Chronic Lymphocytic Leukemia in Hiroshima and Nagasaki, Japan

By Stuart C. Finch, Takashi Hoshino, Takashi Ito, Michito Ichimaru, and Roland H. Ingram, Jr.

Chronic lymphocytic leukemia is a rare disease in Japan. Since the Atomic Bomb Casualty Commission (ABCC) initiated its leukemia case-detection program in 1950 only a few patients with this disorder have been identified in the cities of Hiroshima and Nagasaki. In this report the incidence of chronic lymphocytic leukemia during a 20 year period in both Hiroshima and Nagasaki is compared with the incidence in Japan and the United States.

Throughout most of Japan, chronic lymphocytic leukemia constitutes only 2 to 3 per cent of all leukemia. A recent review of 3,454 cases of leukemia that occurred between 1956 and 1961 showed that 2.6 per cent were chronic lymphocytic in type. The overall incidence of leukemia in Japan is about 30 per million per year. On the basis of these figures the chronic lymphocytic leukemia rate in Japan is about 0.8 per million per year. In the United States the leukemia incidence is about 60 per million per year, with chronic lymphocytic leukemia representing from 20 to 30 per cent of the total.

Thus, the incidence of chronic lymphocytic leukemia in the United States is about 15 per million per year, about 20 times that of Japan. The virtual absence of this type of leukemia in Japan, however, does not entirely account for the great disparity in the leukemia rates of Japan and the United States.

Method of Study

The Leukemia Detection Program at ABCC is conducted uniformly in both Hiroshima and Nagasaki. Attention is focused primarily on the occurrence of leukemia in residents of those cities but many patients with leukemia and related disorders are referred from outlying areas. Within each city all persons with leukemia, whether or not exposed to the atomic detonations of 1945, are carefully studied. The incidence rate of each type of leukemia is compared with the corresponding rate in a standard population or a group of persons in which the incidence of leukemia is well known.
leukemia is calculated for the city populations of Hiroshima and Nagasaki for calendar
year and for age of patient at the onset of the disease.

For the present report, clinical records and histologic material at ABCC were reviewed
for all patients who developed leukemia in the years 1946 through 1965. Particular at-
tention was focused on patients with lymphocytic leukemia. Smears of peripheral blood
and aspirated bone marrow were available from all patients suspected of having chronic
lymphocytic leukemia with the exception of 3 in whom bone marrow aspiration was not
performed.

The diagnosis of chronic lymphocytic leukemia was established on the basis of the
usual cytological and clinical findings which are well described. An increased absolute
count of mature small lymphocytes in the peripheral blood in association with marrow
infiltration with similar cells was observed. Clinical findings on physical examination were
varied according to the progress of disease, but generalized lymphadenopathy and hepa-
tosplenomegaly were considered to be significant abnormalities when inflammatory, toxic,
metabolic and malignant diseases which may cause these findings were excluded. Chron-
icity of leukemia was primarily based on the maturity of the predominant lymphocytes.
Excluded were those patients with lymphocytes containing nucleoli, fine chromatin net-
work or nuclear fissures. Histologic sections made from various organs obtained at autopsy
had to be characterized by marked hyperplasia of lymphoid tissue with destruction of
lymphoid architecture along with generalized tissue infiltration.

RESULTS

The diagnosis of chronic lymphocytic leukemia was confirmed in 6 patients
who were residents of Nagasaki City at the onset of their disease in the
1946-1965 interval. During this 20 year period the diagnosis of any type of
leukemia was confirmed in 170 residents of this population. Thus, chronic
lymphocytic leukemia represented 3.5 per cent of all leukemia in Nagasaki
City (Table 1), and its incidence for this period was 0.88 per million per year.

The total number of patients with leukemia, including those from the sur-
rounding areas, studied at ABCC in Nagasaki during the period for 1946 to
1965 was 364. Among this number, there were 11 cases of chronic lymphocytic
leukemia, representing 3.0 per cent of the total (Table 1).

There was not a single case of chronic lymphocytic leukemia among the
233 patients in whom the onset of leukemia occurred while they were residents
of Hiroshima City in the interval 1946-1965. A meaningful rate, therefore,
cannot be calculated for the Hiroshima City population.

