| All Japan, 1949-58 | Males = 10 085 | | Females = 7 430 | | Ratio = 1.4 | |

[a] Total number of leukaemia cases in non-exposed persons observed in Nagasaki or Hiroshima, regardless of place of residence at onset of disease.

age-group among those resident in Nagasaki at the time of onset.

The data are compatible with an increase in leukaemia incidence at all ages, with a possible disproportionate increase in both types among the youngest age-group, to whom may be shifted the high incidence of chronic granulocytic leukaemia more usual in the middle years of life.

### *Relation between sex and leukaemia incidence*

There seems to be a difference between Nagasaki and Hiroshima in the sex ratio of leukaemia among exposed persons, as shown in Table 8. In the Nagasaki Master Sample (Table 9), the incidence in males is approximately three times that in females in the close-distance group, where radiation is clearly a factor. Furthermore, in Nagasaki females, the incidence was approximately three times the expectation while in males it was seven to eight times, as shown in Table 10. These figures suggest that in those males who had been closely exposed to the bomb the increment in leukaemia incidence is greater than in females. However, in Hiroshima the increase in leukaemia over the lifetime expectation is approximately the same in males and females. This disparity between the findings in the two cities is apparently the result of differences in shielding. It is known that in Hiroshima the more closely exposed females had less shielding than did the males, but in Nagasaki the distribution of available shielding did not show this strong relation to sex.

### *Expected lifetime incidence of leukaemia*

The cause of spontaneously appearing leukaemia in man is unknown. Similarly, the mechanism by which radiation causes leukaemia is unknown. In view of the speculation regarding the aging effect of ionizing radiation, it is important to examine whether or not the number of leukaemias in the exposed population is greater than the lifetime incidence for the non-exposed.

TABLE 9
INCIDENCE OF LEUKAEMIA IN NAGASAKI MASTER SAMPLE, BY SEX, 1950-58

| Sex | Distance from hypocentre | | | |
|---|---|---|---|---|
| | Under 1 500 m | | 1 500 m and over | |
| | Cases | Rate [a] | Cases | Rate [a] |
| Male | 11 | 93 | 5 | 6 |
| Female | 4 | 28 | 3 | 3 |

[a] Rate per 100 000 population per year.

An observation that would be consistent with an aging phenomenon would be that leukaemia occurred earlier in the lifetime of the exposed group but with no increase in the number of cases. Table 10 shows the expected number of cases of leukaemia in each age-group of the Master Sample exposed at under 1500 m, separately for males and females, based on the expected numbers of years of survival of the group and on the current leukaemia rates in Japan (Wakisaka, 1958). In the males, 11 cases were confirmed in the survivors exposed at under 1500 m during the nine years 1950-58. During the entire lifetime of the group of male survivors, 1.39 cases would have been expected from the rates in Japan.

In the females, 4 cases were observed whereas 1.25 cases would have been expected. Thus the data are not consistent with aging being the sole or primary effect.

TABLE 10

CONFIRMED LEUKAEMIA CASES COMPARED WITH LIFETIME EXPECTATION OF LEUKAEMIA AMONG PERSONS EXPOSED AT UNDER 1 500 METRES, BY SEX AND AGE AT TIME OF BOMB, IN NAGASAKI MASTER SAMPLE, 1950-58

| Sex | Age at time of bomb (years) | Nagasaki | | Hiroshima | |
|---|---|---|---|---|---|
| | | Observed leukaemia | Lifetime expectation | Observed leukaemia | Lifetime expectation |
| Male | 0-9 | 6 | 0.37 | 4 | 1.16 |
| | 10-19 | 1 | 0.53 | 3 | 0.71 |
| | 20-39 | 1 | 0.29 | 7 | 0.55 |
| | 40-59 | 3 | 0.19 | 1 | 0.57 |
| | 60 and over | 0 | 0.01 | 2 | 0.05 |
| | Total | 11 | 1.39 | 17 | 3.04 |
| Female | 0-9 | 1 | 0.26 | 3 | 0.89 |
| | 10-19 | 3 | 0.56 | 1 | 0.65 |
| | 20-39 | 0 | 0.32 | 7 | 0.89 |
| | 40-59 | 0 | 0.10 | 5 | 0.63 |
| | 60 and over | 0 | 0.01 | 0 | 0.04 |
| | Total | 4 | 1.25 | 16 | 3.10 |
| Both sexes | | 15 | 2.64 | 33 | 6.14 |

*Natural history of leukaemia in the exposed survivors*

It would be very valuable if radiation-induced leukaemia could be distinguished from the normally occurring disease. However, it has been the general impression of the various physicians who have observed the patients during the course of their disease, during therapy, and at the time of death, and have afterwards reviewed the pathological material, that such a distinction cannot be made.

