Report of the Senior Review Panel on Future Planning for Radiation Effects Research Foundation

Contents

Membership of the Panel

Co-chair:

J. Paul Gilman, Senior Vice President and Chief Sustainability Officer, Covanta Energy Corporation (Formerly Director, Oak Ridge Center for Advanced Studies)

Sadayoshi Kitagawa, Director General, Japan Public Health Association

Member:

Joe W. Gray, Director, Life Sciences Division, Lawrence Berkeley National Laboratory

Tomoko Kusama, President, Oita University of Nursing and Health Sciences

Gloria Petersen, Professor of Clinical Epidemiology, Mayo Clinic College of Medicine

R. Julian Preston, Acting Associate Director for Health, National Health and Environmental Effects Research Laboratory, EPA

Eiichi Tahara, Chairman, Hiroshima Cancer Seminar Foundation

Suketami Tominaga, President Emeritus, Aichi Cancer Center

Senior Review Panel Report

Background on the Formation of the SRP

In early 2006, the United States Department of Energy (DOE) and the Japanese Ministry of Health, Labour, and Welfare (MHLW) entered discussions on the formation of a panel to review future plans for the Radiation Effects Research Foundation (RERF). As a result, the panel, referred to as the Senior Review Panel on Future Planning for RERF (SRP), was established by the two governments. An eight-member panel was created with one Japanese member and one U.S. member as co-chairs. The SRP was asked to review:

- Current and potential RERF activities as they relate to radiation health effects research and radiation risk assessment
- Current and potential scientific personnel and research department structure
- Current and potential management structure
- Current and potential infrastructure, resources, and facilities for conducting research and providing services

The co-chairs and representatives of RERF, MHLW, and DOE met in early December 2006 to plan the study. The first meeting of the SRP was held in Hiroshima beginning on December 11, 2006. A second meeting was held in Hiroshima beginning on May 1, 2007. Both meetings included discussion with the scientific leadership of the RERF, scientific leaders from the Japanese academic community, local government officials, and representatives of atomic bomb survivor groups. On June 19, 2007, the co-chairs of the SRP met with academic leaders from the Nagasaki community, Nagasaki local government officials, and representatives of atomic bomb survivor groups in Nagasaki. On June 20, 2007, the co-chairs of the SRP met with the RERF Board of Directors to seek their input on the issues before the SRP.

The Life Span Study

The Life Span Study (LSS) cohort consists of atomic bomb survivors and an unexposed comparison group who lived in the cities of Hiroshima and Nagasaki at the time of the national and Atomic Bomb Casualty Commission (ABCC) censuses of 1950-53. The cohort contains about 120,000 people of both sexes and all ages who were assembled as a stratified random sample from a master file based on national and ABCC censuses (Figure 1). The exposed individuals had received a range of doses, from less than 0.005 Gy to more than 3 Gy. The distribution of the original cohort by age at exposure is shown in Figure 2. This is one of the few cohorts under study with such a wide age distribution at the time of irradiation. The distribution by estimated radiation dose in Figure 3 shows that the cohort is weighted toward the low-dose end of the spectrum, albeit the higher dose persons are also very important in risk estimation. Some of the unique and valuable properties of the LSS are presented in Table 1.

Figure 1 - RERF Cohorts

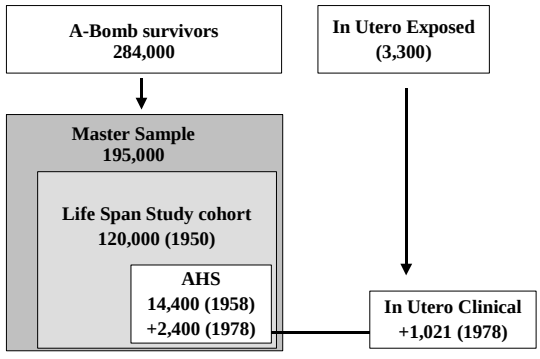


Figure 2 - Original Distribution of LSS Cohort by Sex and Age at Exposure

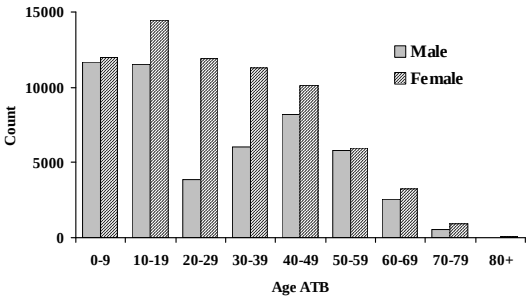
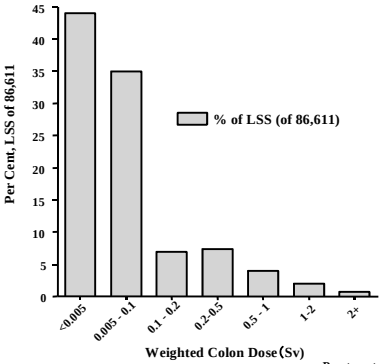


Figure 3 – Distribution of DS02 Doses in the LSS



Preston et al., 2004. Data, 1950 - 2000

Since 1950, the vital status of each LSS member has been confirmed through the Japanese Family Registration System (Koseki System) every two years. For confirmed mortality cases, a death certificate is then obtained. All these procedures have been performed with special permission from the Japanese Government, and therefore, the follow-up has been almost

complete.

As of January 2004, around 50,000 (42%) of the members of the LSS cohort were alive (cf. Figure 4). Ten years from now, those under the age of 20 at the time of the bombs (ATB) will constitute about 95% of the remaining LSS cohort.

Table 1 - Some Unique Attributes of the Life Span Study (LSS)

LSS has more statistical power than most other studies to do the following:

- **to produce lifetime risk estimates for total cancer mortality and incidence**
- **to produce risk estimates for >15 individual organs**
- **to assess the shape of the dose response**
- **to find the lowest doses for which there are statistically significant risks (~0.1 Gy)**
- **to examine the effect of variables such as age and sex**
- **to compare risks from childhood and adult exposure**
- **to evaluate latency and whether the risk of solid tumors decreases with time**
- **to demonstrate cancer risks in sensitive groups such as fetuses.**

Figure 4 - Life Span Study Cohort: Vital Status, Jan. 2003

Closely connected to the LSS are the Tumor and Tissue Registries for Hiroshima and Nagasaki Cities/Prefectures. RERF has been contracted to manage these from 1957 to date, and they provide high quality cancer incidence data [IARC, 2002] and pathology specimens. The previously published landmark report on LSS cancer incidence in relation to radiation dose [Preston, 1994; Thompson, 1994], the update of those data [Preston, 2007], and the current series of site-specific cancer incidence studies [Sharp, 2003; Yonehara, 2004; Kishikawa, 2005; Ron, 2005] would not have been possible without the involvement of RERF in the cancer registry and tissue registry operations.

The Life Span Study is the definitive cohort for assessing radiation-induced cancer and mortality risk in humans. Its results are used by all the radiation protection and radiation risk-assessment bodies as the primary basis for estimating radiation risks to human populations.

The Adult Health Study

The Adult Health Study (AHS) is a program primarily for determining radiation risk for diseases or conditions that cannot be identified through studies of mortality or cancer incidence. The 17,000 individuals in the AHS have had clinical examinations, questionnaires and blood samples taken every two years, with most beginning in 1958. This cohort (Figure 1), which is a subset of the LSS cohort, includes all possible participants who were exposed within 2,000m of the bomb hypocenter and exhibited acute symptoms, matched with groups of lower-dose exposed and unexposed persons.

Due to death, out-migration from Hiroshima/Nagasaki and nonparticipation, in 1982 about 8,000 persons were examined in the AHS. The most recent completed examination cycle in 2002-2004 had over 4,300 participants, where most of the loss in participants between 1982 and 2002 was due to deaths.

The participation rate is excellent for a clinical-examination program. Even after 50 years since the program inception, over 70% of those still living in the contact area continue to participate. About 40% of the AHS cohort were still alive at the end of 2005, and had a mean age of about 72 years. However, more than 80% of those exposed when young (20 years or younger) are still alive.

Recently, a decision was made to increase the number of AHS cohort members who were age 10 or under at the time of the bombs, from 700 to about 3,000. This was done to further enhance the statistical power of the AHS cancer incidence data obtained, especially since the LSS data suggest that those irradiated at young ages have a greater risk for cancer and non-cancer mortality than those exposed at older ages. Increasing the young portion of the AHS cohort will strengthen the ability to evaluate age-at-exposure effects, but it will take some years for the full impact of their inclusion to be seen, as they develop various diseases of interest.

In the AHS study, blood samples are obtained during the biannual clinical examination. They have been obtained from a total of about 16,000 AHS subjects since 1969. Aliquots of serum and blood cell samples are stored for later biochemical, genetic and mechanistic studies. Written consent is obtained for future studies, including genetic studies. The AHS remains the prime source of biospecimens used for biomarker and mechanistic studies; the biospecimens are critically important and have great potential for molecular studies of radiation effects.

The Second Generation (F1) Cohort

The second generation, F1 cohort (Figure 5) consists of 77,000 members, including children born between May 1946 and December 1984 to parents, at least one of whom was exposed to the atomic bomb radiation, and children of unexposed parents. This cohort is unique in having a wide range of radiation doses to parents who were unselected with respect to medical conditions that would arise from being exposed. The F1 cohort will be the most informative human study of possible heritable effects of radiation. F1 cohort members are just reaching the ages at which cancer and multifactorial diseases become common, so much of the valuable information on disease outcomes in relation to parental radiation exposure

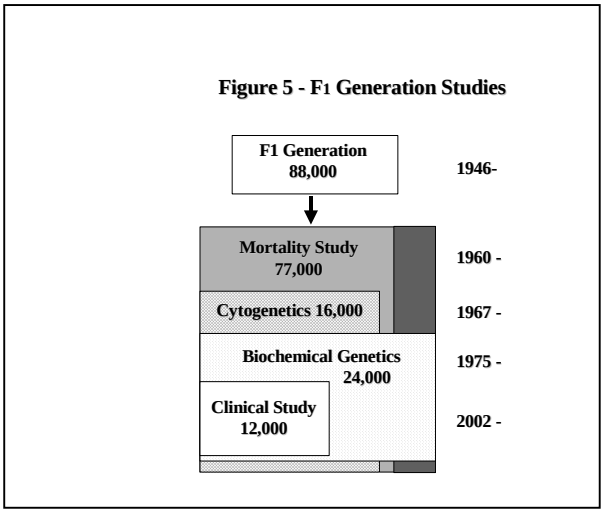


Figure 5 - F1 Generation Studies

levels is yet to be gleaned.

The *In Utero* Cohort

The *In Utero* epidemiologic cohort consists of individuals who were exposed *in utero* to the atomic bomb, along with matched controls. As many exposed individuals as possible were included along with unexposed controls, totaling about 3,300 individuals (Figure 1). As with the LSS, this cohort has been followed up for mortality and for cancer incidence. The *In Utero* epidemiologic cohort provides unique, valuable scientific information. This is because it is the only cohort in the world with: 1) a wide range of well-characterized *in utero* radiation doses; 2) exposures received at all prenatal ages; 3) exposures that were not triggered by medical indications observed among relevant mothers, and with 4) follow-up for many decades to monitor health effects.

In 1976, following the recommendations of the 1975 international advisory committee [Crow, 1975], a sample of over 1,000 individuals who had been exposed *in utero* was added to the AHS biennial examination program. These included as many as possible of those within 2.0 km of the bomb and a sample of those beyond 2.0 km who had calculated doses.

The *In Utero* Cohort will provide the most complete data available on the long-term effects of *in utero* radiation exposure, particularly with respect to non-cancer effects. A majority of the previous publications by outside researchers have looked at only childhood cancer effects from *in utero* exposures.

State of the Budget

Changes in subsidies from U.S. and Japanese governments

From 1975 to 1996, the U.S. and Japanese governments shared the RERF expenses equally, and the U.S. government remitted its subsidy in yen. In 1997, the governments decided that the U.S. government would bear the fixed amount of $14 million because of the government's financial situation and would remit its subsidy in dollars. The practical result is that the costs are no longer equally shared. Since then, a budget structure has arisen in which the amount of subsidy from the Japanese government is adjusted depending on the operational status of RERF and fluctuations of the exchange rate. Most recently, the two governments have agreed that the U.S. government will continue to bear an annual amount of $14 million for the five-year period starting in 2006 (U.S. FY2007). This amount covers about 40% of RERF's total expenditures, with the remaining 60% being borne by the Japanese government.