Only 2 patients with chronic lymphocytic leukemia have been identified

<table>
<thead>
<tr>
<th>Type of Leukemia</th>
<th>City Cases Only</th>
<th>Total Referral Area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Cases</td>
<td>Per cent</td>
</tr>
<tr>
<td>Chronic Lymphocytic</td>
<td>6</td>
<td>3.5</td>
</tr>
<tr>
<td>Other</td>
<td>164</td>
<td>96.5</td>
</tr>
<tr>
<td>Total</td>
<td>170</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 1.—Chronic Lymphocytic and Other Types of Leukemia,
by City and Area of Ascertainment (1946-1965)
CHRONIC LYMPHOCYTIC LEUKEMIA

at ABCC in Hiroshima among all 487 patients known to have developed leukemia in the 1946-1965 period, including patients from the surrounding area. Thus, only 0.4 per cent of all leukemia seen at ABCC in Hiroshima has been chronic lymphocytic in type. Whether the population of Hiroshima actually has a lower risk of chronic lymphocytic leukemia than the Nagasaki population, as suggested by these observations, remains moot. The 0 and 6 division, corresponding to average populations of 442,000 and 367,000 in the 20 year interval, is the least probable sampling result under the null hypothesis, and corresponds to a probability of about .048, but since the rest is not on an a priori hypothesis, any judgment of probability is arbitrary. At the level of 2 per 487 vs. 11 per 364 for the entire referral areas, the discrepancy is more impressive, especially in a two tailed test, but again it is one suggested by the data and thus warrants no more than the verdict "suggestive."

All 13 patients with chronic lymphocytic leukemia had 70 per cent or more mature-type small lymphocytes in their peripheral blood smears and with two exceptions the total leukocyte count exceeded 40,000 per mm³. (Table 2) Every smear of aspirated bone marrow showed the characteristic marked generalized increase in mature lymphocytes, including the above 2 patients whose marrow lymphocytes were 50 per cent or more of the total nucleated cells. The majority of patients had generalized lymphadenopathy and hepatomegaly, and less frequently splenomegaly. The most frequent reason for hematologic investigation was lymphadenopathy, but in 2 patients the disease was discovered accidentally. Response to chemotherapeutic agents was not unusual. Among 13 patients, 7 died within 1 year after the diagnosis was established due mainly to severe complications of tuberculous, viral, fungal or acute bacterial infections. The mean age of onset was 52 years and of the 13 patients, 5 were male and 8 were female. At the time of the atomic detonations in Hiroshima and Nagasaki, 5 of the patients who later developed chronic lymphocytic leukemia were within the city limits but each was more than 3,000 meters from the hypocenter.

DISCUSSION

The present review confirms the rare occurrence of chronic lymphocytic leukemia in Japan. Reasons for the relative infrequency of this particular lymphoproliferative disorder in Japan, however, are not known. It has been suggested that genetic factors probably are of greater importance than environmental influences.14 Although chronic lymphocytic leukemia is primarily a disease of later life, its low incidence in Japan is not accountable for on the basis of reduced life expectancy. It also does not appear that there is a compensatory increase in the other lymphoproliferative disorders. The incidence of malignant lymphoma in Japan is about one third that in the United States and the ratio of death from all leukemia to all lymphoma in Japan is about 1.5 times higher than in the United States.15,16 The lymphoma most frequently confused with chronic lymphocytic leukemia is lymphosarcoma. In Japan 20-30 per cent of all lymphomas have been classified as lymphosarcoma.17-20 In two large series in the United States 25-44 per cent of all lymphomas were diagnosed as lymphosarcoma.21,22 About 20 per cent of all
Table 2.—Chronic Lymphocytic Leukemia in Hiroshima and Nagasaki, 1946-65. Clinical Features and City of Ascertainment.