*Other related disorders in exposed survivors*

The dividing lines between the various myeloproliferative syndromes and the lymphomas and leukaemias are not precise. Table 11 shows the

TABLE 11

DISTRIBUTION OF TOTAL CASES OF LEUKAEMIA AND RELATED DISORDERS AMONG SURVIVORS EXPOSED TO ATOMIC BOMB RADIATION AT NAGASAKI, BY DIAGNOSIS AND DISTANCE FROM HYPOCENTRE, 1947-59

| Diagnosis | Distance from hypocentre (m) | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | 0-999 | 1 000-1 499 | 1 500-1 999 | 2 000-2 499 | 2 500-2 999 | 3 000 and over | |
| Leukaemoid reaction | 0 | 1 | 0 | 1 | 0 | 1 | 3 |
| Aplastic anaemia | 1 | 2 | 0 | 0 | 1 | 7 | 11 |
| Lymphoma | 0 | 3 | 1 | 2 | 5 | 33 | 44 |
| Leukaemia | 6 | 38 | 6 | 2 | 9 | 47 | 108 |

distribution of the observed disorders by type and exposure status among the survivors at Nagasaki. Leukaemoid reactions due to miliary tuberculosis or malignancy are few in number, as are aplastic anaemias. Lymphomas are rather common but the cases cluster in the more distant regions where radiation was minimal.

*Neutron-induced radiation and fallout*

The analyses mentioned above have been done without taking into account the neutron-induced radiation and fallout as a major source of contaminating radiation. The local fallout occurred after the explosion in the western suburbs of Hiroshima and in the Nishiyama area of Nagasaki, both about 3000 m from the hypocentre. The external integrated gamma dose from these radioactive fission products probably amounted to several rads in the Hiroshima black-rain area and to about 100 rads in Nishiyama (Arakawa, 1960). Therefore, fallout can be neglected as a major source of radiation, except for the Nishiyama area. In this area, a remarkable leucocytosis was found among the residents in the early stage after the explosion (Kikuchi, 1953; Irie, 1957); but no cases of leukaemia have been demonstrated.

The estimated doses of neutron-induced radiation in the hypocentre areas have been discussed and calculated very differently by two physicists (Arakawa, 1960; Shohno, 1960). Concerning the integrated dose from the time of the burst to infinite time, Arakawa gives figures of 100 rads in Hiroshima and 50 rads in Nagasaki, while Shohno calculates 1200 rads and 120 rads respectively.

In the case of Nagasaki, the probability of receiving even 50% of the calculated maximum dose is very small because of (1) the short lifetime of the elements, (2) the large decrease in radioactivity with increasing distance from the hypocentre, and (3) the fact that raging fires made entry and stay in this area practically impossible for a day. It seems unlikely that induced radioactivity would add very much to the external radiation received by the survivors. It may therefore be reasonable to estimate the dose for the individual survivors from the air dose curves for both neutron and gamma rays, exposure distance and shielding situation.

However, in the case of Hiroshima, if the higher estimates are accepted, the induced radiation may be significant.

Leukaemia patients were found among persons not directly exposed who entered the city after the burst: 28 cases in Hiroshima (S. Watanabe—personal communication) and 17 cases in Nagasaki (Tables 12 and 13). In Hiroshima, 23 patients out of 28 entered the city within 3 days of the bombing; in the Nagasaki cases there was no particular clustering of entrants. Unfortunately, the calculation of incidence rates of leukaemia in these " early entrants " is impossible at the present time.

Furthermore, the internal radiation from neutron-induced radioactive elements in the body, especially $^{32}P$ in bone, cannot be dismissed. The continued existence of this source of radiation may play an important role in the development of leukaemia by modifying the regeneration mechanism of haematopoietic tissue, even though the dose is small.

TABLE 12

LEUKAEMIA INCIDENCE AMONG PERSONS ENTERING NAGASAKI OR HIROSHIMA SHORTLY AFTER DETONATION OF THE ATOMIC BOMBS

| Year of onset of leukaemia | Time of entry after detonation of bomb | | | | | |
|---|---|---|---|---|---|---|
| | Nagasaki | | | Hiroshima | | |
| | Within 3 days | 4-6 days | 7 days and over | Within 3 days | 4-6 days | 7 days and over |
| 1946 | | 1 | | | | |
| 1947 | | | | | | |
| 1948 | | | | | | |
| 1949 | | | | | | |
| 1950 | | | 2 | 1 | | |
| 1951 | | 1 | | 1 | | |
| 1952 | | | | 1 | | |
| 1953 | 2 | | | 1 | | |
| 1954 | | | 1 | 2 | | |
| 1955 | | 1 | | 1 | | 1 |
| 1956 | 1 | 1 | | 3 | | |
| 1957 | | 1 | 1 | 6 | | |
| 1958 | 2 | | 1 | 2 | 1 | |
| 1959 | 1 | 1 | | 3 | 1 | 1 |
| 1960 | | | | 2 | | 1 |
| Total | 6 | 6 | 5 | 23 | 2 | 3 |

