Radiation Effects Studies of RERF

Burton G. BENNETT

Radiation Effects Research Foundation, Hiroshima and Nagasaki, Japan

Sixty years ago at the end of World War II atomic bombs were dropped on the cities of Hiroshima and Nagasaki with tragic consequences. Many lives were instantly lost, many serious injuries were sustained, families were disrupted and cities were devastated.

It can still be debated whether the atomic bombs should have been used at all. There was at the time the desperation to end the war quickly and decisively. We know however now that the destructive power of atomic bombs is so great that their use in urban areas should not have been considered. Hiroshima was one of several targets selected because it was a centre for military planning and a large number of troops were stationed there.

When the airplane took off with the atomic bomb on August 6, 1945, it could not be sure which area would be selected. The potential targets included Hiroshima, Kokura, Niigata and Nagasaki. Hiroshima was free of cloud cover, and so at 8:16 am of August 6 the atomic bomb was dropped there. It exploded in a brilliant flash at an altitude of 600 meters over the city.

Three days later on August 9, the second atomic bomb was dropped on Nagasaki. The destruction caused by the atomic bombs can only be said to be indescribable. The force of the blast instantly destroyed most wooden structures, and the intense heat started fires in the entire centre of both cities. After the bombings, only the shells of heavy concrete buildings survived. Most people died instantly from the intense heat and blast effects of the bombs within the central areas. Only those sheltered by heavy concrete buildings survived if they were within one kilometre from the hypocenters.

Many people were badly burned and the intense radiation caused nausea, internal bleeding and death within hours, days or weeks depending on the distance from the explosion. Those who survived were mostly beyond one kilometre from the centre. Radiation exposures were significant for all those within 3 kilometres from the hypocenter. Some people just happened to be away from their homes at the time of the explosions or were delayed from arriving at their work in the morning and so were spared injury or death. Only fate could determine where each person found himself at that particular instant.

Investigations into the aftermath of the bombings began immediately after August 6. Japanese scientists were aware within a few days that the weapon was a new atomic device. They identified an area of fallout in the western part of Hiroshima, and they collected materials that would be useful for subsequent dosimetry evaluations. The first non-Japanese investigators arrived in Hiroshima in early September one month after the bombing. These persons did not stay long and could only begin to report on the physical damage caused by the bombing. In October, another group of military officers and scientists called the Joint Commission was sent to Japan to continue the investigations.

A large number of Japanese professionals helped make the activities of the Joint Commission successful. Much of the work of the commission was to report on the physical and early biological damage caused by the bomb. The commission urged that a continuing study of the possible delayed effects of radiation exposure be made. Planning for the longer term medical and biological studies began in 1946, and in early 1947 the permanent study project was formally created.

The new project was called the Atomic Bomb Casualty Commission. A permanent site for work in Hiroshima was chosen on Hijiyama, and a parallel plan of work was started at the same time in Nagasaki. The first scientific project of ABCC was a clinical observation of infants to determine if genetic effects of radiation would become apparent. It was thought that genetic effects might be the most important effects of radiation. This program of examining newborn babies received the cooperation of the local and national Japanese midwives association, and they made a major contribution to this program.

A program of examining young children was next performed, and other studies began based on the individual interests and initiatives of the investigators. In all of this work however, no apparent genetic effects of radiation were seen.

ABCC was funded only by the United States. There were very many Japanese staff, and several US physicians pursued their own ideas in their short terms of assignment in Japan. Although interesting work was being done, there was no continuity or stability of the work pursued.

In 1955, a review committee called the Frances Committee recommended the establishment of fixed study groups that could be followed for as long as necessary into the future. This was accepted,

Address correspondence: Burton G. Bennett, Ph.D., Former Chairman, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815 JAPAN
TEL: +81-(0)82-261-3131, FAX: +81-(0)82-263-7279, E-mail: burtonbennett@aol.com
and a solid foundation for the work of ABCC was established. In 1975 Japan and the US decided to share the costs of the ABCC program.

At that time the joint US-Japan organization called the Radiation Effects Research Foundation (RERF) was established. RERF conducts its activities at locations in Hiroshima and Nagasaki. The staff number at present is 263. Similar epidemiological and clinical studies are conducted at both locations, but biological research is conducted only in Hiroshima, where most of the professional staff is located. There are 45 research staff.

For nearly the entire period of 60 years since the atomic bombings, the Radiation Effects Research Foundation, continuing on from the Atomic Bomb Casualty Commission, has been studying the effects of radiation in survivors of the bombings in Hiroshima and Nagasaki. The large study cohort from a general population of both sexes and all ages, encompassing a wide range of accurately known doses and incorporating accurate disease incidence and mortality recording makes this a very valuable and informative study. The results are heavily relied upon to establish radiation protection guidelines used throughout the world.

In conducting its studies, RERF collects both clinical and epidemiological data on the health status and mortality of the survivors and their children. To help interpret the findings, genetics and radiobiological studies are carried out. Many publications arise from these findings, and the following is just a brief overview of the scientific program and recent findings.

