Activities and Future Plans of the Radiation Effects Research Foundation

S. Nagataki, M.D., Ph.D.
Radiation Effects Research Foundation, Hiroshima and Nagasaki
(A Cooperative Japan-United States Research Organization)
5-2 Hijiyma Park, Minami-ku, Hiroshima, and 1-8-6 Nakagawa, Nagasaki, Japan.

INTRODUCTION

The Radiation Effects Research Foundation (RERF) was established in 1975 with a view to contributing to the maintenance of the health and welfare of the atomic bomb survivors and to the enhancement of the health of all mankind. RERF is a binational research foundation supported by the Ministry of Health and Welfare, Japan and the Department of Energy, United States. RERF continues the work of the Atomic Bomb Casualty Commission (ABCC) which was established in 1947 by the National Academy of Sciences with funding from the US Atomic Energy Commission.

The ABCC/RERF study cohorts were selected from a Master Sample of about 200,000 people among 280,000 who, at the 1950 Japanese National Census, were reported to have been exposed to the atomic bombs in 1945. The study populations consist of the Life Span Study (LSS) cohort of 120,000, the Adult Health Study (AHS) cohort of 20,000, and the In-Utero cohort of 3,300 people born within 9 months of the bombings. In addition, genetic studies are carried out in a cohort of 88,000 F1 offspring born to the survivors between mid-1946 and 1984.

The location and shielding data obtained from interviews for individual survivors are combined with calculations involving the yield of the bombs and the transport of the radiation through the air to produce the exposure estimates. The present dosimetry system (DS86) provides estimates of the dose for various organs in individual survivors in the study cohort.

RERF has following research divisions; Epidemiology (including Pathology and the Tumor Registry), Clinical Studies (including the Clinical Laboratory and the collecting of biological specimens), Genetics, Radiobiology, Statistics and Information Technology. The mission of the research departments is to investigate the health effects of radiation to the atomic bomb survivors and their children using the above cohorts.

EPIDEMIOLOGICAL STUDIES

INTRODUCTION: Departments of Epidemiology and Statistics have been following up mortality, population-based cancer incidence, and pathology based cancer incidence in the LSS, In-Utero, and F1 cohorts. Using the unique Japanese family registration system, death certificates were obtained for 99% of the cohort members who died during the study period. Death certificates issued by a doctor responsible for the patients are reliable when cancer is the cause of death. Agreement between death certificates and the diagnosis at autopsy is about 90% for solid cancers as a whole, and 95% for leukemia. In the case of thyroid or breast cancers, which are not the cause of death in many members, the results of incidence studies are particularly important. In the LSS incidence study, diagnosis of solid cancers was made through the tumor registry and tissue registry system in Hiroshima and Nagasaki, by autopsy, surgery, clinical examinations, etc. About 75% (90% for thyroid or breast cancers) of the diagnoses of solid cancers were confirmed by histological examination.

CANCER RISK: Epidemiological data have shown increased risks of leukemia and solid cancers by radiation exposure among the survivors (1,2,3). Excess leukemia risks, especially for children, were markedly elevated 5 to 10 years after exposure and have continued at reduced levels. Excess solid cancer rates became apparent within 10 years after exposure, increasing throughout life in rough proportion to background rates. Excess rates were observed in stomach, lung, colon, breast, thyroid, and urinary tract cancers. The increase in risk may be larger for those exposed to radiation as children than for those exposed as adults; however, further follow-up of this population to necessary to answer this important question.

SHAPE OF DOSE RESPONSE: Excess leukemia risks exhibit an upward curving dose response pattern while the solid cancer excess appears to be linear by dose with no apparent threshold (1,2,3). The results of recent analyses of LSS solid cancer mortality and incidence data as regards low dose risks can be summarized as follows: a) No evidence of departure from linearity was found over 0-4 Sv range. b) There is a significant dose-response in the 0.005-0.2 Sv range. c) The dose response between 0.005 Sv and 0.05 Sv is not significantly different from the dose response between 0.005 and 0.2 Sv, but it is also not significantly different from 0. d) The
low dose risks either over the range 0.005 to 0.2 Sv or 0.005 to 0.1 Sv are consistent with the predictions of a linear extrapolation from higher doses. e) The 95% upper confidence limit of a possible threshold is less than 0.1 Sv.