<table>
<thead>
<tr>
<th>Master File Number</th>
<th>City</th>
<th>Year of dx</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Generalized adenopathy</th>
<th>Hepatomegaly</th>
<th>Splenomegaly</th>
<th>Hgb Gm.%</th>
<th>WBC x1000 /mm.³</th>
<th>% lymphs P. Blood</th>
<th>% lymphs marrow</th>
<th>Survival in Months</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>181-537</td>
<td>N</td>
<td>1951</td>
<td>42</td>
<td>M</td>
<td>Adenopathy</td>
<td>Skin rash</td>
<td>+</td>
<td>+</td>
<td>14.4</td>
<td>61</td>
<td>95</td>
<td>95</td>
<td>205</td>
<td>(living)</td>
</tr>
<tr>
<td>178-876</td>
<td>N</td>
<td>1958</td>
<td>49</td>
<td>F</td>
<td>Adenopathy</td>
<td>Weakness</td>
<td>+</td>
<td>+</td>
<td>8.5</td>
<td>73</td>
<td>92</td>
<td>&gt;90</td>
<td>38</td>
<td>Died of Bronchopneumonia.</td>
</tr>
<tr>
<td>052-463 *†</td>
<td>N</td>
<td>1959</td>
<td>57</td>
<td>M</td>
<td>Weakness</td>
<td>Skin rash</td>
<td>+</td>
<td>+</td>
<td>13.4</td>
<td>127</td>
<td>88</td>
<td>73</td>
<td>4</td>
<td>Died of bronchopneumonia and liver abscesses.</td>
</tr>
<tr>
<td>119-208 *†</td>
<td>N</td>
<td>1959</td>
<td>51</td>
<td>F</td>
<td>Malaise</td>
<td>Nausea</td>
<td>0</td>
<td>+</td>
<td>9.9</td>
<td>199</td>
<td>70</td>
<td>30</td>
<td>5</td>
<td>Died of miliary tuberculosis.</td>
</tr>
<tr>
<td>029-711 *†</td>
<td>N</td>
<td>1960</td>
<td>51</td>
<td>M</td>
<td>Malaise</td>
<td>Night sweats</td>
<td>±</td>
<td>+</td>
<td>14.7</td>
<td>87.5</td>
<td>90</td>
<td>58</td>
<td>7</td>
<td>At autopsy had cytomegalic inclusion disease and active pulmonary tuberculosis.</td>
</tr>
<tr>
<td>Case No.</td>
<td>Sex</td>
<td>Age</td>
<td>Symptoms</td>
<td>Fever</td>
<td>Weakness</td>
<td>Malaise</td>
<td>Skin Rash</td>
<td>Adenopathy</td>
<td>Death Cause</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
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<tr>
<td>194-144</td>
<td>F</td>
<td>45</td>
<td></td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13.5</td>
<td>50</td>
<td>Died of cryptococcal meningitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>087-309</td>
<td>M</td>
<td>59</td>
<td>Weakness</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12.8</td>
<td>53</td>
<td>(living) 69</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>187-078</td>
<td>M</td>
<td>64</td>
<td>Malaise</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>13.6</td>
<td>48</td>
<td>At autopsy had thyroid cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>737-344</td>
<td>F</td>
<td>39</td>
<td>Adenopathy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>11.6</td>
<td>18.3</td>
<td>(living) 36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>080-513</td>
<td>F</td>
<td>61</td>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15.2</td>
<td>35</td>
<td>(living) 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>740-686</td>
<td>F</td>
<td>55</td>
<td>Ankle edema</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>8.5</td>
<td>143</td>
<td>Died of advanced pyelonephritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>446-757</td>
<td>M</td>
<td>49</td>
<td>Adenopathy</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8.0</td>
<td>56.7</td>
<td>Cause of death unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>447-815</td>
<td>M</td>
<td>59</td>
<td>None</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14.0</td>
<td>169.5</td>
<td>Died of bronchopneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patient was resident in the city at the onset of leukemia.
† Patient was in the city district of Nagasaki at the time of atomic detonation.
N—Nagasaki
H—Hiroshima
leukemias in our study were of the subacute or acute lymphocytic types. In several large leukemia studies in the United States and England from 15 per cent to 30 per cent of all patients with leukemia were acute lymphocytic in type.\textsuperscript{23-25} The figures may vary, however, from virtually 100 per cent in children to somewhere between 4 per cent and 7 per cent in persons over ages 30.\textsuperscript{24,25} In Hiroshima and Nagasaki leukemia in children practically always is of the acute lymphocytic type, but in persons over 30 years it has been observed in less than 5 per cent of all leukemia in that age group.\textsuperscript{6} Thus there is no evidence for an increase in either lymphosarcoma or the more acute forms of lymphocytic leukemia to account for the low incidence of chronic lymphocytic leukemia in the populations of Hiroshima and Nagasaki. Perhaps the study of chronic lymphocytic leukemia in the Japanese residents of other countries will help to determine reasons for its rarity in Japan.\textsuperscript{26}

The fact that only 2 patients with chronic lymphocytic leukemia have been detected among the large number of leukemia patients in the Hiroshima area in contrast to the 11 found in the relatively smaller Nagasaki area was of some interest. Kawakita has reported that 6 per cent of all leukemia in the Kumamoto area is chronic lymphocytic in type.\textsuperscript{27} This region is in close proximity to Nagasaki. If, indeed, the incidence of chronic lymphocytic leukemia is higher in Nagasaki than in Hiroshima and elsewhere in Japan, it would be intriguing to consider the possibility that Western influences may be relevant, for Nagasaki was the only port continuously open to Western trade between 1637 and 1859.