As a result of the revision of the equal-sharing system, RERF's budgeted expenses are calculated by research project, and any excess amount borne by the Japanese government compared with the U.S. budget is explained through the creation of "Japan sole-share" projects. Since 1997, the Japanese government alone has supported two projects, the AHS and the F1 study, with the remaining projects supported by the two governments equally. This separation of sole- and joint-share projects has complicated RERF's budgeting and accounting procedures and at times distorts the true presentation of costs.

Differences in Fiscal Years

In recent years, the Japanese government has remitted its subsidy to RERF unevenly -- about 40% of the subsidy is remitted in May, 30% in July, 20% in October, and the remaining 10% in January -- to make up for the absence of remittance from the U.S. government in the first half of the Japanese fiscal year. The U.S. government remits its subsidy to RERF in the latter half of the Japanese fiscal year, about two or three million dollars in November and the remainder in January.

The amount of the U.S. subsidy cannot be finalized until the monies are received and converted to yen based on the exchange rate at the time of remittance, making the settlement of the subsidy amount only possible in January, quite late in the fiscal year. This has adverse effects on RERF's accounting, such as postponement of budget execution and concentration of accounting work for purchases and facility repairs at the end of the fiscal year.

Exchange rate fluctuations

If the U.S. remittance converted to yen (estimated exchange rate used currently at RERF: $1=¥100) fails to reach the expected amount of equal-share subsidy (1.4 billion yen) due to a stronger yen (i.e.,

less than ¥100 to the dollar), the reduction in funds will affect the Japanese subsidy, because RERF must return the portion of the Japanese equal-share subsidy exceeding the amount of the U.S. subsidy in yen to the Japanese government (MHLW).

Differences in budgeting practices between the two governments

For the Japanese subsidy, the personnel budget is estimated using the cap imposed by the Japanese government on personnel numbers every year and the operational budget by summing up estimated, project-specific expenditures. For the U.S. subsidy, the budget is estimated by summing up the estimated expenditures of each research project. The Japanese government strictly separates the categories of personnel and operational funds, prohibiting diversion of monies between these two categories, while the U.S. government does not impose such constraints, providing a higher degree of flexibility on U.S. fund usage.

RERF prepares different accounting documents for the different budgeting systems and constraints on usage for both parties, leading to a complex work mode and increased costs.

Prior External Reviews of RERF

Francis Committee – 1955

In 1955, the first outside review committee, the Francis Committee, reviewed the research programs at ABCC on exposed persons and recommended adoption of a Unified Study Program as a permanent research guide. This was the first 'future planning' document. The recommendations of this committee continue to provide the basis for much of the present epidemiological and clinical follow-up of the survivors in Hiroshima and Nagasaki. Other far-reaching and foresighted recommendations of this committee were to clearly define groups with various levels of exposure (including unexposed), to seek to obtain detailed location/shielding data on a large number of survivors; to set up a systematic epidemiological network for disease and mortality ascertainment; to collect clinical examination data in a standardized fashion; to integrate the autopsy and pathology programs; and to further develop the laboratory program.

Crow Committee – 1975

In 1975 (the year ABCC became RERF), the Crow Committee reviewed the program and made additional recommendations regarding continued investigations of this population. The committee's recommendations played a role in RERF's developing a cancer incidence data collection program, increasing the emphasis on objective laboratory measurements in the AHS, further developing the Tissue Registries in Hiroshima and Nagasaki (which play a large role in the detailed studies of individual cancer sites), adding the *in utero* cohort to the AHS clinical program, and giving impetus to the F1 studies and laboratory-based genetic research.

Blue Ribbon Panel – 1996

The 1996 Blue Ribbon Panel Report made numerous recommendations. A number of the recommendations provided strong support for the continuance and extension of existing programs, such as the LSS, key AHS studies, the F1 cohort, informative analyses of those data, biological dosimetry, storage of biological samples, and the genetic, immunological, and molecular epidemiology investigations. The panel recommended a more detailed assessment of the F1 cohort, accompanied by research based on new molecular genetic techniques. It also recommended that a clear policy regarding the ethical sharing of biospecimens be implemented and that links be established or strengthened with universities and other research institutes in Japan.

A Vision of RERF's Future

All the international organizations contacted during the course of this review agreed that the work of ABCC/RERF is of high quality and essential for reliable radiation protection standards (see Appendix 2). They also supported the continuation of the core studies at RERF. The SRP believes that the LSS, AHS, Second Generation (F1) Cohort, and the *In Utero* Cohort should be followed at least over the next 20 years or until the cohorts have expired. There will be a period for data analysis that will require an additional period of at least 5 years.

The difficult question for the U.S. and Japanese governments and the RERF is what the RERF should be beyond the conclusion of these core studies. The SRP believes there is a wide range of possible forms that RERF could take. They range from a very minimal institution, perhaps housed at a Japanese university, that would be the caretaker of records and clinical samples that could be made available to appropriate independent researchers upon request. At the opposite end of the spectrum of possibilities from this "warehouse" option is an institution that continues to be a focal point for the world in radiation-related health effects research and also non-radiation related health effects research that is enabled by the accumulated cohort data and clinical samples. In this form, RERF would be considered to be a "Center of Excellence" for radiation health effects studies. The importance of the accumulated information, clinical samples, and expertise at RERF is so great that the SRP believes this latter option of a very vibrant research institution is the appropriate one. Achieving this vision will not be easy, however. Key steps for achieving it will be discussed below but it is important to emphasize that the difficulty of these steps is such that the U.S. and Japanese governments do not have the luxury of a great deal of time in which to contemplate whether they wish to allow RERF to seek to achieve this vision. The U.S. and Japanese governments and the RERF should, over the next two years, draw a conclusion regarding attainment of this vision.

Steps toward achieving the vision of being a Center of Excellence

During the period in which the U.S. and Japanese governments are deliberating their view of the nature of the RERF beyond the completion of the core studies, RERF management should take several steps. These include:

- engage the Hiroshima and Nagasaki communities in discussions about future activities and resources (including options for relocation) for the next 20 years and beyond,
- continue to solicit the views of Hiroshima and Nagasaki local liaison councils as to their opinions about the future of the RERF and its facilities,
- directly engage the DOE and MHLW to improve the mechanics of the budget cycle and the transfer of operating funds,
- an agreement with RERF, DOE, and MHLW should also be developed that will allow the hiring of a new generation of researchers,
- develop procedures that reward performance and provide incentives for new staff, and
- develop, as discussed more below, a system for planning and approving new research projects. Fund and manage that work on a project basis, also.

These steps will help assure that the operations of RERF are efficient, of high quality, and continue to enjoy the high participation rate of the current study participants.

Collaboration

The RERF must expand its international collaborations in radiation-related health effects research. In fact, a formal relationship with the International Atomic Energy Agency should be pursued.

RERF has acquired a world heritage collection of blood and other biological samples from survivors and their children that are unique and invaluable research resources. The longitudinal clinical and epidemiological databases are sources of important future research activities that need not be limited to elucidating the health effects of radiation. In the future, observation/analysis using all causes of death other than cancer as endpoints will become important. Data concerning all causes of death and related survival periods will be not only useful for clarifying effects of atomic bombs on all causes of death and related survival periods, but also for elucidating the genetic/environmental factors regulating (or, modifying) the aging process (healthy longevity, in particular). The long-standing cohort affords opportunity for studies of the prevention, early detection, and therapy of lifestyle diseases and cancer and of factors that contribute to healthy longevity. It is necessary to consider how present strengths and resources can best be utilized in the future. RERF should seek to develop project proposals with outside collaborators and additional funding beyond its radiation-related research funding with which to carry out these collaborations. As discussed further below, these projects should be managed inside RERF by a Principal Investigator on a cross-departmental basis.

The local universities for the Hiroshima and Nagasaki RERF laboratories are current collaborators and have the greatest potential for new research collaborations. New collaborative research projects will need new funding. Radiation-related research funded by the U.S. and Japanese governments should not be diverted to non-radiation related research. The RERF will have to expand the sources of its research funding for new collaborations. RERF has been successful in doing this to the extent it has sought funds from other sources in the past (e.g., funding from the U.S. National Institutes of Health).

Research Planning and Prioritization

As the very long list of new research ideas presented by RERF scientists indicate, there are many possibilities to be pursued for collaborative and in-house research. In fact, the possibilities and opportunities are so great that unless RERF's research prioritization process is strengthened, insufficient effort will be able to be assigned to the highest priority projects (i.e., there will not be a critical mass of investigators). Therefore, timely completion will be compromised and the prospects for being regarded as a Center of Excellence might well be lost.

A rigorous project prioritization and selection process in consultation with the Science Council is essential. Some projects (e.g., LSS, AHS, and F1) should not be subject to this review because they are regarded as the pillars of the research program. Criteria for this prioritization process have to be established. They might include:

- Who wants the research conducted and requires the output?
- What would be the impact of the research
  (a) to A-bomb survivors?
  (b) to radiation protection regulation?
  (c) to basic scientific knowledge?
- Are the necessary resources available in-house?
- If resources are not available in-house, can they be obtained by collaborations?

There should also be a research plan developed in 5-year increments. The research projects could be organized and prioritized around approximately 5-10 research themes and planned in about 3-year increments. A Research Committee (or equivalent) would be responsible for the selection of the projects (or priority programs) that would constitute the RERF research plan. The selection could be made from proposals submitted as part of a request for proposals (RFP) process. The Research committee could consist of RERF Senior managers and Research Scientists and also could include ad hoc non-RERF experts. The exact process can be developed through additional discussions.

Departments are currently the recipients of funding and decision on research priorities are made at that level. To encourage cross-departmental cooperation the selected research projects should be managed and funded on a project-by-project basis instead of through Departments.

Research Infrastructure

Since agreement between DOE and MHLW is essential for enhancement of construction of new facilities or facility relocation, further effort should be made to achieve agreement between the two agencies. To achieve the vision of a vibrant research institution 20 years from now, the planning for new facilities should begin immediately. Innovative financing approaches may be key to achieving this end. RERF management should explore financing by non-government sources for constructing a new laboratory in Hiroshima. A number of National Laboratories operated by the DOE in the United States, for example, have used this general approach. In Japan also, based on the PFI law, enacted in 1999, construction of public institutions utilizing private-sector funds has been promoted. RERF should also explore the possibility of housing related research groups in the same facility or locating the facility proximate to such groups so as to improve the opportunities for collaborative research.

Current efforts to preserve and protect documents and clinical samples are exemplary. However, no effort should be spared in this regard. RERF management and its Board of Directors should continuously review the opportunities to improve its practices even more and bring older written materials into its electronic database infrastructure. These materials are irreplaceable, and less than state–of-the-art curation/stewardship does a disservice to the people who have so selflessly

participated in the RERF studies.

Developing an optimal workforce to meet the vision of a Center of Excellence will be critical. Current and past budget pressures have resulted in reductions in scientific personnel. This trend needs to be halted or even reversed. To this end, the SRP needs clarification as to why a bi-national organization funded by two countries would have to implement across the entire institution personnel reductions mandated by only one of the countries. In addition, an agreement with RERF, DOE, and MHLW should be developed that will allow the hiring of a new generation of researchers, including exploiting the recruitment of strong non-Japanese scientists by the National Academy of Sciences (NAS) in order to retain the binational interests of this project, instill a diversification of expertise, and inject fresh ideas into the RERF research program.

Current Collaborative Research at RERF

RERF investigators have collaborations with many scientists at numerous other Japanese institutions. One hundred and sixty-four collaborations have been active at one time or another from the year 2000 to the present, and many of them are still continuing. It is notable that some 44 collaborations were with foreign scientists (including 12 that included external collaborations with both external domestic and foreign scientists). A total of 133 collaborations involved scientists at other institutions in Japan. The collaborations have covered the gamut from laboratory investigations, to providing clinical expertise, to interacting to generate new hypotheses to be tested, to helping collect additional epidemiologic or pathologic data, to collaborating in statistical analyses or developing applicable statistical methods. The origins of the collaborations show a robust set of interactions. Ideas for collaborations have originated within RERF (32%), from external investigators (56%) or jointly from both (12%).

The number of publications that RERF investigators have authored or co-authored from 2000 to the present were 565. Of these, 372 (66%) included external investigators, indicating that the external collaborations are fruitful.

Another finding from the publications inventory is that there are numerous inter-departmental collaborations as well, for 183 (32%) of the published papers included authors from multiple departments.