Figure 1. Solid Cancer Dose Response

AGE AND TEMPORAL PATTERN OF RISK: The most important new developments in the long term are likely to be the better understanding of age and temporal findings in the cancer risks. Although there is a widely held view that age-at-exposure is the a primary determinant of the effect of radiation exposure (1,3), recent data suggests that much of the apparent age at exposure effect on excess cancer rates can be explained by allowing excess relative risks to decrease with increasing attained age (4). While relative risks are decreasing, it now seems clear (as it was not even 15 years ago) that radiation-associated excess solid cancer rates increase throughout lifetime for the survivors. Insights into the age and time patterns of the solid cancer risk is providing (and will continue to provide) insights into the mechanisms of radiation carcinogenesis. New analyses focusing on survivor data in the low dose region will further highlight the direct relevance of the survivor data to the discussion and debate about the nature of radiation effects on cancer risks at low doses.

NON-CANCER RISK: Clarification of the nature of the non-cancer risks will be extremely important since based on current descriptions if the non-cancer effect is linear in dose then the number of radiation-associated non-cancer deaths in the cohort could be 50% or more of the number of radiation-associated solid cancer deaths (5). Incidence studies will be important in helping us better understand differences and similarities between the risks for different types of solid cancer.

IN UTERO COHORT: Persons exposed in-utero exhibit a broad range of dose-related effects including delayed growth and development and higher rates of microcephaly. The next 15 to 20 years will see a marked increase in the number of deaths and cancer cases in the in-utero cohort and despite the relatively small number of exposed in-utero survivors, it should become possible to clarify similarities and differences in the radiation effects seem among those exposed in-utero and those exposed as children (6).

F1 COHORT: No demonstrable evidence of increased cancer or noncancer disease risks has been obtained. It is essential that we continue the follow-up of the F1 cohort or the majority of the cohort subjects are still under age 50.

DOSIMETRY: Hopefully there will soon be a resolution to the questions about possible biases in the current survivor dosimetry system. Once a new dosimetry system has been prepared, we will move rapidly to produce new individual dose estimates and reexamine risk estimates based on these new dose estimates. The availability of new doses will almost certainly lead to increased interest in the nature of the radiation dose response for solid cancer.

CLINICAL STUDIES

INTRODUCTION: The Adult Health Study (AHS) is one of the largest and longest running clinical cohort studies in the world. The AHS cohort comprised about 20,000 subjects, as a subset of the Life Span Study
(LSS) cohort about half of whom were within 2,000 m of the hypocenter, a quarter beyond 3,000 m, and the remainder not in the city at the time of bombing. Since 1958, subjects have been invited to participate in biennial health examinations conducted by the ABCC-RERF clinical staff that included clinical evaluations and routine laboratory assessments. The AHS cohort was supplemented from the LSS-extended cohort in 1977 with about 2,400 subjects. About 1,100 in-utero-exposed persons have been added to the AHS since 1978. The primary purpose of AHS has been to determine the types of diseases and abnormalities in physiologically or biochemically determined values which may have occurred as a consequence of previous exposure to ionizing radiation, and to collate this information with other life experiences and death. The study also functions as a source of biological materials for various studies. Biological specimens, such as stored sera, blood cells, and teeth for Electron Spin Resonance (ESR) dosimetry, have been collected and stored after informed consent from the AHS participants.

RESEARCH ELEMENTS: The major research elements of AHS can be categorized as follows: 1) characterization of cancer types in relation to various confounders of radiation effects, 2) radiation related non-cancer diseases (benign tumors, cardiovascular diseases and other chronic diseases), 3) aging associated with exposure, 4) radiation related changes in physiological measurements, 5) medical dosimetry, 6) psychosocial changes associated with exposure, and 7) health status of the in-utero exposed.

NON-CANCER DISEASES: AHS data has provided accumulating evidence of an increase in non-cancer diseases morbidity (7), such as cardiovascular disease, radiation cataract, hyperparathyroidism (8), thyroid diseases (9), uterine myoma (10) and chronic liver disease (Fig. 3). This potentially important and largely unexpected relationship could never be properly studied using death certificate data alone. The findings for cardiovascular disease and chronic liver disease (including liver cirrhosis) are consistent with the report of increased mortality from cardiovascular disease and liver cirrhosis. An enormous body of laboratory measurements acquired in the course of serial medical examinations has revealed an increase in total-cholesterol level (11) and serum calcium level (12) as a consequence of exposure to ionizing radiation. The AHS data are essential for the development of a better understanding of radiation effects on cardiovascular disease and other non-cancer diseases. Systematic detection of various benign tumors will be continued. Consideration is also given to the conduct of a study of benign thyroid tumors and other thyroid disorders.