There was some evidence from this study that chronic lymphocytic leukemia might even be overdiagnosed in certain areas of Japan. Several patients referred in Nagasaki with the diagnosis of chronic lymphocytic leukemia eventually were found to have either subacute lymphocytic leukemia or lymphoma with blood stream invasion. The general reporting of the more acute forms of lymphocytic leukemia differed little in the two cities, however. (Table 1).

Chronic lymphocytic leukemia usually can be distinguished from leukosarcoma and other forms of malignant lymphoma with peripheral blood involvement although sometimes their precise differentiation is most difficult. The short survival of about half of our patients suggested involvement with a form of lymphoproliferative disease more malignant than chronic lymphocytic leukemia. On the other hand, the clinical presentation of each patient was quite characteristic of chronic lymphocytic leukemia, and early death was attributed to some severe complication, usually infectious in nature. The possibility of a lymphocytic leukemoid reaction to tuberculosis was considered in our two patients with this disease.\textsuperscript{28} Lymphocytosis, however, rarely occurs with tuberculosis and in both our patients tuberculosis was felt to be a complication of the underlying leukemia.\textsuperscript{29}

Previous exposure to ionizing radiation is not related to the development of chronic lymphocytic leukemia in Hiroshima and Nagasaki. Although 5 of the 13 with this disorder were within the city limits of Nagasaki at the time of the atomic detonation in 1945, none was closer to the hypocenter than 3,000 meters. The dose of ionizing radiation from the bombs at a distance
of 3,000 meters from the hypocenters has been estimated at less than 1 rad.\textsuperscript{30} Reports from ABCC have failed to demonstrate an excessive leukemia incidence beyond 1,600 meters from the hypocenter.\textsuperscript{6} If exposure to ionizing radiation had been an important factor, one would have expected chronic lymphocytic leukemia to have developed more frequently in the proximally exposed populations of both cities. This has not been observed. Other studies in man have not found chronic lymphocytic leukemia to be related to excessive radiation exposure.\textsuperscript{31} On the other hand, Anderson et al. have noted some increase in occurrence of total malignant lymphoma among the heavily irradiated subjects in Hiroshima and Nagasaki on the basis of studies of autopsy and surgical pathology materials at ABCC.\textsuperscript{20} Further study on the incidence and type distribution of lymphoma in relation to radiation exposure is in progress at ABCC.\textsuperscript{32} It is anticipated that these studies will provide additional conceptual support for the interrelationship between leukemia and lymphoma.

**SUMMARY**

In Hiroshima and Nagasaki chronic lymphocytic leukemia is rare in comparison to the United States. No patient with this disorder was identified among the residents of Hiroshima City during a 20 year period of study. The incidence of chronic lymphocytic leukemia in Nagasaki City, however, was similar to that for all Japan. There is no evidence that the development of chronic lymphocytic leukemia in these cities was related to exposure to the atomic detonations of 1945.

**SUMMARIO IN INTERLINGUA**

In Hiroshima e Nagasaki, chronic leucemia lymphocytic es rar in comparation con le Statos Unite. Nulle patiente con iste disordine esseva identificate inter le residentes del Citate de Hiroshima durante un periodo de observation de 20 annos. Tamen, le incidentia de chronic leucemia lymphocytic in le Citate de Nagasaki esseva simile a illo de Japon in general. Il existe nulle evidentia in supporto del these que le disveloppamento de chronic leucemia lymphocytic in le mentionate citates esseva relationate al exposition al detonations atomic in 1945.

**ACKNOWLEDGMENT**

The authors are deeply indebted to the many physicians in the Hiroshima and Nagasaki area who have permitted evaluation of their patients with leukemia by physicians at ABCC. The authors also wish to thank Dr. Toranosuke Ishimaru and Dr. Paul S. Anderson for their valuable assistance in statistical analysis of the data and in revision of this report.

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