These statistics demonstrate that RERF scientists have been extensively engaged in collaborative research. However, we believe that more can be done particularly to promote international collaborations. The SRP understands that there is a plan to seek out more opportunities for these in the future.

RERF has two major formal international collaborations, i.e. [1] Radiation Research Partnership Program and [2] U.S. National Cancer Institute Joint Program. These provide significant leverage to the internal research activities, as the non-RERF investigators involved spend time both at RERF and at their own institutions analyzing, interpreting, and writing papers on the results of their collaborative efforts with RERF. The Radiation Research Partnership Program began only in 2005, so most of its activities are still in their infancy, whereas the U.S. National Cancer Institute Joint Program collaboration has existed for a number of years and has produced a long list of publications. In addition to these formal collaborations, RERF investigators have a substantial number of ad hoc international collaborations.

Potential Future Studies Identified by RERF

The panel's views about RERF's future projections regarding follow-up studies of the LSS, AHS, *In Utero* and F1 cohorts follow. More specific and detailed research projects that have been proposed by RERF scientists are included in Appendix 1.

Multidisciplinary Research on Cancer from Radiation Exposure

Determination of Lifetime Radiation-induced Cancer Risks, Especially after Childhood Exposure: The excess cancer mortality (and cancer incidence from 1958 onwards) throughout the lifespan has been documented for those who were over age 40 at the time of the bombs (ATB), but will not be fully determined for those exposed when young for another 25 or more years. Results of these studies indicate that those who were young ATB have a higher cancer risk to date than those exposed at older ages, but there is still uncertainty as to whether this higher risk will continue for a lifetime or will risk eventually taper off to levels similar to those who were irradiated at older ages.

Cancer Incidence: Although initial evaluations of risk estimates relied on mortality data, increasing emphasis is being placed on cancer incidence data. Besides the smaller mortality numbers, the reliability of cause of death on death certificates is lower than that in cancer registries, and mortality is a poor index of cancers with a low fatality rate. Thus, incidence studies provide more and better cancer risk data than those from mortality studies. In addition, they provide information of particular importance to the living survivors. Given the dose distribution in the LSS cohort and the approximately 50% increase in risk per Gy, the number of cancers detected (incidence) in the cohort is about 10% greater than expected absent radiation exposure.

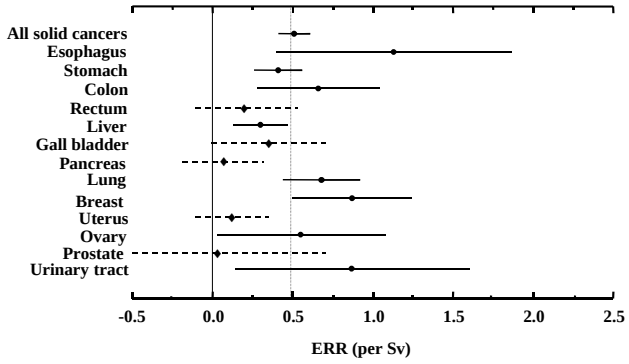
Shape of the Dose-response Curve for Solid Tumors: The shape of the dose-response curve for solid tumors is still somewhat uncertain. Past data for solid cancers largely supported the characterization of the radiation dose response as a linear non-threshold relationship (LNT model), although recent data suggest there may be modest upward curvature for solid cancers in the restricted dose range of 0 – 2 Sv [Preston, 2004]. This assessment can only be refined by obtaining more data, which requires a long-term follow-up of the LSS cohort. This, of course, has important implications for estimating the cancer risk associated with low-to-moderate doses of ionizing radiation.

Low-Dose Applications: A wide range of doses from <0.005 to 3+ Sv is encompassed in the LSS cohort, but about 90% of the LSS survivors received doses of less than 0.2 Sv. Hence, the RERF epidemiological study is able to contribute to estimates of risk at relatively low doses and will be informative at even lower doses as the data continue to accumulate. But a significant effort for the future will be to analyze how the RERF acute doses relate to the low dose rates received through occupational and environmental exposures.

Risk Estimates for Specific Tumor Sites: Risk estimates for specific organs and tissues are of considerable importance, because most medical radiation exposures and occupational or environmental exposures to radionuclides are to a few organs and not the whole body. Therefore,

accurate estimates of organ-specific risks are of considerable practical importance in radiation protection. For this reason, the International Commission on Radiological Protection (ICRP) extensively uses a system of "tissue weights" for risk estimation and radiation protection purposes [ICRP, 1991]. To date, significant radiation risks have been ascertained for numerous malignancies: leukemia, esophagus, stomach, colon, liver, gall bladder, lung, breast, ovary, bladder, skin and central nervous system tumors (Figure 6). Currently the risk estimates for specific cancer sites have considerable uncertainty. Careful cancer mortality and incidence follow-up over the next 20 or more years can provide more precise information on the slope/shape of the dose-response curves, the impact of age ATB and the temporal course of risk for these and other types of tumors.

Figure 6 – Cancer Excess Relative Risks (LSS, Mortality Follow-up, 1950-97)



Birth-cohort and Temporal Effects: Recent analyses of the LSS cancer mortality and incidence data have indicated that the radiation risk is not constant over time: the excess relative risk decreases with time (and attained age), while the excess absolute risk increases with time and attained age. However, the temporal function for those who were young ATB is only partially known because they are just reaching the ages of high cancer expression. To complicate matters, there are birth-cohort and/or time-period effects in the background rates for a number of types of cancer, and these tend to obscure the interpretation of the data. Disentangling birth-cohort, age and latency effects with respect to radiation requires a longer follow-up.

AHS and Cancer Data: Obtaining cancer data in the AHS is advantageous for at least three reasons. First, the AHS provides a systematic, unbiased (across the dose range) set of screening data for tumor sites, such as thyroid, which are susceptible to surveillance bias. Second, the AHS dataset includes much more extensive data on potential cancer risk factors than does the LSS dataset, so a more full analysis of potential confounding or effect-modifying factors can be performed with the AHS data. This will be especially true in the years to come as the numbers of cancers in the AHS cohort increase, so as to have greater statistical power and precision. Third, biological samples are available for AHS members, which permits the detailed analysis of biological and genetic pathways and mechanisms associated with cancer induction. These biospecimens represent a rich resource for future investigation.

Confounding or Effect-Modification of Radiation Effects: Confounding variables and modifying

factors such as smoking and diet need to be considered in estimating the risk associated with radiation exposure. Such confounding factors are important to include because they often affect the magnitude of the radiation effect under study, and this may vary by tumor site. The simultaneous action of radiation and these factors clearly has the potential to alter in an additive, multiplicative, or even antagonistic manner, the net effect of the apparent radiation response. In other words, it is difficult to understand true radiation risk accurately without considering confounding factors and risk modifying factors in the analysis.

Multidisciplinary Research on Non-Cancer Effects of Radiation Exposure

Importance of Non-Cancer Radiation Effects: A high-priority need is to follow up preliminary LSS findings suggesting that radiation increases the mortality of non-cancer diseases. The current LSS estimate of excess relative risk for non-cancer mortality is about 0.12 per Gy, but when multiplied by the large background incidence, this represents an appreciable number of excess cases, accounting for approximately 70% of the number of excess cancers. Dose-related risks for mortality and incidence are suggested by studies on major non-cancer diseases, including cerebrovascular disease, heart disease, respiratory disease, cataracts and liver disease in relation to radiation exposure. But these data are not yet firm. For example, the dose response for cardiovascular disease in the LSS shows a convincing response only at higher doses, although the slope of the line is significantly positive; thus, more data are urgently needed. Some of these diseases may have a dose threshold in occurrence or upward curvature in the dose response, and multiple etiologies are no doubt active, necessitating careful investigation.

Studies using stored biological samples collected from the AHS population are expected to aid in elucidating the interaction between radiation and environmental and genetic factors. By continuing to monitor for an increased number of cases, it should be possible to evaluate risk more accurately and to clarify issues such as the shape of the dose-response curve for different diseases. RERF also will stimulate hypothesis-driven research in A-bomb survivors, supplemented by studies using appropriate *in vitro* and *in vivo* experimental models, that addresses the mechanisms by which radiation affects these disease processes.

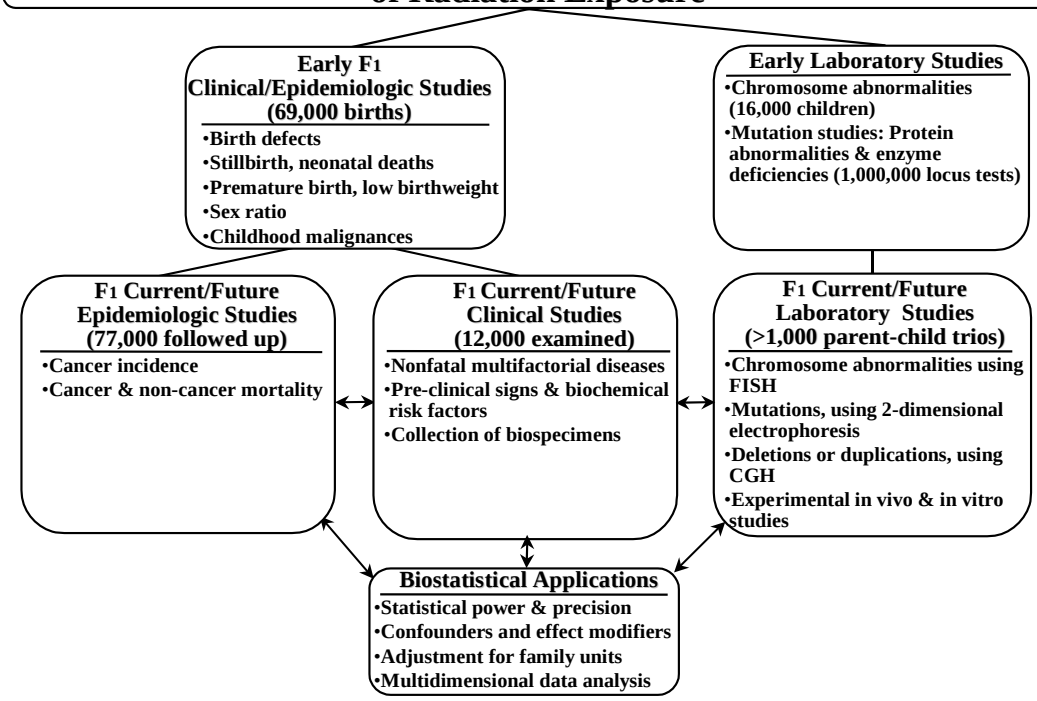
Age at the Time of the Bomb (ATB) and Attained Age Effects for Non-cancer Diseases: There are unresolved questions about whether and to what degree age ATB may modify the degree of risk, e.g., a recent analysis of the AHS data suggested that the dose-response for cardiovascular disease was significant only in those under age 40 ATB. Clearly resolving questions about the impact of age-at-exposure and temporal factors requires further data, which can only be achieved by an extended follow-up of the LSS and AHS cohorts.

Multidisciplinary Studies of the Heritable Effects of Radiation Exposure

Thus far, no radiation-related heritable effects have been found in the F1 epidemiologic cohort

(synopsis of studies is shown in Figure 7). However, this is probably due to the current limited statistical power due to the rather young ages (average age of 46 at latest follow-up), with relatively few deaths or incident cancers, and hence it is premature to conclude that there are no such heritable effects But this issue is of great importance to the well-being of the survivors and their children, as well as everyone in the world who will be or has been exposed to radiation before or during childbearing years. It is essential that these F1 studies be continued until definitive answers are established, which will require at least 30 more years. A finding of no heritable effects observed will have important implications for setting standards for radiation protection.

Figure 7 - Multidisciplinary Studies of the Heritable Genetic Effects of Radiation Exposure



Other Key Scientific Issues

Broad-Based Medical Research: The importance of the longitudinal AHS and *In Utero* Clinical health databases extends well beyond the elucidation of the long-term health effects of ionizing radiation, to being able to address an extraordinary number of scientific questions. They can, for example, be used to understand natural aging processes, the natural history of disease(s), and disease progression. If the F1 Clinical Cohort becomes longitudinal, as hoped, it will make a considerable contribution to these aims also because of the large numbers from a more contemporary-lifestyle generation. Similarly, the LSS epidemiologic database can address many questions concerning potentially modifiable risk factors for a variety of diseases.

Mechanistic studies: RERF has made important contributions in the purely basic radiobiological sciences. The focus of RERF lies in the coordination of basic and translational research, namely its assessing the applicability of the basic research findings to humans using *in vivo* or *in vitro* systems.