The core epidemiological project of RERF is the Life Span Study. It consists of a large cohort from a general population of both sexes and all ages. It encompasses a wide range of known accurate doses and incorporates accurate disease incidence and mortality recording. These features make this a very valuable and informative study. There is a commitment to continue the follow-up for the complete lifetime of all participants. Both cancer incidence and mortality from all causes are investigated.

The original cohort comprised 120,000 survivors of whom 86,000 have assigned doses. There are large representative groups of young persons included in the cohort, and these are the subjects presently being monitored. As these younger persons may have been more sensitive to radiation than older age survivors, the continued follow-up now is very important. At present about 43% of the cohort is still alive.

Cancer mortality in LSS is continuing to increase in relation to the age of the population. The cumulative numbers of cancer anticipated in this population at the end of the study, mainly from background normal causes, is 27,000. Thus far the number of cancer deaths has reached over 50% of that ultimate total number. With so many cancer deaths yet to be recorded, an important phase of the study is still ahead of us.

The latest publication of life span study results (LSS report 13) covers the period from 1950 to 1997. This evaluation was based on the DS86 dose estimates. As a new dosimetry system, DS02, has now been completed, an update of the evaluation has been prepared. The first update of total mortality results with three additional years of follow-up through 2000 was published last year.

Although leukemia cases are no longer occurring in significant numbers, solid cancers are continuing to appear in small but detectable proportions (Table 1). The results through 2000 include 10,127 solid cancers, of which 477 are estimated to be in excess. These cases are not distinguishable from normally occurring solid cancers. They are only evident from a statistical point of view. Many of the excess cancers were recorded in the recent years of recording, indicating that as these individuals further age and go through the cancer prevalence periods in their lives, significant additional radiation related cancer deaths can be expected in the population.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Subjects</th>
<th>Deaths</th>
<th>Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 mSv</td>
<td>38,507</td>
<td>4,270</td>
<td>2</td>
</tr>
<tr>
<td>&gt;5 mSv</td>
<td>48,104</td>
<td>5,857</td>
<td>477 (8 %)</td>
</tr>
<tr>
<td>Total</td>
<td>86,611</td>
<td>10,127</td>
<td>479 (5 %)</td>
</tr>
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Excess solid cancer deaths represent 5% of the total solid cancer deaths in the cohort or 8% considering only those exposed individuals. The analysis of excess deaths for individual types of cancer is difficult due to the limited numbers of the various types of cancer recorded. Large numbers of deaths have been recorded for stomach, lung and liver cancer, but the excess cancer deaths in these exposed members of the cohort are estimated to occur in relatively small proportions of the total. Other factors than radiation caused most of these cancer deaths.

Cancer incidence data may be more informative on specific cancer risks. Tumor registries in Hiroshima and Nagasaki began collecting incidence data in 1957. Although the incidence follow-up time is shorter than mortality, the number of recorded cases is at present greater by about 30%. Evaluation of the incidence data through 1998 is presently being prepared for publication (Dr Ron will speak about these results). Both for total cancer mortality and incidence, the dose responses appear to be linear, even down to the lowest radiation doses.

Non-cancer deaths are showing a small but significant relationship with radiation exposure (Table 2). The total excess of 250 deaths is 1.4% of the non-cancer deaths in the exposed individuals. This proportion is a factor of 6 lower than that for cancer. Non-cancer diseases that are shown to be related to radiation exposure include heart disease, stroke, respiratory diseases, and digestive diseases.

<table>
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<tr>
<th>Dose</th>
<th>Subjects</th>
<th>Deaths</th>
<th>Excess</th>
</tr>
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<tbody>
<tr>
<td>&lt;5 mSv</td>
<td>37,458</td>
<td>13,832</td>
<td>0</td>
</tr>
<tr>
<td>&gt;5 mSv</td>
<td>49,114</td>
<td>18,049</td>
<td>250 (1.4 %)</td>
</tr>
<tr>
<td>Total</td>
<td>86,572</td>
<td>31,881</td>
<td>250 (0.8 %)</td>
</tr>
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Although the effect of radiation on non-cancer diseases is evident at about 0.75 Sv with apparently linearity of response, a non-linear relationship with a threshold of about 0.5 Sv cannot be ruled out. Thus, the effect of low dose radiation on non-cancer diseases is still in some question.

The in-utero cohort study is a unique evaluation of the lifetime health consequences in a specially exposed population. The cohort size is 3654. Thus far there have been very few cases of cancer and death in this group. The most recent publication dealt with cancer mortality through 1992, but an update through 1998 is under preparation. During this period, 90 incident cases of cancer have been recorded. The mortality data for both cancer and non-cancer diseases are being updated, but so far they show no significant differences from those of the youngest radiation exposed survivors. The continued study of this cohort through middle and old age until mortality will be highly informative.