TABLE 13

TYPE OF LEUKAEMIA AMONG PERSONS ENTERING NAGASAKI OR HIROSHIMA SHORTLY AFTER DETONATION OF THE ATOMIC BOMBS

| Time of entry after detonation (days) | Nagasaki | | | Hiroshima | | |
|---|---|---|---|---|---|---|
| | Acute leukaemia | Chronic granulocytic leukaemia | Total | Acute leukaemia | Chronic granulocytic leukaemia | Total |
| 1 | 2 | 1 | 3 | 4 | 3 | 7 |
| 2 | 2 | | 2 | 5 | 5 | 10 |
| 3 | | 1 | 1 | 1 | 5 | 6 |
| 4 | 3 | 1 | 4 | | | |
| 5 | 1 | | 1 | | 2 | 2 |
| 6 | | 1 | 1 | | | |
| 7-14 | 4 | | 4 | 1 | 2 | 3 |
| 15-28 | 1 | | 1 | | | |
| 29 and over | | | | | | |
| Total | 13 | 4 | 17 | 11 | 17 | 28 |

## DISCUSSION

Concerning the relation of leukaemia to ionizing radiation, there are several other studies in which the data are sufficiently numerous and where statistical coverage of the material is such that a comparison of findings is worth while. These include the studies of Court-Brown & Doll (1957) in the United Kingdom on leukaemia in persons given therapeutic radiation for ankylosing spondylitis, those in the USA of Simpson et al. (1955) on X-ray therapy in childhood for thymic enlargement, and a more recent study by Murray et al. (1959) on radiation exposure as related to leukaemia in children. Perhaps the most controversial studies have been those of Stewart et al. (1958) in the United Kingdom which relate foetal radiation exposure during X-ray pelvimetry to increased risk of childhood malignancies. Similar studies have been done by Ford et al. (1959).

These various studies are all epidemiological approaches to malignant disease done in retrospect, and each has certain deficiencies and limitations. Examination of consistencies and inconsistencies in the findings of the various studies must take into account the fact that the series are not directly comparable.

The Japanese studies are unique in that they cover a wide range of ages and both sexes and that there was a single intense exposure to whole-body radiation of varying amounts. There is no apparent reason why the population of Nagasaki and Hiroshima should have a rate of leukaemia occurrence higher than that in the general Japanese population other than that it has been exposed to ionizing radiation. Further, the Japanese studies are, at least in part, prospective in design. The intensity of effort in case-finding has probably varied from year to year. Unquestionably the great amount of interest in leukaemia as " A-bomb disease " in the two cities has resulted in much heavier reporting of leukaemia than there would have been had there been no suspicion of a causal relationship; however, it seems unreasonable to assume that the great increase in the observed rates in exposed persons reflects scientific interest rather than radiation effect.

### *Incidence and dose response*

From the data presented there can be little doubt that the increased incidence of leukaemia in the atomic bomb survivors was large and was dependent on dose. The number of observed cases in persons exposed at less than 1500 m already exceeds the estimated number of cases which would have occurred in the entire lifetime of the population. The British series of X-irradiated patients with spondylitis, in which good estimates of dose are available, supports the dose-dependency hypothesis of leukaemia induction.

An estimate of the dose-response curve based on present dosimetric methods has been made. Evidence derived from 25 leukaemia cases in persons who were exposed in lightly shielded locations has been plotted against relative dose, and the curve appears to best fit a linear relation. Considerable confidence can be placed in the curve from 100 rads up to 1000 rads.

The complications of exposure geometry, inaccurate dosimetry, insufficient numbers of cases, and lack of knowledge of neutron RBE preclude accurate calculations at the present time. None the less, it seems necessary to present this preliminary information regarding the possible shape of the dose response relation.

*Age sensitivity*

The present data suggest that young people may be more sensitive to radiation induction of leukaemia than the older age-groups. The only other information regarding possible differences in age sensitivity of humans comes from therapy series. Court-Brown & Doll (1957) found that the most sensitive portion of the spondylitic irradiated group was in the older age range, but there were no very young individuals in this series. The data of Simpson et al. (1955) show a very high incidence of leukaemia in individuals exposed to radiation therapy in the early years of life for enlarged thymus glands.