Potential Future Directions Identified by Panel Members

Radiation-related research should continue for at least another 20 years. At that time, data collection on the LSS, AHS, and the F1 should be terminated. Special consideration might have to be given to continuing some form of follow-up for members of the LSS who were under the age of 10 at the time of the bomb. During the intervening period, plans for the maintenance of tissue samples and databases should be developed. These could be housed in a successor institution that could be established for this purpose or it could be transitioned to other international or academic organizations. Any new RERF radiation-related studies developed in the intervening years could also be housed at other organizations. But if the U.S. and Japanese governments agree that RERF should be continued as a COE for radiation health effects research, then the intervening period should also be focused on:

- the recruitment of new researchers,
- the relocation of the Hiroshima laboratory, and
- the strengthening of collaborative research relationships to maximize the benefits of RERF research for the improvement of human health.

Similarly, if some alternative to the COE is chosen, such as the transfer to an academic or international institution, transitional activities will need to be the focus of the intervening time

AHS should be supplemented with additional participants to increase representation of those younger than 10 ATB.

The idea to decode the human genome was conceived by researchers who believed that with the basic genetic code we could identify genetic events that contribute to radiation induced cancer. Along with the sequencing of the human genome has also come some very powerful tools. They are not just at the level of DNA, but at the level of RNA, proteins, and cellular systems. Collectively, they hold promise to do the very thing that those researchers contemplating the sequencing of the human genome initially sought. By combining studies of animal models of cancer, molecular epidemiology, tumor genetics, gene expression in tumors, and cell culture studies we can identify disease-causing genome aberrations. The RERF has many valuable things to bring to these studies. A very well annotated cohort is one. The blood, serum, and lymphocyte lines that have been preserved are also key elements of the new broad based approaches.

A genome analysis relating the development of cancers among A-bomb survivors to other risk factors should be among the first projects to be evaluated and ranked for future support. It might consist of these elements

- Genome analysis study regarding the development of solid cancers among A-bomb survivors
- Genome analyses of solid cancers using A-bomb survivors' tissue samples.
- Genome-wide analyses on the development of solid cancers among A-bomb survivors, using microarray CGH methods
- Immunogenome-based study on cancer and radiation susceptibilities
- Translational research on correlations between single nucleotide polymorphisms (SNP) and blood biomarkers and risk factors of disease
- Examination of non-coding RNA within the F1 generation and in comparing with family members to determine if there are radiation effects.
- A reevaluation of the biodosimetry work at RERF should be undertaken to determine how advances in this work could contribute to the LSS and to provide new findings for establishment of biodosimetry in the future.

Current and Potential Scientific Personnel and Research Department Structure

Current structure

A major reorganization of research departments has not occurred since 1996, when the Department of Radiobiology in Nagasaki was merged with the same department in Hiroshima. In accordance with trends in research projects and personnel during the intervening period, the number of researchers and research assistants is not evenly distributed among the different departments.
As always, any organizational structure should be flexible such that it can meet the changing needs set by the highest priority research. Consideration should be given to organizational models that are structured around the “Priority Projects” and the “Fundamental Research”. In this regard the Japan National Institute for Environmental Studies has an organizational structure that is that is described as being a “Strategic and dynamic framework that makes the best use of our assets”. Other models can be considered as best practices.

Recommendations on Structure and Staffing

An agreement between RERF, DOE, and MHLW should be developed that will allow the hiring of a new generation of researchers, including exploiting the recruitment of strong non-Japanese scientists by the National Academy of Sciences (NAS) in order to retain the international interests of this project, instill a diversification of expertise, and inject fresh ideas into the RERF research program.

For many years the RERF has trained and taught professionals from around the world in radiation related health studies. These are valuable activities and RERF should look for further opportunities to provide training and education.

In order to better utilize existing research resources and to promote cross-disciplinary research, the SRP believes some new approaches to the management of research and possibly reorganization of the RERF’s Departmental structure may be needed at some point in time. The first step would be to implement a greater focus on interdepartmental project planning, prioritization, and implementation as discussed above. The second is to identify key tools for research that should be supported on a cross-departmental basis. For example, cross-departmental resource groups for genomics, biostatistics, and image analysis could reduce the cost of these services and improve interdisciplinary research at RERF. Lastly, if these efforts to promote interdisciplinary research fall short, a Departmental restructuring combining the Departments of Epidemiology and Statistics and the Departments of Radiobiology and Genetics into single departments might be in order.

Current Management Structure

1) The Board of Directors: The Board of Directors is the highest decision-making body relating to operation of the Radiation Effects Research Foundation (RERF). It currently comprises one full-time chairman, one full-time vice-chairman, two permanent directors, and six visiting directors, for a total of ten members (this number may total up to 12, according to the Act of Endowment). The permanent and visiting directors consist of an equal number of members from Japan and the United States, respectively. The term of office of the directors is four years, and they may be re-elected.

2) The Scientific Council: The Scientific Council, which consists of five members each from Japan and the U.S., for a total of 10 members, reviews RERF's scientific research programs, and makes recommendations to the Board of Directors with respect to adoption of new research programs and/or review evaluations of ongoing programs.
The scientific councilors are selected and appointed by the Board of Directors, from among those who are possessed of expert knowledge and experience pertinent to carrying out the activities of RERF. The term of office of the scientific councilors is five years, with possible reappointment for one term only.

3) Supervisors: Two supervisors, one from the U.S. and the other from Japan, are appointed to audit the execution of the directors' duties and the financial status of the foundation. The term of office of the supervisors is four years, with reappointment possible.

4) Local Liaison Council: The Local Liaison Council comprises organizations established both in Hiroshima and Nagasaki, with the presidents of Hiroshima and Nagasaki Universities serving as chairmen at the request of RERF. The council also consists of representatives of local governments, medical associations, A-bomb related medical institutes, A-bomb survivor organizations, and the media. Local Liaison Council meetings have been held separately in Hiroshima and Nagasaki once each year, as a general rule.

Since members of the Board of Directors and the Scientific Council are not selected from among A-bomb survivors and related local persons, the Local Liaison Council meetings are the only formal opportunity to hear opinions and requests from such people in order to pursue the aims of the establishment of RERF, including improvement of RERF's research activities and of the welfare of A-bomb survivors. The meetings have provided a necessary function for smooth operation of RERF, as they have resulted in many constructive proposals regarding relocation of the Hiroshima Laboratory and RERF's Open House events.

Recommended Changes

The Scientific Council will serve an important role in supporting RERF in its decisions about future research directions and in choosing specific projects. To do this effectively it will need changes to broaden its members' expertise. It will also need more frequent interaction with RERF researchers. These points should be taken into account when considering revisions of the Articles of Incorporation (the Act of Endowment) in accordance with reform of the public-interest corporation system in Japan.

Research Infrastructure

Research material preservation

A wide array of research materials are created, analyzed, and stored at RERF. These include recorded materials from the various cohort studies, biological samples, and dosimetry samples. These various research resources are contained in or accounted for through various electronic databases. These databases are essential to current and future research productivity. The ability of researchers to relate the information in these databases is increasingly important. An ongoing challenge is to make the databases interactive and easily used and, at the same time, protective of study participants' personal privacy.

Recorded materials from cohort studies

ABCC/RERF have traditionally examined health issues, including death and disease, by establishing certain study cohorts consisting of Hiroshima/Nagasaki A-bomb survivors, their children and controls. The study subjects have been registered individually and managed collectively. Data obtained from continuous studies are collected and archived for study subjects individually. The Department of Epidemiology has archived basic information (name, birth date, gender, conditions at the time of A-bomb exposure, etc.) and death information obtained from the Life Span Study (LSS), *In Utero* Study, and Health Effects Study of Children of A-bomb Survivors (F1 study). The Department of Clinical Studies has archived results obtained from the Adult Health Study (AHS), including diagnostic findings, ECG reports, and X-ray images. In archiving personal data, RERF has given careful consideration to secure management of the data.

In addition, the research departments concerned have archived materials such as original survey sheets for the following studies:

- Basic studies for the above cohort studies: A-bomb survivor study using the attached survey for the 1950 National Census, which was used as the information resource for cohort samples; Master Sample Questionnaire (MSQ) survey for 1956-1961, in which identity information and exposure status were studied; shielding survey records (1954-1965), etc.
- Studies conducted before the above cohort studies include Major Genetic Study (initiated in 1948), Major Pediatric Program (initiated in 1948), Adult Medical Survey (initiated in 1950), and Leukemia Study (initiated in 1950).

Biological samples

Clinical samples: Over 577,000 clinical samples (blood, blood fractions, and urine) have been collected and stored from 27,928 AHS and FOCS subjects (as of September 7, 2006, as per ITD records). Specimens from AHS subjects have been systematically collected during the course of their periodic health examinations and stored from as early as 1969, whereas to date, clinical specimens from the F1 study subjects have been collected only once per subject, starting in 2002. While

specimen collections ceased for F1 study subjects at the end of September 2006, specimen collections for AHS subjects still continue. For the temperature-liable clinical specimens, samples are stored under refrigeration using a combination of either low (-20 C), ultra-low (-80 C) mechanical freezers, or large scale, auto-fed, liquid nitrogen (liquid/vapor phase storage; approx. −190℃) storage tanks.

Pathologic tissues: In terms of pathologic tissues (as per Department of Epidemiology's records), 932,250 tissues have been collected, fixed and embedded from some 143,000 case studies (i.e., pathologic tissues collected from individuals, either living and undergoing surgery, or following death and subsequent autopsy). From these tissues, well over 2 million slides have been prepared, examined, and stored. Pathologic specimens are stored under ambient conditions (generally in air-conditioned rooms), at various locations within the departments of the Hiroshima and Nagasaki laboratories.

Specific clinical/pathologic tissues have been collected as well, and processed and stored for designated "Research Protocol" (RP) -related studies. In aggregate, approximately 165,254 of these specimens from 19732 subjects are in the archive and consist of whole blood samples, specific cell fractions (e.g., RBCs, PMNs, Lymphs, etc.), experimentally modified cell samples (EBV-transformed lymphocytes), and blood plasma/sera. These specimens are generally being stored in the frozen state at ultra-low temperatures (i.e., either -80℃ in mechanical freezers, or in liquid nitrogen at approximately −190℃).

Cytogenetic materials: A sub-archive of cytogenetic materials is also being maintained by the Genetics Department and consists of some 300,000 slides of chromosome spreads derived from blood lymphocytes of AHS participants

Teeth: Approximately 1,400 teeth from individuals of the AHS cohort during routine dental extractions have been collected and stored for radiation dose estimates using electron spin resonance (ESR).

Dosimetry samples: Exposure estimates have been largely developed through physical dosimetry of systematically collected and analyzed materials obtained from buildings located at set distances from ground zero. The archive consists of both outdoor construction materials and indoor, household-related items collected from various structures within the two cities, Hiroshima and Nagasaki. Some 740 samples have been collected and analyzed from approximately 21 outdoor (634 specimens)/indoor (106 specimens) sites.

Information Processing System

RERF's Information Technology Department (ITD), which is in charge of information processing, has robustly supported research by developing programs required for research, preparing research analysis files, and processing data while assuring strict protection of personal information of study

participants. The department is one of RERF's strengths and IT departments with similar capabilities are not in evidence at other research institutions in Japan.

Centralized management and interrelated use of all databases

In 1991, transition from traditional general-purpose large computers to distributed workstations started, and database construction on such workstations has since been fully implemented. Initially, the Master File Database (database of basic information on RERF research subjects) and the Tumor and Tissue Registry Database were created. Then, a research analysis database was created, and an application system for its operation was fully developed. Although the concept of databases was widely known then, no other institution in Japan had a centralized system using relational databases that managed all the data within the organization. Therefore, it can be said that RERF's efforts in this regard were on the cutting edge technologically. The ITD also centrally manages computer-related equipment and software packages for their effective use and for cost reduction.

Separation of databases containing personal information and research analysis databases containing anonymized information

From the viewpoint of personal information protection, it is not appropriate for RERF to manage databases that are completely integrated, as the foundation has both clinical and research analysis departments. (While an integrated database structure facilitates application design and management, the various tables in the databases are accessible by all departments in an organization, potentially violating subject privacy.) At RERF, therefore, databases have been divided into those for clinical departments and those for research analysis departments, with the two databases being independent of each other. This solves various issues in one stroke, such as (1) risk of personal information leaks, (2) burden on database servers, and (3) effects of structural changes of tables at the request of research analysis or clinical departments on application programs. Based on this structure, an extremely sophisticated procedure has been established: ITD manages databases consisting of multiple database servers in an integrated manner to handle information including laboratory data of the study subjects and digital images of their chest X-rays and other such data, and convert and transmit the data from these databases to the research analysis database. For personal information protection, Master File numbers used by the clinical departments are automatically replaced with randomly produced numbers in the research analysis database to ensure that study subjects cannot be identified.

