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Late Medical Effects of Atomic Bombs Still Persisting after over Sixty Years

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Sixty years ago, on August 6 and 9, 1945, two atomic bombs with similar physical powers were used to destroy the two cities of Hiroshima and Nagasaki. The physical effects of the bombs were the most enormous ever used as a weapon and destroyed the two intermediate-size cities in Japan almost completely. About 120,000 and 75,000 people of Hiroshima and Nagasaki, respectively, including many civilians and children in the two cities died instantaneously or of acute effects of radiation exposure. Almost the same number of people, having survived the acute effects, eventually faced the fear of late effects of atomic bomb irradiation such as leukemia and cancers.

Induction of cancer among proximally irradiated persons began to appear as early as three years after bombing. The first cancer was leukemia. The leukemia registry started around 1946 and most of the RERF epidemiological studies started around 1950. The incidence rate of leukemia quickly increased within five years (Figure 1) and reached its peak around 1950-55. There were three major types of leukemia, acute myeloid leukemia (AML), acute lymphoid leukemia (ALL) and chronic myeloid leukemia (CML).

Therefore the A-bomb irradiation induced 3 major types of leukemia, AML, ALL and CML, excluding CLL. CLL is basically a very rare disease in the ethnic Japanese population, in contrast to Caucasians. ALL and CML risks were elevated earlier and declined rapidly, whereas the AML risk was elevated relatively late, declined slowly, and persisted over decades. AML and CML were most prevalent among adults and ALL among children.

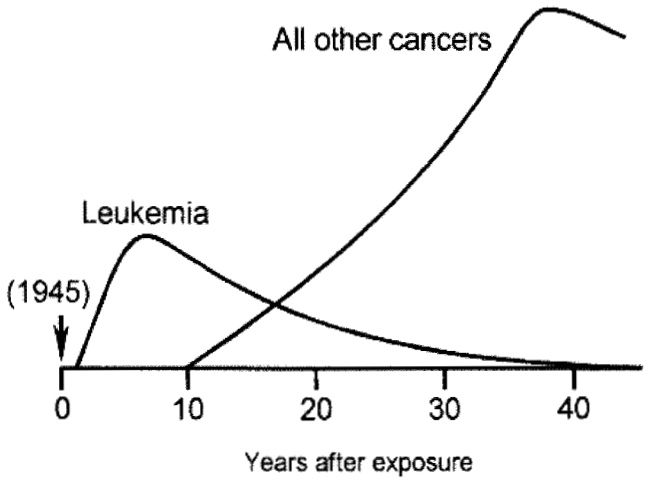

Figure 1. The atomic bomb irradiation induced leukemia as shown in the figure.

Especially among children, the leukemia rate almost jumped to fifty-fold times higher. The most recent summary results of statistics suggest that the leukemia risk begins to increase at an exposure dose of approximately 200 mSv in the form of a linear quadratic curve. This dose response curve is clear and direct evidence to the fact that atomic bomb irradiation actually induced human leukemia.

The elevated leukemia incidences declined rapidly for ALL and CML after 1955-1960 and gradually for AML over 1970-1980. However recent epidemiological investigation suggests an elevated incidence of myelodysplastic syndromes (MDS) among the proximally exposed persons during 1980-2004. MDS is a disease closely related to leukemia that was previously called pre-leukemia.

The myelodysplastic syndrome (MDS) is a disease of bone marrow and a disease of the elderly. MDS is a preleukemic state; about 25% of patients later develop acute myeloid leukemia (AML). MDS is a clonal disease originated in a stem cell, manifesting anemia and various kinds of cytopenia. In addition, the morphology of blood cells is abnormal. The disease entity of MDS was established in 1983. Thus it was not included in the previous epidemiological studies on atomic bomb survivors.

Anemia is the main symptom of MDS patients and as mentioned before, about 25% of them later develop acute leukemia. This finding is being observed both in Hiroshima and Nagasaki.

Previous publications on MDS in A-bomb survivors are few, consisting of only two publications. One is from survivors of the Life Span Study (LSS) cohort by the Radiation Effects Research Foundation (*in 1986, by Matuo T. et al.; and in 1998 by Oda K. et al.*) in which 12 MDS cases were identified among 190 cases of leukemia in the LSS cohort. A positive relation was found between the radiation doses (DS86) and incidence of MDS. Also 26 MDS cases were detected in Hiroshima among survivors of Hiroshima city (*in 2001, by Kimura A. et al.; and in 2002, by Takeuti et al.*) in which again a positive relation was found between the radiation doses (ABS97D)

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and incidence of MDS.