In the Nagasaki and Hiroshima survivors exposed *in utero*, no case of leukaemia has been identified to date. However, the size of the group at risk is small, owing to high stillbirth, abortion and neonatal death-rates. There are fewer than 500 *in utero* survivors known who were exposed at distances under 2000 m. Many of these had been heavily shielded. Despite these problems the absence of detected cases is certainly of interest.

*Latent period*

The first increase in incidence among the Japanese survivors occurred 18 months to 2 years following exposure. The small number of cases and uncertainty as to the size of the population at risk make any estimate of rate for these early years quite undependable. The number of cases, however, is above what can be expected to have occurred " spontaneously " during this period, accepting even the highest population estimates. The observed annual incidence was apparently greatest at between 4½ years and 7½ years after exposure. However, it is apparent from the data that the risk of leukaemia has continued in the population as late as 14 years after exposure. There is no convincing evidence of any apparent waning of the effect.

There is good agreement with other data, particularly those of Court-Brown & Doll (1957), that during the 18 months to 2 years following radiation exposure leukaemia incidence begins to rise. A peak in the British series occurred approximately 4 years after radiation. Estimations from the data of Simpson et al. (1955) also fairly well support this figure of approximately 4 years for maximal incidence. One difference is that the increased leukaemia risk in the Japanese atomic bomb survivors continues at least as long as 14 years, whereas in the British series a definite waning occurred 8 years after exposure.

*Types of leukaemia observed after irradiation*

There is controversy as to the types of leukaemia thought to show an increase following radiation exposure. The various series utilizing patients irradiated at different times in life, through various portals, for varying lengths of time, and for different underlying pathological conditions, have differed in the type of leukaemia predominating. In the patients with ankylosing spondylitis who received radiation therapy, acute granulocytic leukaemia occurred most commonly. In the patients irradiated during childhood because of thymic enlargement, the increase was predominantly in acute lymphocytic leukaemia. In the Nagasaki survivors, it is apparent that both acute leukaemia of all types and chronic granulocytic leukaemia are most increased. It is also seen that 67% of the 21 cases of chronic granulocytic leukaemia occurred in people located at less than 2000 m whereas only 41% of all acute leukaemias occurred in this group. Thus, it would seem that the chronic granulocytic leukaemias are disproportionately clustered in the inner zones of exposure. In Hiroshima, the figures are respectively 89% and 79%. Court-Brown & Doll (1957) have suggested that the difference between the British and the Japanese series may indicate that the persons exposed to high doses delivered at high dose rates from the atomic bomb expired acutely, whereas patients who received high therapeutic doses of irradiation given chronically survived comparable doses and developed acute leukaemia. This implies that both dose rate and total dose affect the type of leukaemia. The fact that the incidence of chronic granulocytic leukaemia is greater in Hiroshima than in Nagasaki may have interesting implications as to the types of post-irradiation leukaemia, inasmuch as the components of radiation, neutrons and gamma rays, are different in the two cities.

## RÉSUMÉ

Poursuivant l'étude de la fréquence des leucémies chez les survivants des bombardements atomiques d'Hiroshima et de Nagasaki, l'auteur donne un compte rendu détaillé des données réunies à Nagasaki au cours des 15 dernières années, auprès des survivants qui avaient été exposés aux risques d'irradiation, c'est-à-dire se trouvant dans un rayon de 10 km de l'hypocentre de l'explosion. A la fin de 1959, on avait relevé parmi les survivants, 108 cas de leucémie, 3 cas de réaction leucémoïde, et 11 cas d'anémie aplasique. Le taux de leucémie chez les survivants les plus proches de la zone d'explosion est de 101,4 par 100 000 habitants (contre 2-3 en temps normal, au Japon). Ce taux s'abaisse à mesure que l'on s'éloigne du centre de l'explosion, et à 2 km, il n'est plus que de 3,4.

Les conséquences du risque accru de leucémie semblent s'être manifestées 4,5-7,5 ans après l'explosion, c'est dire qu'elles ont été particulièrement nettes durant la période 1950-52; elles étaient cependant sensibles encore en 1959. Tous les types de leucémie aiguë, et la leucémie granulocytaire chronique sont compris dans cette augmentation. Les hommes, et les sujets des groupes d'âge inférieurs semblent avoir été particulièrement sensibles.

Le risque de leucémie radio-induite est en rapport avec la quantité de rayonnement reçue. Les données concernant les doses faibles sont trop peu nombreuses pour que l'on puisse tirer des conclusions sur les conséquences des faibles doses de rayonnement. Cependant, on peut affirmer que s'il existe un seuil d'intensité de rayonnement provoquant la leucémie, il est moins élevé que celui à partir duquel se manifeste le syndrome clinique d'irradiation aiguë.

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