ITD has achieved high performance and assured strict personal information protection to ensure that varied and voluminous data collected over the past 60 years can be used efficiently for research analysis. This is a unique strength of the RERF information system not seen at other research institutions in Japan. The excellent achievements thus far have mainly been due to this information processing system that has been developed within the organization, as well as staff members' efforts and active willingness to solve problems.
With the reduction in number of staff members, however, it is becoming increasingly difficult to maintain and transmit the "institutional memory" and the expertise of the information system

developed within the organization.

Research documents, databases, and reference materials

ABCC/RERF has studied radiation health effects using information on radiation doses received by A-bomb survivors in Hiroshima and Nagasaki and their health status or death after exposure, and has published research protocols and scientific reports. Furthermore, research information has been stored in databases and a portion of such information has been made available to the public through RERF's website. Reference materials collected by ABCC/RERF have been maintained by the RERF library.

Appendix 1

The research studies presented briefly below represent a fraction of those that RERF investigators have proposed as future plans. In addition, it should be noted that the basic follow-up studies of the LSS, AHS, *In Utero* and F1 cohorts, and the epidemiologic issues regarding cancer and non-cancer diseases, have already been summarized above, so they will not be repeated here.

1) Questions to be Addressed in the Future Concerning Non-Cancer Diseases

◇ *Ischemic Heart Disease (IHD) – Mechanisms of Radiation Effects at Low/Moderate Doses:* Although the pathology of high-dose (i.e., >5 Gy) radiation effects upon blood vessels and the heart has been extensively studied, there has been little examination of possible mechanisms by which IHD may be instigated or promoted by low-to-moderate radiation doses. Scientists at RERF plan to examine several plausible mechanisms for such effects using physiological, biochemical and genetic indicators of damage or malfunction. A brief outline of hypotheses for planned studies is given below:

A. *Endocrinologic Hypothesis of IHD:* The renin-angiotensin system (RAS) not only exerts control over blood pressure by several mechanisms, it also promotes atherosclerosis by affecting the migration/proliferation of blood vessel smooth-muscle cells and the induction of matrix metalloproteinases, cytokines and oxidative stress [Grote, 2004]. Aldosterone also alters blood pressure, promotes oxidative stress and induces blood vessel inflammation [Rocha, 2000; Keidar, 2004]. Little is currently known about the impact of radiation exposure upon these endocrinologic systems [Lebaron-Jacobs, 2004], but this will be investigated and related to IHD.

B. *Role of Endothelial Progenitor Cells (EPCs) and IHD:* EPCs, which are stem cells derived from the bone marrow, play an important role in cardiovascular function/disease in that they repair endothelial damage and thereby help maintain an endothelium that resists atherosclerosis. Depletion of EPCs through chronic endothelial damage and repair, and perhaps from radiation damage, can lead to increased atherosclerosis and impaired re-endothelialization of eroded plaques, with a consequent propensity for thrombosis and vascular occlusion [Szmitko, 2003].

C. *Radiation-induced Inflammation, Immune Dysfunction and IHD:* RERF has already conducted a series of studies on inflammation as an intermediate factor in the pathway(s) by which radiation induces IHD and stroke [Neriishi, 2001; Hayashi, 2005]. Radiation-related alterations in the immune system have also been documented [e.g., Yamaoka, 2004], and additional research will be conducted to further elucidate the immunological mechanisms of these radiation effects.

D. *"Thrifty" Genotype, Nutrition and IHD:* In brief, Dr. James Neel [Neel, 1962] proposed that a purported "thrifty" genotype confers a survival advantage when there is nutritional deprivation or other stresses, but those with the "thrifty" genotype are at elevated risk from multifactorial diseases (e.g., diabetes mellitus, obesity, atherosclerosis, etc) when there is nutritional abundance. The hypothesis broadly fits the time trend in multifactorial disease mortality among atomic bomb survivors: no

radiation-related excess was seen for the first 20 years after the bomb, which included a period of chronic undernutrition, but excess multifactorial disease appeared 20+ years after the bomb once abundant nutrition was available. It will be examined by assessing disease outcomes and biomarkers and genetic markers for factors related to the hypothetical "thrifty" genotype, such as markers for adipogenesis, visceral fat, thrombolysis, plaque rupture, oxidative stress and inflammation.

E. *Early Life Origin of Adult IHD:* Severe conditions *in utero* or in early childhood, including radiation exposure, could induce apoptotic changes in arterial epithelial cells, a decrease in nephron number, and endocrine system alterations, resulting in cardiovascular disease, type 2 diabetes and hypertension in later life [Rando, 2006]. Preliminary evidence suggests that those exposed at young ages may be at higher risk of cardiovascular disease, as this hypothesis suggests. A combination of existing data in the Adult Health Study and new measures of arterial, renal and endocrine function will address these hypotheses.

◇ *Radiation and Cataracts:* The international radiation-protection community has long held the assumption that only doses above about 2 Gy will produce cataracts [ICRP, 1991], but RERF's recent research results have shown excess cataracts at low-to-moderate doses among atomic bomb survivors [Minamoto, 2004; Nakashima, 2006]. However, many of the cataracts diagnosed in RERF's examination program were early, subclinical opacities. It was decided therefore to conduct periodic re-examinations of the AHS population to evaluate the progression of the early opacities and obtain a better assessment of the potential for clinically significant cataracts. RERF is also arranging to obtain operative cataract tissues from atomic bomb survivors to study biological factors in the induction of radiation cataracts.

◇ *Interaction of Radiation with Infectious Agents in Liver Disease:* AHS and LSS reports have shown increases in hepatitis B carriers and hepatocellular carcinoma (HCC) with radiation dose. One hypothesis is that radiation exposure may accelerate the progression of liver fibrosis and HCC occurrence after hepatitis B or C virus infections. To address this, in collaboration with the Liver Research Project Center, Hiroshima University, RERF has conducted preliminary planning of animal experiments to study the role of radiation using human-hepatocyte chimeric mice with lowered immunity. Another approach is molecular epidemiological studies to investigate whether genetic factors affect the rate of carrier status following HCV infection, the progression of liver fibrosis and the development of HCC after HCV infection.

◇ *Molecular Epidemiology of Thyroid Tumors:* A study is underway among atomic bomb survivors to determine if RET/PTC rearrangements or BRAF mutations are found in adult-onset thyroid cancer tissue samples as they have been among childhood or early-adult thyroid cancers after Chernobyl. Another study will examine polymorphisms in DNA repair and cell cycle checkpoint genes (e.g., TP53, ATM, MDM2, XRCC1, DNA-PK) among those who developed thyroid cancer.

2) Questions to be Addressed in the Future Concerning the Effects of *in utero* Irradiation

- *Cancer Risk Estimates after in utero Exposure:* Because the *in utero* irradiated cohort is, of necessity, relatively small (3,300 individuals) and is just approaching the ages when cancers become common, RERF does not yet have good estimates of cancer risk after *in utero* radiation exposure, owing to the relatively young age of this cohort. More follow-up time is needed to assess the risk with confidence.

- *Non-Cancer Risk Estimates after in utero Exposure:* A first report on non-cancer disease and disease-predisposing conditions in relation to radiation dose among those in the *in utero* clinical subcohort is currently being prepared, based on information collected in the AHS. However, since this cohort is now only about 61 years old, 2-3 more decades of observation are needed to accurately assess possible radiation-related excesses of non-cancer mortality (LSS study) and disease incidence (AHS study).

- *Evaluation of Neurodegenerative Disease:* The fact that the *in utero* exposed subjects who were 8-26 weeks post-conception ATB showed mental retardation and IQ deficits in a dose-related manner during childhood [Schull, 1986; Otake, 1996] raises the question of whether radiation is impacting cognitive function and the development of neurodegenerative disease in adulthood. RERF has begun to study these endpoints in the AHS [Yamada, 1999; Yamada, 2002], and will particularly study them among the *in utero* exposed in the coming years.

- *Brain Anatomy and Function:* As a follow-on to the studies of mental retardation and IQ after *in utero* exposure, a very small MRI study of a few high-dose individuals with mental retardation revealed highly interesting preliminary findings of aberrant neuronal migration and cortical organization in the brain [Schull, 1991]. With the great power of modern MRI technology, it may be possible to learn much more about the effects of ionizing radiation upon the developing brain in a sample of *in utero* survivors. RERF plans to test the feasibility of such a study.

3) Questions to be Addressed in the Future Concerning Heritable Genetic Effects (the F1 Cohort – Children of Atomic Bomb Survivors)

- *Genetic (Inherited) Risk of Cancer or Multifactorial Disease – Follow-up for Mortality and Cancer Incidence:* The F1 cohort of 77,000 was on average only 46 years old at the time of their last mortality and cancer-registry follow-ups, far too young for us to draw definitive conclusions as to whether the radiation exposure of their parents may have had an impact upon the development of cancer or multifactorial diseases among them. Since the hereditary risk of radiation exposure upon cancer or multifactorial diseases is so important an issue and there are virtually no human data to address it, it is essential that the F1 cohort follow-up be continued for another 30-40 years to evaluate lifetime risk.

◇ *Genetic (Inherited) Risk of Cancer or Multifactorial Disease – Clinical Examination Program:* The first F1 clinical examination cycle obtained data on about 12,000 F1 individuals, children of parents with a range of radiation exposure levels. The statistical analysis of these data will be completed in a few months. The clinical examination included evaluations for diabetes mellitus, myocardial infarction, stroke, hypertension, hypercholesterolemia, and pre-clinical risk factors. The implications of inherited risk are important to the many thousands of people who may receive gonadal radiation exposures at or before childbearing ages. Thus, it is essential that the F1 clinical-examination studies be continued another 30 or more years until definitive answers are established.

◇ *Molecular DNA Evidence for Genetic (Transgenerational) Detriment:* The F1 clinical examination program acquired blood samples with proper informed consent which can be used for various molecular studies. These are discussed under Basic Genetics Research.

4) Questions to be Addressed in the Future Concerning Dosimetry

◇ *Location of Individuals in Relation to the Bomb Hypocenter:* The original U.S. Army maps used to locate structures vis a vis the bomb had inaccuracies and missing streets which led to incorrect locations in assigning map coordinates to survivors in the 1950s and 1960s. Further, many individuals' locations were only recorded to a precision of 100 yards. Using an electronic Geographic Information System (GIS) and modern maps, it will be possible to correct most of the cartographic inaccuracies and thereby improve dose estimates.

◇ *Improved Shielding Information:* Further work will also be conducted to better utilize individual information on shielding configurations and to check shielding histories (e.g., with respect to intervening buildings and small hills) against aerial photos and elevation data on maps. It may also be possible to improve the understanding of shielding of workers at a large factory in Nagasaki.

◇ *More Extensive Biodosimetry Data:* RERF plans to obtain two-color FISH (fluorescence in situ hybridization) on more LSS individuals and multi-color FISH on targeted subsets. In the future, it may be possible to exploit rapid, high-throughput, flow-cytometry-based assay(s) to assess chromosomal translocations, both qualitatively and quantitatively, for improved cytogenetic evaluations and exposure estimates for radiation exposed individuals. Such method(s) could be applied not only to atomic bomb survivors and their progeny, but also to casualties of nuclear/radiological accidents as well.

5) Questions to be Addressed in the Future Concerning Statistical Applications to RERF Data

First and foremost, the Statistics Department provides invaluable expertise on most of the research projects conducted at RERF beginning with the design and statistical power considerations and culminating with the analysis and interpretation of the data. However, members of the Department also will continue to conduct research on statistical problems related to issues encountered with

RERF data, of which the following are examples:

- ◇ *Risk Assessment Based on Individual Rather than Grouped Data:* Potential advantages to using individual data include the ability to incorporate mechanistic hypotheses and family relationships (possible clustering in terms of radiation sensitivity); model missing-data mechanisms (e.g., for mail-survey data), develop flexible methods of making inference about the shape of the dose response (especially the low-dose response), and account for uncertainties in dose estimates. RERF also will begin implementing modern Bayesian methods to provide greater flexibility in modeling the often-complex RERF data.