SOLID CANCERS AND POTENTIAL CONFOUNDERS: Cancers continue to be one of the most prevalent diseases among AHS subjects. Cancer screening will continue to be one of the objectives of the Adult Health Study, and special emphasis will be placed on screening for those cancers such as skin, breast, and thyroid cancer which are often not fatal. A new analysis including potential confounders and risk modifiers using the information obtained by various questionnaires and clinical measurements at the time of the routine AHS examinations, such as dietary factors and medications, will be conducted. A case-control study will be conducted on various cancers related to nutrients, hormone and other potential carcinogens such as viral infections using stored serum for analysis in the future.
AGING: Aging-related study such as osteoporosis study, senile dementia study, physiologic aging study will continue. Studies on the health of the offspring (F1 generation) of the survivors will be conducted to assess the effects of radiation exposure on the health and genetic constitution of the F1 population. This study consists of mail survey and clinical health examinations and the storage of blood cells for DNA analyses.

GENETIC STUDIES

Past studies include birth defects (about 65,000 newborns, 1948-1954), sex ratio (140,000 births, 1948-1966), chromosome aberration (16,000 children, 1967-1985), electrophoretic variants of serum and erythrocyte proteins (23,000 children, 1975-1984) (13). No radiation effects were observed in any of these studies. Table 1 summarizes results of birth defects. Since 1985, blood samples have been collected from about 1000 families (both parents and their children) and stored in liquid nitrogen so that they may be used for DNA studies in the future. Currently, small-scale pilot studies are under way (14). As clinical examinations were conducted mainly soon after the birth, some genetic diseases of adult onset may not have been detected. Thus, a new clinical examination will be conducted in the near future.

<table>
<thead>
<tr>
<th>Mothers’ dose (Sv)</th>
<th>Fathers’ dose (Sv)</th>
<th>&lt; 0.01</th>
<th>0.01-0.09</th>
<th>0.10-0.49</th>
<th>0.50-0.99</th>
<th>≥ 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.01</td>
<td>2,257 / 45,234</td>
<td>60 / 1,104</td>
<td>21 / 510</td>
<td>122 / 238</td>
<td>17 / 268</td>
<td></td>
</tr>
<tr>
<td>0.01-0.09</td>
<td>179 / 3,790</td>
<td>27 / 700</td>
<td>5 / 138</td>
<td>2 / 27</td>
<td>2 / 45</td>
<td></td>
</tr>
<tr>
<td>0.10-0.49</td>
<td>81 / 1,655</td>
<td>9 / 124</td>
<td>13 / 209</td>
<td>2 / 41</td>
<td>0 / 20</td>
<td></td>
</tr>
<tr>
<td>0.50-0.99</td>
<td>44 / 651</td>
<td>0 / 19</td>
<td>1 / 24</td>
<td>4 / 47</td>
<td>1 / 17</td>
<td></td>
</tr>
<tr>
<td>≥ 1.0</td>
<td>19 / 388</td>
<td>2 / 21</td>
<td>0 / 9</td>
<td>1 / 9</td>
<td>1 / 15</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Summary of birth defects including malformation, still birth, and perinatal death. (Number of the cases/number examined) (17)

BIODOSIMETRIC STUDIES

CYTOGENETIC STUDY: Peripheral blood lymphocytes were used to examine frequencies of chromosome aberrations, which provide a biological indicator of radiation dose to individuals. The results indicate that the dose response is higher in Hiroshima than in Nagasaki (15). This is probably, at least partly, due to overestimation of DS86 doses to factory workers in Nagasaki. Those survivors exposed in Japanese houses, however, still show consistently higher abnormality frequencies in Hiroshima. Currently, a new fluorescence in situ hybridization (FISH) method is being used to help us obtain a better understanding of the city difference.

ELECTRON SPIN RESONANCE (ESR) STUDY: Recently, tooth enamel was found to be a useful material for retrospective evaluation of radiation dose by means of ESR. Our results demonstrated that ESR-estimated dose and cytogenetically estimated dose are in close agreement, which provided support for the continued use of cytogenetic information for biodosimetry. We also found that ultraviolet light induces an ESR signal indistinguishable from that produced by ionizing radiation and concluded that only molars would be used for dosimetry in the future (16).

RADIOBIOLOGICAL STUDIES

INTRODUCTION: There is a great deal of epidemiological data on the effects of radiation exposure on humans, but the biological mechanisms underlying many of these effects are only just beginning to be understood. The studies currently under way or being planned in the Department of Radiobiology are primarily aimed at increasing our knowledge of the various molecular events which take place between exposure to a given radiation dose and the development of a discernible biological effect (e.g., a tumor). To this end, studies are being conducted to examine some of the molecular mechanisms which may be responsible for translating the effects of atomic bomb exposure into deleterious health outcomes in three separate but related projects.