Now we have planned an MDS project in Nagasaki City with many collaborators including the Nagasaki Municipal Hospital, the Nagasaki Municipal Medical Center, Amenomori clinic, St. Francis Hospital in Nagasaki, The Japanese Red-Cross Nagasaki Atomic Bomb Hospital, Nagasaki Atomic Bomb Casualty Council (the Health Management Center), and the Atomic Bomb Disease Institute (Biostatistics section) from Nagasaki University Graduate School of Biomedical Sciences.

At the first step we got the crude number of MDS cases from January 1980 till March 2004 which included 1,222 cases. After data linkage, 647 cases were fixed from among them. Then at the second step a data linkage was done with the survivors' database so that 204 crude MDS cases were fixed. Finally at the third step a diagnostic review confirmed 162 cases as MDS among whom 119 cases had full information on distance from the hypocenter. Then we did a statistical analysis using stratification, descriptive analysis, and the Cox hazard regression model and calculated the cumulative incidence rate per 100,000 person during from 1980 to 2004, the incidence rate (IR) per 100,000 person-years, the relative risk (RR), and hazard ratio (HR).

The retrospective cohort size in 1981 was 87,496 Atomic bomb survivors in Nagasaki. This population was followed up until 2004. 3.31. MDS cases were followed until the date of diagnosis, and other non-MDS cases were followed up until the date of death. Stratification was done for "exposure distance" (0-1.5 km, 1.5-2.5 km, 2.5-3 km, over 3km), "age at bombing" (<10 yr, <20 yr, <30 yr, <40 yr, over 40 yr), "sex" (male vs. female), "age at diagnosis" (<50 yr, <60 yr, <70 yr, <80 yr, over 80 yr), and "FAB subtypes" (RA, RARS, RAEB, RAEB in T, CMML).

The summary of our findings is that MDS risk was higher in survivors who were exposed at more proximal distance from the hypocenter, and in survivors who were exposed at an older age. Also there was an inverse relationship between the relative risk of MDS and the distance from the hypocenter, suggesting a dose response relation. Another finding was that the relative risk of MDS by distance was greater in high risk types of MDS (RAEB/RAEB-t) than the low risk types of MDS (RA/RARS).

This study has been the first comprehensive study with the largest scale so far, to measure the MDS risk in A-bomb survivors. The results of this study imply that MDS risk is also increased among A-bomb survivors similar to leukemia risk. We suggest that, although leukemia risk seems to have declined to the background level, MDS has become an important hematological disease over half a century after bombing.

We are now conducting a dose response analysis for survivors with estimated bone marrow radiation doses. For the final comprehensive dose response estimation, a Hiroshima survivors study for MDS will soon be started by Hiroshima University.

Solid tumors such as cancer of thyroid, breasts, stomach, lungs, colon, ovaries, skin and brain began to increase in incidence after 1960-1965, following the decline of leukemia incidences. The most recent statistical summary suggests that the elevated incidences of solid cancers have still persisted in the period 1980-2004.

A statistical estimation was recently reported by the Radiation Effects Research Foundation (RERF) for the number of future cancer occurrence based on the assumption that cancer and MDS risk will never cease and will persist over the whole lives of the proximally exposed survivors; about one third of solid cancers have been developed from the proximally exposed population during 1965-2004 period and two third of solid cancers are expected to develop during the period 2005-2020.

In 1995, we studied the chromosomal abnormalities of blood cells circulating in proximally exposed persons with moderate (1Gy) to high (4Gy) exposure doses, who were otherwise healthy. We found that 5 to 20 % of blood cells carried chromosome abnormalities. The percentage would increase proportionately to exposure dose. This is good evidence that the atomic bomb irradiation actually induced chromosomal abnormalities.

Such chromosomal abnormalities were compared between lymphocytes that are immune cells and red blood cells. In several persons chromosome abnormalities were identical between lymphocytes and red blood cells, strongly suggesting that blood forming stem cells are targets of radiation damage. It is also well known that only stem cells can continue to live long enough to maintain blood formation over the whole life of a person. Thus, it could be a reasonable hypothesis that the stem cells were irradiated and damaged at chromosome and eventually DNA by the atomic bomb irradiation in 1945, and they are persisting after over half a century, giving rise to cancers.

The study of chromosomal abnormalities caused by radiation injury among healthy atomic bomb survivors has shown that lymphocytes and erythroid progenitor cells are carrying the same chromosomal abnormalities. The rate of these chromosomal abnormalities is radiation-dose dependent, suggesting that multipotent blood stem cells are directly or indirectly injured by the atomic radiation.

There are many questions remaining on the subject of leukemia-MDS biology in relation to radiation carcinogenesis: (1) Which cells are the targets of radiation injury?; (2) Which cells are transformed after several decades, almost half a century since the A-bombing?; (3) What are the leukemia stem/MDS cells?; (4) What are the genetic/molecular abnormalities resulting from the radiation injury and the eventual transformation?; and (5) What is the role of stroma cells in terms of radiation injury?