- ◇ *Estimating and Correcting for Uncertainties in the Dosimetry:* A reassessment of the methods to adjust statistically for dosimetry measurement error has been begun. A standard approach has been used in the past to correct for dose error [Pierce, 1990], but other, potentially more complete, statistical approaches will be examined to see if they afford improvements in estimating "true" doses. Accounting for shared as well as individual measurement uncertainties is also being planned. In addition, biodosimetry data (currently chromosome aberration data on about 4,000 individuals and electron spin resonance measurements of teeth on 200) are available which can be used as "instrumental variables" to help improve the estimates.

- ◇ *Analysis with Intermediate Variables:* Methods to perform analyses involving intermediate (mediating) factors have generally not been adequately developed or used for epidemiologic and clinical-type data, although it is a common problem with biomedical data. The problem also is commonly encountered in RERF datasets (e.g., radiation effects on cardiovascular disease may be mediated by radiation-induced inflammation). RERF will adapt or develop proper methods for such analyses.

- ◇ *Analysis of Multiple Endpoints ("Multidimensional" Data):* The basic science departments are increasingly generating dense data with numerous endpoints (e.g., microarrays, genome-wide scans). Statistical methods are rapidly evolving in this area. Development and application of methods in bioinformatics and exploratory statistical methodologies will be pursued to identify potential relationships and patterns in the increasingly complex RERF data.

6) Questions to be addressed in the Future through Basic Genetics Research

- ◇ *Stem cell studies:* RERF has recently observed that survivors exposed *in utero* did not exhibit chromosome aberrations in their blood lymphocytes when examined 40 years later, unlike those exposed at older ages [Ohtaki, 2004a]. Subsequent study in mice not only confirmed the observation but disclosed that spleen cells and bone marrow cells had the same characteristics, so it appears that hematopoietic stem cells are refractory to conservation of chromosome aberrations. It will be important to clarify if stem cells in other tissues such as thyroid or breast might have the same characteristics. For this purpose,

RERF hopes to develop collaborative studies with outside researchers.

◇ *Biodosimetry:* Obtain multicolor FISH (fluorescence in situ hybridization) assessments of chromosome aberration frequency as a biodosimeter among AHS subjects to gain insights on potential bias problems with the physical dose estimates. The FISH information on the same subjects but examined repeatedly at different ages might also provide unique health-related information on the study subjects.

◇ *Mechanisms of Somatic Genetic Effects:* To assess individual variation in genetic makeup and its contribution to radiation-induced pathologies of long-surviving A-bomb exposed individuals, that is, identifying and characterizing genotypes associated with increased (or decreased) susceptibilities to given radiation-induced diseases. Disease susceptibility following radiation exposure will be related to prominent founder mutations, as well as polymorphisms in DNA repair genes, etc.

◇ *Aging Study:* Identification of polymorphisms or Comparative Genomic Hybridization (CGH) markers associated with healthy longevity by using array systems on stored lymphocytes. An aging study may be a strong way to re-direct future research at RERF.

◇ *Molecular Heritable Genetics Research:* Cell lines for >1,000 family trios of parents and children have been established, and research based on advanced technologies, including 2-dimensional gel electrophoresis (2-DE), array comparative genomic hybridization technique (array CGH), and a multicolor FISH technique, has been initiated. A comparison of 2-DE gels in parents and offspring is effective for detecting offspring mutations without having to pre-specify which loci to study. The array CGH is effective for detecting large genomic deletions or duplications. Multicolor FISH is the most effective method for detecting translocations, a stable type of structural aberration of chromosomes. With these powerful technologies, RERF will be able to detect previously undetectable genetic aberrations within offspring and their parents in relation to radiation exposure. In addition, RERF hopes to exploit new biomolecular technologies to detect small deletions or duplications in offspring genomes that might have occurred as a result of parental exposure to radiation. RERF would follow this by molecular characterization and disease linkage-analyses of the inherited mutations detected by high resolution DNA array assays.

◇ *Genomic instability in the Offspring of Irradiated Parents:* The issue of inherited genomic instability is currently under study, e.g., increased frequency in minisatellite mutations or tumor incidence in the offspring of irradiated parents (in humans and mice, respectively), but the results have not been very reproducible. Thus, it is important to use animal models suitable for answering specific questions.

◇ *Meiotic checkpoint:* Basic research is needed on the mechanisms for induction of chromosome aberrations in germ cells. For example, the translocation frequency in spermatogonia cells is much lower than in blood lymphocytes in mice and some other

animals. Therefore, it appears that germ cells have developed a mechanism to avoid transmitting aberrant chromosomes to the offspring, which might be a meiosis-specific checkpoint. A careful animal study will examine this question.

◇ *Molecular Prevention of Radiation-Induced Epigenetic Effects:* Genomic instability appears to play an important role in the pathogenesis of some cancers. Insofar as both radiation-induced genomic instability and pre-disease changes are epigenetic, there may be ways to prevent disease development by developing or exploiting molecular mechanisms that counter pertinent radiation-induced epigenetic alterations. However, an essential step is to develop an assay system that permits rapid enumeration of unstable cells in culture, which in turn will facilitate the screening of classes of chemicals that may suppress the instability. RERF is working on developing such an assay system.

7) Questions to be Addressed in the Future through Basic Research in Radiobiology/Molecular Epidemiology

The objectives of this program are to investigate mechanisms of radiation effects, including:
(a) elucidating mechanistic relationships between radiation exposure and development of selected cancers, that are further categorized by molecular events (e.g., RET/PTC rearrangement or BRAF mutation in thyroid cancer, and microsatellite instability in colon cancer);
(b) developing possible causal relationships between chronic radiation-induced inflammatory states or alterations in immunosurveillance networks and susceptibility to cancer and non-cancerous diseases (e.g., cardiovascular disease and diabetes mellitus) [Hayashi, 2005; Kyoizumi, 2005];
(c) characterizing the role of radiation exposure in the etiology and prevention of aging-related diseases. RERF already has data to suggest that radiation hastens immunological aging [Hayashi, 2005], and the foundation plans to examine various other physiological parameters as well.
Some of the lines of study include the following:

◇ *Radiation, Structural Alterations of DNA and Cancer:* To clarify mechanisms underlying the increased incidence of thyroid, colon and lung cancers among atomic bomb survivors, RERF has begun to assess the molecular characteristics of these cancers in terms of structural alterations in DNA (rearrangements, LOH, microsatellite instability, etc.) found in cancer tissue specimens of A-bomb survivors. In addition, some molecular events (e.g., DNA methylation, DNA oxidation) that occur at an early stage of radiation-associated carcinogenesis may also exist in non-malignant cells of atomic bomb survivors, so they are being examined. These observations are being supported by *in vitro* and *in vivo* experiments to investigate the biological significance of genetic alterations found in relation to radiation exposure.

◇ *Individual Mutability and Cancer:* To assess whether individuals with higher sensitivity to radiation-induced genetic damage have a higher risk of radiation-related cancer, RERF will

analyze associations between individual mutability following radiation exposure, genetic background and cancer risk in the AHS participants. Biological endpoints used for assessing individual mutability are several genetic-damage markers, such as glycophorin A mutations, phosphatidylinositol glycan-class A mutations, micronuclei, and phosphorylated histone H2AX levels; these markers will also be studied in relation to the genotypes of DNA repair genes.

◇ *DNA Damage and Repair Capacity:* Other than immunological aging, RERF may be able to estimate radiation effects on the acceleration of other facets of physiological aging. Specifically, RERF is interested in the DNA repair capacity and self-renewal capacity of stem/progenitor cells, which attenuate with aging and are involved in the development of aging-related diseases. A sophisticated methodology to measure DNA repair capacity and radiation sensitivity, with and without ex vivo radiation exposure to peripheral lymphocytes, is under development. This can be applied to the stored lymphocytes of AHS participants. RERF will investigate genetic factors involved in individual differences in radiation susceptibility by phenotype-genotype association analysis, and also the interaction between the aging-related decline of DNA repair capacity and radiation exposure. Such insights may help predict individual differences in DNA damage and repair responses to radiation.

◇ *"Immunological Aging":* In a continuing study of the AHS cohort, an apparent acceleration of immunological aging by radiation exposure has been observed, persisting for periods of 40 to 50 years after the atomic bombings, which may result in increased susceptibility to illnesses. Immunological aging is mainly characterized by 1) a decrease in thymic T-cell production, 2) frequent clonal expansion of memory cell populations, 3) unregulated autoimmune responses, and 4) enhanced inflammatory reactions. RERF has shown that there are radiation dose-dependent and long-lasting impairments in immunological functions. RERF will also investigate radiation-induced acceleration of immunological aging and its associations with development of non-cancer diseases using potential animal models.

◇ *Immunogenome:* RERF will associate genotypes of immune-related genes with diseases and with phenotypic immunological markers. This will provide new clues for assessing individual differences in disease risk among atomic bomb survivors and identifying high-risk groups for radiation-associated diseases. It also may be possible to identify key genes that control the aging process in the immune system. This study will mainly involve polymorphisms of immunity- and inflammation-related genes such as those encoding HLA class I and II molecules, NK receptors, cytokines, and chemokines, in relation to both cancer and non-cancer disease endpoints among atomic bomb survivors.

◇ *Stem/progenitor Cell Studies:* RERF hypothesizes that aging is closely related to the attenuation of stem/progenitor cell functions, specifically self-renewal capacity. Stem/progenitor cells are direct targets of radiation carcinogenesis and also are implicated in bystander effects and adaptive responses to low-dose radiation. The effects of radiation on

stem/progenitor cells will be studied in terms of gap junction intercellular communication and the microenvironment of these cells, using both *in vitro* and *in vivo* experimental models, e.g., transplantation of irradiated stem/progenitor cells into mice or irradiation of mice into which have been transplanted human stem cells. This study will require several steps:

A. *In vitro and in vivo experiments:* RERF has already established various stem/progenitor cells: nonmalignant human peritoneal mesothelial cells (HPMC), human mammary epithelial cells (HMEC), and human mesenchymal stem cells (MSC), and have used them to study signal transduction of radiation effects [Ogawa, 2004; Ogawa, 2005]. RERF also has characterized human hematopoietic stem cells (HSC) from stored lymphocytes of AHS participants. RERF plans to investigate radiation effects on stem/progenitor cells using various senescence markers such as self-renewal capacity, senescence associated-beta-Galactosidase (SA-beta-gal) activity, and p16 expression. In vivo experiments will also be performed with hematopoietic stem cells taken from irradiated mice at different ages, with measurement of these parameters.
B. *DNA damage in organ stem/progenitor cells:* A goal is to find how and how much radiation generates DNA damage in organ stem/progenitor cells, which may cause cancer or other abnormalities in some cases. At present, it is possible to identify stem/progenitor cells in organ tissue by immunostaining with stem-cell-specific proteins. In the future, when molecular analyses can be performed with small numbers of cells, RERF will be able to analyze DNA damage in stem/progenitor cells isolated by laser capture microdissection from stored non-cancerous autopsy tissues of A-bomb survivors.

Appendix 2. Opinions from International Organizations

The International Commission for Radiological Protection (ICRP)
Chairman, Lars-Erik Holm

March 22, 2007

Here is my quick and short answer. I hope this is sufficient. The numbers refers to the numbers of the questions in your letter.

Q1. Do you believe that continuing the Life Span Study of 120,000 individuals of all ages (of whom 40% are surviving) is important for the purposes of your Commission?

A1. Yes, the continuation of the unique Life Span Study is very important for the purposes of radiological protection and for ICRP's work? The Commission is of the opinion that the Life Span Study will continue to provide important new information on radiogenic solid cancer risks for another 15 - 20 years.

Q2. RERF is considering whether to expand part of the clinical studies cohort (the Adult Health Study) who were under age 10 at the time of the Bomb in order to better understand the sensitivity of the young to radiogenic effects. Is this work relevant to your Commission? In your opinion, should it be done?

A2. Yes, everything that can reasonably be done to increase the understanding of the sensitivity of children to radiogenic effects should be given priority. Increased understanding of these issues is of great importance to the Commission.

Q3. Does your Commission find the study by RERF of non-cancer diseases and their induction by radiation of value?

A3. Yes, they are valuable and can provide more important information in the future. We need to know more about non-cancer effects, and the RERF cohorts are ideal for this purpose.

Q4. The F_1 cohort (the children of atomic bomb survivors) has been studied beginning in 1946. The subjects are now about 50 years old on average. Is the continued study of the cohort of value to your Commission?

A4. Yes, definitely.

Q5. Are there modifications to these primary research activities of the RERF that you believe would be helpful to the mission of your Commission?

A5. No comment.