MOLECULAR ONCOLOGY: The primary objective here is to obtain a better understanding of the relationship between radiation exposure and the onset of a particular type of radiation-induced cancer. There are several important assumptions involved in adopting this approach, and it is important therefore that we seek to examine the basis for these assumptions as we continue with our analysis of the two main types of radiation-induced cancer we are currently studying, namely those affecting the female breast and the thyroid (18,19). In particular, we intend to spend much more time examining the possible role of radiation-induced non-sequence
changes to DNA structure and function (i.e. epigenetic changes) in the complex processes that are now known to be involved in multistage oncogenesis.

MOLECULAR EPIDEMIOLOGY: With the accumulating epidemiological data quantifying the carcinogenicity of the atomic bomb radiation and the rapidly advancing knowledge in the molecular biology of cancer, there is an ever-increasing need to bridge these two disciplines. Such a link should greatly improve our understanding of the biological mechanisms of radiation carcinogenesis. The primary aim in this area involves identifying as many of the genes as possible that have become heritably altered in the predominant types of cancer that are found among the atomic bomb survivors in significant dose-related numbers (18,19,20). (Fig.4) We will then seek to acquire an understanding of the patterns of mutant genes that may serve to distinguish radiation-associated cancers from cancers with other etiologies. These investigations require us to analyze tissue samples from survivors who have been exposed to various doses of radiation using state-of-the-art molecular biological techniques. This basic approach will need to be continued for a number of years, but it is anticipated that changes in the art and knowledge of molecular cancer biology, together with the rapid improvements in our knowledge of the structure of the human genome, may help us to speed up progress quite considerably in the near future.

BASIC IMMUNOLOGY: Immunological work currently focuses on four main areas, and involves studies of: 1) immunological imbalances between the various T cell subsets (21,22); 2) immunological aging (by monitoring levels of T cell production, by determining the numbers of naïve T cells that bear circular DNA molecules which form in the process of TCR gene rearrangement in the thymus, and by analyzing telomere length in both naïve and memory T cells); 3) the immunological background to disease development (e.g. by examining the relationship between infection by certain pathogenic microorganisms and the risk of cardiovascular and other non-cancer diseases among A-bomb survivors, and by examining the relationships if any between autoimmunity and diabetes or thyroid diseases); and 4) the relationship between polymorphisms and mutations of the HLA class I and II genes and certain diseases including noninsulin dependent diabetes in the AHS cohort. All of these studies are being conducted in a multidisciplinary fashion, in collaboration with the Departments of Clinical Studies, Statistics, Epidemiology, and Genetics.

Department of Information Technology

The department is responsible for managing all the RERF data for use via the network. The responsibility includes the network management and database development for research. All the RERF
buildings are connected by the fastest gigabit Ethernet, which makes it easier for researchers to access databases to satisfy their needs. Information on databases necessary for research can be retrieved from a PC on a desk. Such important information is protected from outside by means of a firewall. Within the foundation, the information is protected by various methods, such as use of a different password for each set of information and granting of access right only to the designated PCs. Future tasks include development of databases mainly composed of image files, strengthening of network security, and further computerization of materials from the establishment of ABCC.

FUTURE PLANS

CONTINUATION OF EPIDEMIOLOGICAL STUDIES: In 2000, 90% of survivors younger than 9 years old at the time of atomic bomb are still alive. Traditional epidemiological studies have been so important in quantifying the health effects of the radiation from the atomic bomb, and continued follow-up of survivors exposed as children is essential to understanding the age-temporal pattern of excess risks and life-time risks of solid cancer. Numbers of survivors are decreasing but information for analysis is increasing and new information may provide useful insights into the biological mechanisms by which radiation causes cancer. Studies on radiation-associated increases in non-cancer disease risks have to be continued and taken into account in
LOW DOSE RADIATION: During the past 50 years numerous epidemiological studies of adult human populations exposed to radiation from medical, occupational or military purposes have been conducted. The lowest dose at which a statistically significant radiation risk has been shown is ~ 100 mSv. Fundamental questions about the shape of the dose-response curve and mechanisms of effects of radiation at low doses are unlikely to be answered in the near future. The RERF cohort includes about 35,000 low dose survivors with doses between 5 and 200 mSv, and a roughly equal number of survivors with estimated doses below 5 mSv. The low dose portion of the LSS cohort offer a unique opportunity to assist in reducing scientific uncertainties in risk and in elucidating mechanisms of radiation health effects. Studies on mechanisms may include DNA repair, oxidative stress versus low dose in initial effects, and epigenetic and epimutational effects, and possibly also genetic instability, bystander effects, adaptive response, hormesis among the later effects.