As for the origin of leukemia and MDS in stem cells of a general population, there is already some evidence available. For instance, it is well established that CML, the most prototypic A-bomb leukemia, has a multipotent stem cell origin. Also most, if not all of leukemias (AML and ALL) originate from a stem cell. MDS is also known as a multipotent stem cell disease. However, we still have no direct evidence for stem cell injury by radiation.

The stem cell theory for carcinogenesis is being widely accepted. Based on this theory we are speculating that not only blood stem cells but also other stem cells in various organs of survivors received chromosomal damage and hence DNA injury. Further studies are currently being conducted to prove that the life-long effects

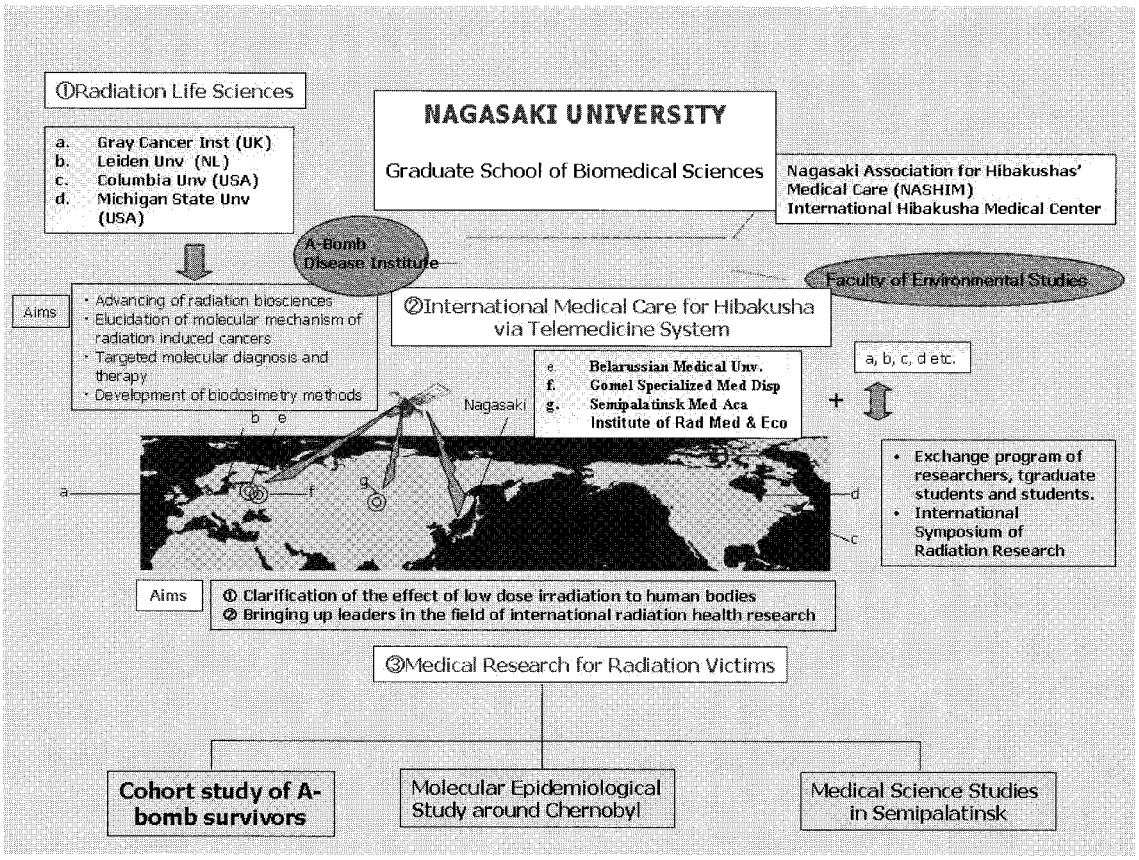

Figure 2. Activities of the International Consortium for Medical Care of Hibakusha and Radiation Life Science.

of the atomic bombs can be explained by this stem cell hypothesis.

In summary, atomic bomb irradiation as a single but massive irradiation of human bodies is still inducing malignant diseases after over half a century, i.e. for the whole lives of the survivors. The organ stem cell hit theory well explains this long-term development of tumors in human bodies by radiation exposure.

If proved, nuclear weapons must be considered more dangerous than we thought previously. Currently in our COE Projects we aim to understand the ultimate effects of radiation on human organs at the stem cells level (Figure 2). Our study on atomic bomb survivors conducted by the joint teams of Nagasaki University, Hiroshima University and Radiation Effects Research Foundation thus clearly indicated that the atomic bomb irradiation-induced genetic damage persists well over half a century and probably for the whole lives of survivors. This finding provides discrete evidence that all nuclear weapons are dangerous because of emitting radiation and should be totally abandoned.