AEN
NEA

AGENCE DE L'OCDE POUR L'ÉNERGIE NUCLÉAIRE

OECD NUCLEAR ENERGY AGENCY

Le Directeur général
The Director-General

MM. Paul Gilman and Sadayoshi Kitagawa
Co-chairs
Senior Review Panel on Future Planning
for RERF
Japan

Issy-les-Moulineaux, 11 April 2007

(Letter sent by email to Mr. Solvie's attention at solvie@rerf.jp)

Dear Dr. Gilman and Dr. Kitagawa,

Thank you for your letter of 15 March requesting input for your Senior Review Panel on the Radiation Effects Research Foundation (RERF). The work of the RERF has, for many years, formed a key basis for our knowledge of radiological risks and continues to be of considerable use to the OECD Nuclear Energy Agency (NEA) member countries. Therefore I appreciate the opportunity to comment on the RERF's plans for future work.

In general, the high scientific quality and the long-term nature of the RERF studies make them a unique resource that forms a key element for building radiological protection policy and regulation at the national-level. Through analysis by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) to the policy-level recommendations of the International Commission on Radiological Protection (ICRP), the work of the RERF brings a solid and coherent foundation to radiological protection regulations in every NEA member country. Maintaining and further developing a sound epidemiological basis for radiation protection is of particular importance when considering that currently 24% of the electricity in NEA member countries is nuclear generated, and that many governments are increasingly concerned with climate change, greenhouse gas emissions and security of energy supply and are discussing increasing their use of nuclear energy. For these reasons, the past and future work of the RERF will continue to be central reference points for radiological risk assessment.

In responding to the five specific questions in your letter, I draw on work by the NEA's Committee on Radiation Protection and Public Health (CRPPH). The CRPPH has for a long time followed radiological science developments, and for the past two years the CRPPH has been developing a document titled "Scientific Issues and Emerging Challenges for Radiation Protection", which will be approved by the Committee at its upcoming May 2007 meeting. The draft report states that: "The main issues in radiation epidemiology today are:

- the estimation of risk at doses below 100 mSv;
- the effects of different types and qualities of radiation;

Le Seine St-Germain 12, Boulevard des Iles 92130 Issy les Moulineaux - France
Tel. : (33-1) 45 24 82 00 - Fax (33-1) 45 24 11 10 - http://www.nea.fr/

- the effects of different exposure patterns (e.g. chronic or acute exposure, internal or external exposure);
- the effects of modifiers, both genetic and other, of radiation risk;
- the effects of age and gender on risk;
- the consideration of non-cancer effects (i.e. cardiovascular diseases, immune response, cataracts...);
- the integration of radiobiological information in the design, analysis, interpretation of studies; and
- the follow-up of current epidemiological studies over the full lifetime of the cohorts under investigation."

Based on this body of experience coming from the CRPPH reports on scientific research, I would like to address your five questions as follows.

1. *Do you believe that continuing the Life Span Study of 120,000 individuals of all ages (of whom 40% are surviving) is important for the purposes of your Agency?*

   The continuation of the LSS is seen by the NEA's members as very important. While it is recognised that it is policy challenge to maintain financial commitments to long-term epidemiology studies, the CRPPH report none-the-less recommends the following:

   "Populations of specific interest for future research on cancer include:
   - A-bomb survivors: it is important that the follow-up of this cohort is continued until the extinction of the cohort, in order to fully characterise and quantify risks. Because of its long follow-up and relatively high number of medium to highly exposed individuals, this cohort forms a unique data source to study time and age related patterns of radiation-induced risk."

2. *RERF is considering whether to expand part of the clinical studies cohort (the Adult Health Study) who were under age 10 at the time of the Bomb in order to better understand the sensitivity of the young to radiogenic effects. Is this work relevant to your Agency? In your opinion, should it be done?*

   This work would be very relevant to the work of the NEA. The CRPPH report notes that experience from many epidemiological studies indicates the heightened sensitivity of children to radiation exposure, and as such the expansion of LSS clinical studies as is suggested here would seem to be an important step forward. In fact, the CRPPH report clearly identifies the significance of understanding these risks to policy decisions:

   "Further, epidemiology has provided, and will continue to provide, important information on effects of age at exposure, time since exposure, and various host and environmental factors that may modify radiation risk and thus be of importance for radiation protection of sensitive groups.....

   Within the coming decade there will be a significant increase in epidemiological studies of risks from exposure to protracted radiation, of risks from internal exposures, of risks of diseases other than cancer (in particular vascular diseases), of risks to sub-groups of mutation carriers and of risks to those

exposed in infancy and childhood. Only time will tell what impact these studies will have on the risk estimates that currently underpin radiation protection standards – some change is, however, almost inevitable. Policy makers need to remain abreast of developments in this area and be prepared to respond appropriately to new findings."

3. *Does your Agency find the study by RERF of non-cancer diseases and their induction by radiation of value?*

Over the past few years, the study of non-cancer diseases, in particular circulatory diseases, has increased in importance. Much of the epidemiological evidence suggesting the significance of these diseases has arisen from the LSS work. These new risks could have an effect on the overall estimate of risks from radiation exposure, and are thus an important area of new study. As such, I fully support the RERF work in this area. The draft CRPPH report specifically cites these epidemiological studies as important, and suggests useful paths forward:

"In addition, it is important to expand the studies of non-cancer effects, in particular of cardiovascular diseases. To maximise the information that can be drawn from studies of low dose exposures, it is important that the following methodological issues be addressed in future studies:

- The combination of studies with similar exposures and endpoints. Pooling of studies will, in principle, lead to more precise estimates of risk and offer an opportunity for understanding differences and similarities between the studied population groups;
- The reduction of dosimetric uncertainties. The assessment and validation of doses by means of different methods and the involvement of dosimetrists with diverse background and experience might help to better determine the main sources of uncertainty and their magnitude and how the latter can be decreased;
- The further improvement of the methods of analysis, so that the uncertainties in dose estimates and other factors and those resulting from exposure to different types of radiation can be taken fully into account in establishing confidence levels on risk estimates derived from epidemiological studies; and
- The use of radiobiological information in the design, analysis, and interpretation of the studies."

4. *The F_1 cohort (children of atomic bomb survivors) has been studied beginning in 1946. The subjects are now about 50 years old on average. Is the continued study of the cohort of value to your Agency?*

While the genetic risk remains only a small component of the overall risk coefficient, this does not detract from the importance of full understanding of these risks. In fact recent work has brought more to light the phenomenon of genomic instability. However, this is, for the moment, based on cellular studies, and thus it seems to be essential to continue the study of the progeny of the a-bomb survivors for evidence, or not, of this effect at the level of the organism. The CRPPH draft report states:

"Radiation-induced genomic instability means that the progeny of irradiated cells show, for many generations, an increasing occurrence and accumulation of new

mutations and/or new chromosomal aberrations or other genomic damage. Affected progeny also demonstrate high levels of lethal mutation, which may be measured as delayed reproductive cell death and/or delayed apoptosis. These effects also occur in cells that were not exposed to radiation. Genomic instability occurs in the progeny of irradiated cells at a frequency that is several orders of magnitude higher than would be expected for a mutation of a specific gene. Therefore a mutation in, for example, a repair gene is not a likely explanation, and the induction of genomic instability is more likely a second order event."

5. *Are there modifications to these primary research activities of the RERF that you believe would be helpful to the mission of your Agency?*

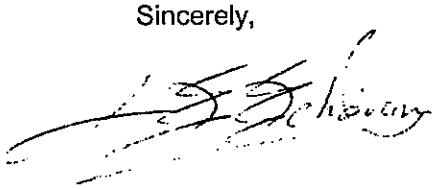
   The research lines that the RERF is currently following, and those that are described here that may be pursued, address most of the key issues identified by the NEA's recent report. However, current work performed at the NEA would suggest to consider further focus on three interlinked aspects

   - Although it is epidemiologically difficult, any further information that can be drawn from the LSS data concerning the estimation of risks below 100 mSv would be extremely useful.
   - In addition, and perhaps in co-ordination with this, further study on the effects of radiation risk modifiers, both genetic and other, would be useful, in particular new insights into the effects of age and gender.
   - These latter studies need not be tuned to exposures of less than 100 mSv, but any information in this range, where most exposures of regulatory concern occur, would be useful.

Understanding that priorities are necessary in any work being undertaken within a budgetary envelope, of the five points addressed in your questions, I would say that, in support of the work of the NEA, the continuation of the LSS to its conclusion would have the highest priority, followed by further work on non-cancer diseases. The continued work on risk assessment in exposed children and on genetic effects would have equal importance in my view. Finally, our suggestions for the augmentation of ongoing work on risk modifiers, and on low-dose effects would be of great interest to the NEA's members.

I would again like to thank you for the opportunity to provide these comments to your review process. I wish you success in this important endeavour, and would appreciate being kept abreast of your work and its results.

Sincerely,



Luis E. Echávarri
Director-General

UNITED NATIONS NATIONS UNIES

UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS OF ATOMIC RADIATION
(UNSCEAR)

VIENNA INTERNATIONAL CENTRE
P.O.BOX 500, A-1400 VIENNA, AUSTRIA

TEL: 0043 (1) 26060 / 4330
E-MAIL: Malcolm.Crick@UNSCEAR.org

FAX: 0043 (1) 26060 / 5902
WEB SITE: www.unscear.org

19 April 2007

Dear Drs. Gilman and Kitagawa,

Thank you for your letter of the 6 April 2007 soliciting my views, as Secretary of UNSCEAR, on specific issues relating to the future activities of RERF. I appreciate very much your request for feedback, because the RERF activities are indeed of crucial importance to UNSCEAR and its beneficiaries. With regard to the specific questions, please see my responses below:

1. *Do you believe that continuing the Life Span Study of 120,000 individuals of all ages (of whom 40% are surviving) is important for the purposes of your Committee?*

   Continuing the Life Span Study is absolutely crucial to the work of UNSCEAR in performing its reviews for the General Assembly, scientific community and the general public of the risks of ionizing radiation. The UNSCEAR reviews provide the basis for the development of the international basic safety standards for radiation protection. The dose limits established for members of the public and workers and other radiation protection policy and practice are traceable in many countries back to UNSCEAR's reviews. UNSCEAR uses the results of the LSS as its most fundamental source for deriving risk coefficients. Until the LSS cohort has completely expired, it is unthinkable to stop the Life Span Study.

2. *RERF is considering whether to expand part of the clinical studies cohort (the Adult Health Study) who were under age 10 at the time of the Bomb in order to better understand the sensitivity of the young to radiogenic effects. Is this work relevant to your Committee? In your opinion, should it be done?*

   This work is extremely relevant to the Committee, and to its end users (Governments and International Organizations). Knowledge of the risks to people exposed at young ages is critical for decisions on emergency planning, for setting discharge limits and for waste management. One of the best sources of information on this subject is and would be the work conducted by RERF. This cohort should be followed until it has completely expired.

../2

Drs. Paul Gilman and Sadayoshi Kitagawa, Co-chairs
Senior Review Panel on Future Planning for RERF
Radiation Effects Research Foundation
5-2 Hijiyama Koen, Minami-ku
Hiroshima 732-0815
JAPAN

3. *Does your Committee find the study by RERF of non-cancer diseases and their induction by radiation of value?*

This study is extremely important to the work of UNSCEAR. The RERF study is one of the very few in the world that can provide authoritative scientific conclusions on this contentious and important subject, which has serious ramifications for decisions regarding medical treatment and for emergency planning, among others. Indeed more should be done in this area, particularly on cataracts, and on cardiovascular, digestive and respiratory diseases.

4. *The F1 cohort (children of atomic bomb survivors) has been studied beginning in 1946. The subjects are now about 50 years old on average. Is the continued study of the cohort of value to your Committee?*

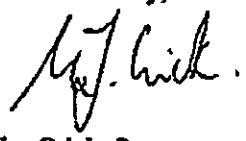
Again, this work is indeed of value to UNSCEAR. It provides authoritative data on the risk of hereditary effects in humans. Although such effects have been seen in animals and can be projected to occur in man, it will only be through careful study that the level of these effects can be quantified. Continued study until the cohort has completely expired is important. Even null results in this area are extremely important for the Committee and its end users, the standard-setting community, because they confirm upper limits to the magnitude of any effects.

5. *Are there modifications to these primary research activities of the RERF that you believe would be helpful to the mission of your Committee?*

I believe it would be helpful to review existing work, and where necessary conduct feasibility studies, on the possibility to discriminate the effects of confounding factors, such as the initial exposure to electromagnetic radiation, physical trauma, genetic susceptibility, subsequent lifestyle, diet etc..