GENETIC STUDIES: Future directions of genetic studies are 1) Epidemiological follow up, 2) DAN study, and 3) Clinical genetic study. A mortality survey on 88,000 children has been conducted since 1946 and will be continued. Blood samples from more than 1000 family members, father-mother-children are already collected at RERF and the effect has been continued. Mutations in the offspring will be sought using various molecular techniques, such as DNA chip and 2 D electrophoresis. Finally clinical health examination will be conducted with careful ethical considerations to find late-onset genetic disorders that were not detected at birth and to screen for multifactorial diseases and/or adult-onset diseases. Clinical health examination will start in this year (2000).

UTILIZATION OF INVALUABLE RESOURCE OF STORED BIOLOGICAL SAMPLES: Biological specimens at RERF are serum, plasma, blood cells obtained from AHS participants together with autopsy tissues stored at RERF. Furthermore, cancer tissues used for diagnosis are accessible through the Hiroshima and Nagasaki Tissue Registries (more than 90% of LSS cohort members) and are stored in paraffin which can be used for molecular analyses. Cancer tissues are the most important sources of biological specimens. These biological samples are highly regarded universally, not only because of the type of exposure received by such large numbers of subjects, but also because of the high quality of the information which has been recorded about exposure histories. These samples represent the most comprehensive collection of human materials and associated documentation related to radiation exposure in the world, and the fact that they can be used in attempts to understand the origins of radiation-induced disease makes them uniquely valuable. Until recently, the only comprehensive studies of radiation-induced disease that have been particularly informative have been those involving epidemiological parameters and/or animal models. The biological samples available at RERF are vital for the conduct of current and future molecular biological studies, both in RERF itself and in collaborating laboratories. It cannot be emphasized too much that these resources provide the foundation upon which our growing knowledge of radiobiological mechanisms is being built. Studies on stored biological samples would be greatly assisted if the clear and straightforward guidelines were provided on the ethical and human rights issues involved in the immortalization of these unique biological materials in the not-too-distant future.

<table>
<thead>
<tr>
<th>Type of specimen</th>
<th>Method of Preservation</th>
<th>Approximate Number of specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>Frozen</td>
<td>72,000</td>
</tr>
<tr>
<td>Plasma</td>
<td>Freeze-dried</td>
<td>63,000</td>
</tr>
<tr>
<td>Cells-blood, mononuclear (Lymphocytes)</td>
<td>Frozen</td>
<td>3,400</td>
</tr>
<tr>
<td>Blood on paper filter disks</td>
<td>Frozen</td>
<td>6,900</td>
</tr>
<tr>
<td>EBV-immortalized lymphocytes</td>
<td>Freeze-dried</td>
<td>2,600</td>
</tr>
<tr>
<td>Cancer case tissues</td>
<td>Frozen</td>
<td>1,000</td>
</tr>
<tr>
<td>Post mortem tissues</td>
<td>Paraffin blocks</td>
<td>Stored in community hospitals</td>
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<tr>
<td></td>
<td></td>
<td>Identifiable through RERF tissue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>registries (includes 14,700 LSS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cohort members)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stored at RERF for cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>autopsied from the late 1940’s to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the mid 1970’s.</td>
</tr>
</tbody>
</table>

Table 2. Biological specimens preserved at RERF or accessible through tissue registries in Hiroshima and Nagasaki.
THE POSITION OF RERF:

The mission of RERF is to provide long-term follow-up of the large cohort of atomic bomb survivors for the world of science. The vast amount of information collected by RERF will continue to be a source of important data on radiation risks and human health for years to come. An important task faced by RERF is to organize and document these data in a way that ensures that they will be accessible for future research.

Although each scientist may analyze data according to his or her own ideas, hypotheses or methodologies, RERF has to seriously consider all suggestions, proposals of collaboration and criticisms from outside of RERF because the follow-up data of RERF are unique. To this end the scientific achievements of RERF are reviewed regularly by multinational peer review panels, our science council consisting of Japanese and American experts, and our research directions are regularly revised in the light of their recommendations.

The research findings of RERF have long been used by numerous international bodies as a principal basis for establishing radiation protection standards. In addition, knowledge derived from RERF studies is being employed in understanding and policy making in the relief of radiation victims in the world. Continued research at RERF is important for extending our understanding of radiation health effects and for enhancing the health and welfare of atomic-bomb survivors and, ultimately, of all people in the world.

REFERENCES

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