A clinical study of a sub-cohort of the Life Span Study, called the Adult Health Study, is being carried out to study age- and radiation-related physiological changes and to evaluate the radiation-related risk of non-cancer diseases. Examinations of atomic-bomb survivors are conducted every two years, providing a continuing health profile of an aging population. In addition, blood samples are collected for future analysis. This study is establishing the radiation related risk of non-cancer diseases and investigating age- and radiation-related physiological changes. It will be continued through the lifetime of the survivors. Of the initial cohort of 23,000 at the beginning of the study in 1957, about 50% are alive, and most of these individuals still participate in the program. About 2,500 examinations are performed each year.

The report updating the results of the Adult Health Study was published last year in Radiation Research. The results through 1998 indicate a positive linear dose-response relationship for the incidence of thyroid disease, chronic liver disease, uterine myoma and cataract. A negative dose-response relationship was found for glaucoma. The evidence of radiation effects for cataract, glaucoma, and hypertension was new in this report. RERF is investigating these non-cancer diseases findings in a series of special clinical studies. It will be important to continue the Adult Health Study to evaluate all of the non-cancer effects and to quantify the risk levels.

The children of atomic-bomb survivors are being studied to determine whether genetic effects might be apparent that could be related to parental exposures. Initial study of post-natal defects did not demonstrate discernable effects. The mortality follow-up is continuing. The initial size of F1 mortality cohort was 77,000. With 94% of this population still alive, the results today are still not conclusive. The evaluated risks with increasing paternal or maternal dose are not significant, and the pattern of mortality is not different from the normal pattern of unexposed persons.

A new study of the F1 generation has recently started to determine if radiation effects on chronic diseases in the now middle-age individuals might be evident. A health questionnaire was conducted by mail, and a clinical examination on each study participant is being carried out. About 11,000 second-generation persons will be examined. This project will be completed within one more year. It cannot be known if a statistically significant risk will be found, but even if not, it will be valuable to establish an upper limit for the risk level.

Along with the cohort studies, radiobiological, genetic, immunological, and molecular epidemiological studies are continuing. They provide important supplementary findings on the effects of radiation and the mechanisms of disease induction. This will make use of our long term collection of blood samples and apply new technologically advanced methods of analysis. This area of research will provide us with much of the basis upon which our future studies are likely to be developed.

An important part of the RERF epidemiological studies is the accurate specification of radiation doses for the cohort members. In the last few years, a significant reevaluation of the dosimetry took place. More sensitive measurements of neutron activation products in environmental samples were performed, removing the uncertainties in earlier measurements. The calculations were considerably upgraded with a thorough review of all parameters, new interaction cross sections and greater computer power. All of the new results indicate very good agreement between measurements and calculations. Only minor revisions in the survivor doses resulted, but the uncertainties are reduced in the new system called DS02. High confidence can now be placed on the dose estimates.

Revisions of our risk estimates have already been completed. Although the DS02 calculation system was completed in 2002 and approved by a senior committee in early 2003, we have had a long wait for the report of the Working Group to be completed, as some deliberations on presentation of the system continued. Those have now been completed. We have the cover design of the report (Figure 1), which will be published in two volumes, as it is nearly 1,000 pages.

It might be anticipated that mortality in the aging population is rapidly depleting the cohort and the value for the follow-up will be diminishing. However a very important phase of the follow-up of the younger exposed cohort members is just beginning.

Of the Life Span Study, 43% of the cohort is still alive. Some survivors will still be alive in 2045 (Figure 2). We would like to continue the study at least down to the 10 percent level in size of the cohort, which will be reached in 2030, and hopefully over the complete lifetime of all the survivors.

The peak mortality rate from cancer will occur in about 2015. So far we have recorded just over 15,000 cancer deaths of the 27,000 anticipated, so still a large number of cancer deaths are yet to be recorded (Figure 3).

The results of the RERF studies have figured prominently in international efforts to establish the health risks of radiation exposures. The main organization responsible for reviewing the scientific evidence of radiation effects is the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). In all of UNSCEAR reports, the results of RERF have figured prominently. The evaluations of UNSCEAR are used by the International Commission on Radiological Protection (ICRP) to derive recommendations for
radiation protection that have been adopted by most countries. It brings a great sense of pride to know that the results of RERF studies have been able to play such an important role in international radiation effects evaluations and in formulation of radiation protection guidelines.

From the experience of the atomic bombing has come just not an opportunity but a responsibility to investigate the effects of radiation, to contribute to the welfare of those affected, and to understand and quantify the effects, and to provide a scientific basis for radiation protection worldwide. The contributions of ABCC and RERF have been of substantial value in meeting these objectives, and a high scientific reputation of the foundation has been established (Figure 4).

There is a clear need to continue these informative studies for the full duration of the lifetimes of the survivors. This seems to be recognized by our government sponsors, who are presently making firm commitments for future funding.
Figure 4. The major activities of Radiation Effects Research Foundation (RERF) are presented in the RERF website.