I hope that this letter conveys how critical the continued studies of RERF are to the work of UNSCEAR and thereby to the international scientific and standard-setting community for radiation safety and risk assessment. The work of RERF is both truly valuable and valued.

Yours sincerely,



Malcolm Crick, Secretary
United Nations Scientific Committee
on the Effects of Atomic Radiation

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)
Former Secretary, Burton G. Bennett

Dear Dr. Gilman,

I know you are working on the review of future plans for RERF. I hope the task is developing smoothly. Of course, I had much interest in this and worked to develop some of the initial planning documents.

Joe Weiss has encouraged me to submit some comments on the value of the RERF data to international programs of risk assessment. I had many years experience with UNSCEAR and worked first hand with both RERF staff and the LSS data. The atomic-bomb survivor data were crucial to our international work. I am sure that this is already clear to your committee. But just to reiterate that, I have attached a brief statement. I hope you will find this useful.

If I could be of any further help in any way, please feel free to contact me.

Contributions of RERF to International Radiation Risk Assessment

The careful investigation at RERF of the health effects of radiation in survivors of the atomic bombings has contributed substantially to the evaluations of the health risks of radiation exposures by international organizations. These evaluations form a firm basis for understanding radiation response in humans and for the establishing radiation protection guidelines for workers and the public. The evaluations of the international organizations have at times been delayed, awaiting the latest updates of the essential RERF data.

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). UNSCEAR recognizes the pre-eminence of the RERF results. Because of the features of the Life Span Study (the large study population of all ages and both sexes, the wide range of individual and accurately determined doses, and the precise and complete morbidity and mortality recording), the RERF data are described as the gold standard for epidemiological investigation of radiation effects. Other epidemiological results, including radiation treatment of medical patients (often with partial body exposure mainly to adults or to one sex or the other) and worker exposure experience (often with low and chronic exposures of imprecisely determined doses), have limitations that make them supplemental to the primary results of the Life Span Study.

The International Commission for Radiological Protection (ICRP) uses the UNSCEAR evaluations to estimate radiation risks and to formulate recommendations for radiation protection that are accepted and used by most countries. RERF staff and the survivors themselves recognize the great value of the RERF investigations and are willing to participate in the studies for the substantial contributions made to the benefit of everyone worldwide.

UNSCEAR was established in 1955, some 8 years after ABCC began its work. The first report of UNSCEAR was issued in 1958. Included was a summary of the leukemia experience in Hiroshima. The summary was prepared by Niel Wald, who had just completed two years of work at ABCC. The peak in leukemia incidence was observed in 1951-53, and the decreasing trend seemed to indicate that most leukemia cases would be recorded before 1960. As it turns out, a few further radiation-associated cases continued to be seen even after that time, as reported by ABCC. Dosimetric evaluations were not then available, but a strong relationship in the leukemia incidence rate with distance from the hypocenter was noted, implicating radiation exposure as the causative factor.

The UNSCEAR reports of the 1960s mainly reported on the environmental contamination caused by testing nuclear weapons in the atmosphere, and the importance of natural background radiation was also recognized. Attempts were made to evaluate the genetic effects of radiation, thought then to be the main risk of exposures. It began to appear, however, that such effects would not be dominant, as the ABCC data could not substantiate genetic effects. On the other hand, evidence began accumulating of the excess incidence of cancers other than leukemia. Thyroid, lung, and breast cancer in atomic-bomb survivors were among the first types of cancers associated with radiation exposure. Other cancer types were subsequently added.

The UNSCEAR report of 1972 included the first comprehensive report of radiation carcinogenesis in man. Dr. Tomio Hirohata, who was closely associated with the ABCC work, participated in the preparation of this report. Much of the analysis was based on the ABCC study results. The first BEIR report, prepared by the National Academy of Sciences, appeared also in 1972. The Life Span Study results, of course, featured prominently.

The 1977 UNSCEAR report included an updated survey of radiation carcinogenesis in man. Excess rates of leukemia and several other cancers could be estimated. The Life Span Study results were supplemented mainly by the studies of ankylosing spondylitis patients in the UK and of uranium miners.

The UNSCEAR reports of 1988, 1994 and 2000 included analysis of the more and more numerous epidemiological studies of radiation effects. Estimates of radiation-induced cancer were made based on both absolute and relative risk models. Jack Schull, a long-time RERF researcher and director, took responsibility for the technical annex preparation of the 1988 report, and Dale Preston, RERF

statistician, provided modelling and lifetime risk estimates for the 1994 and 2000 reports, based heavily on the results of the studies at Hiroshima and Nagasaki. Not only could quantitative estimates be made of the risk of late-occurring solid cancers, the presence of non-cancer disease risks that were beginning to be discerned from the RERF data could be reported.

Although the knowledge gleaned from the ABCC/RERF studies has been of immense importance in radiation risk evaluations, the data collection must still be completed over the next several years to fill in the still unknown facts, especially the lifetime risks of the youngest exposed survivors, which presently depend on uncertain projections of future risks. Risks for some cancers persist for decades after exposure, remaining rather constant in time, and others may show decreasing trends over many years. This time dependence of lifetime risks is an important issue yet to be clarified. Further efforts are also still needed to describe and quantify the risks of non-cancer effects. The Life Span Study presents a unique opportunity to study this important aspect of radiation exposure.

Since the completion of the DS02 dosimetry system, it would seem worthwhile to apply modern methods and maps to refine and improve survivor location and shielding determinations. Some earlier methods of grouping data on wide location grids and approximating individual locations and shielding would no longer be needed and could be replaced by more accurate techniques. Although this could be a labor-intensive task, efforts should be made to be sure that the most precise analyses have been included in this most valuable data set.

In addition to the essential data derived from the ABCC/RERF studies, it should also be noted that basic training of radiation epidemiologists has also been taking place in Hiroshima and Nagasaki. In the past, young scientists often spent one or several years at ABCC/RERF, participating in the research projects and becoming familiar with the accumulating data. These scientists later became prominent epidemiologists and key contributors to the evaluations performed by the international organizations. It is hoped that RERF can continue to serve as a training center for radiation epidemiologists and that RERF scientists will be able to make further active contributions to the international risk assessment work.

Even after 60 years, the legacy of the atomic bombings still marks the lives of atomic-bomb survivors. From this experience, however, has come not just an opportunity, but a responsibility to investigate the effects of radiation to contribute to the welfare of those affected, to understand and quantify the effects, and to provide a scientific basis for radiation protection worldwide.

The contributions of ABCC/RERF have been of substantial value in meeting these objectives. The high reputation of this research project has been gained by the unique, high quality of the acquired data and the dedication of many individuals associated with this project over so many years.

It is of greatest importance to maintain a strong research staff at RERF during the next decades to complete the essential studies. The experience of the atomic bombings will not be repeated. It is a one-time opportunity to determine the lifetime risks of radiation exposure in a large human population and to quantify the upper limit on the possible genetic effects conferred on the children of the survivors. The international organizations strongly support and depend on the continuation of the RERF studies that provide such valuable information to science for the benefit all of mankind.

Radiation Effects Research Foundation (RERF)
Senior Review Panel Questionnaire

1. Do you believe that continuing the Life Span Study of 120,000 individuals of all ages (of whom 40% are surviving) is important for the purposes of your Commission?

The Nuclear Regulatory Commission (NRC) considers the Life Span Study (LSS) cohort to be a source of some of the most important radiation-induced health effects information upon which the U.S. system of radiological protection is based. The LSS cohort has several features that make it particularly valuable:

- the number of individuals included in the cohort is large,
- the cohort includes members of both sexes and a variety of ages at the time of radiation exposure,
- the radiation exposures attributable to an atomic bomb range from negligible to several Sieverts, and
- the members of the cohort have been monitored for over 50 years.

The recent inclusion of cancer morbidity information has increased the value of the cohort. Continued monitoring of the survivors in this cohort is especially important because many of these individuals were relatively young at the time of exposure.

The LSS should be continued for the next 15 to 20 years. Much information on cancer incidence and non-cancer disease occurrence, especially health effects information from the youngest members of the LSS cohort, will be obtained during the next two decades. However, there is relatively little epidemiological information for healthy groups of individuals exposed to low doses of ionizing radiation. Additional information on cancer incidence attributable to radiation exposure less than 100 mSv is needed by the nuclear regulatory community in order to continue to support NRC regulations, and assure that there is adequate protection of public health, safety, and the environment. This work is also important to continue efforts to bridge the gap between epidemiology studies of radiation exposure and cellular/molecular radiation biology. More important, additional information on non-cancer disease occurrence and cataracts (e.g., posterior subcapsular cataract) formation is desired. Both categories of late occurring illness/injury are thought to be deterministic in nature. However, recent scientific publications involving atomic bomb survivors and emergency responders to, and cleanup workers at, the Chernobyl nuclear power plant suggest that the threshold for induction health effects may be many times less than previously believed. The International Commission on Radiological Protection (ICRP) recommends an annual equivalent dose to the lens of the eye of 0.15 Sv. For example, the ICRP recognizes that additional information on the sensitivity of the eye is forthcoming and will review their recommendations when it becomes available. The NRC lens dose limit is 0.15 Sv (15 rem) per year. Consequently, additional information from the LSS, and other radiation exposure cohorts, is needed to confirm that the NRC lens dose limit is adequately protective for occupational workers.

2. RERF is considering whether to expand part of the clinical studies cohort (the Adult Health Study) who were under age 10 at the time of the Bomb in order to better understand the sensitivity of the young to radiogenic effects. Is this work relevant to your Commission? In your opinion, should it be done?

Understanding the delayed health effects attributable to radiation exposure, especially exposure to more sensitive members of the general public (i.e., children) is of interest to the NRC. There are relatively few data sources for pediatric radiation exposure and long term non-cancer disease surveillance. The issue to consider is whether there is a sufficient number of members in the LSS cohort that were younger than 10 year old at the time of radiation exposure. The RERF should demonstrate that there are sufficient numbers of children in the LSS for inclusion into the Adult Health Study for there to be sufficient statistical power to conduct meaningful analyses on non-cancer health endpoints. There are a number of sources of bias and confounding variables that will need to be considered. Unless there is a reasonable expectation that additional information will be obtained, the expansion of the clinical studies cohort should not be a high priority.

3. Does your Commission find the study by RERF of non-cancer diseases and their induction by radiation of value?

Since 1990 evidence has accumulated that the frequency of non-cancer diseases is increased in some irradiated populations. The strongest statistical evidence for the induction of these non-cancer effects at effective doses of the order of 1 Sv derives from the most recent mortality analysis of the Japanese atomic bomb survivors followed after 1968 (Preston et al., 2003). That study has strengthened the statistical evidence for an association with dose – particularly for heart disease, stroke, digestive disorders and respiratory disease. However, the Commission notes current uncertainties on the shape of the dose-response curve at low doses and that the LSS data are consistent both with there being no dose threshold for risks of disease mortality and with there being a dose threshold of around 0.5 Sv.

4. The F_1 cohort (children of atomic bomb survivors) has been studied beginning in 1946. The subjects are now about 50 years old on average. Is the continued study of the cohort of value to your Commission?

The U.S. National Academies in the BEIR VII report noted that the principal messages from the Japanese studies is that there is "no significant adverse effects in over 30,000 progeny from parents with estimated conjoint gonadal dose of the order of about 0.4 Sv or less." In a February 2007 news release, RERF investigators reported that there was "no evidence suggesting increased risk associated with parental radiation exposure" and a "negative association of parental dose and prevalence rate of multi factorial diseases." RERF studies on birth defects, mortality, chromosome abnormalities, and serum proteins also indicate there is no radiation effect on the F_1 cohort. With these observations in mind, continued study of the F_1 cohort is not a high priority to the NRC and probably should not be a high priority to the RERF.

5. Are there modifications to these primary research activities of the RERF that you believe would be helpful to the mission of your Commission?

Risk communication to members of the public should be a programmatic priority for each RERF research activity. Members of the public do not perceive radiation as a weak carcinogen. Rather, any illness or death often is attributed to possible radiation exposure. Yet, data from the RERF LSS does not support this perception. For example, information obtained from the RERF website indicates that as of the end of 1990, a total of 4,687 nonleukemia cancer deaths had occurred among the 50,113 LSS survivors with significant exposure (5 mSv or more). If this population had not been exposed to radiation, RERF estimates that 4,306 cancer deaths would have occurred during this time. The number of cancer deaths attributable to atomic bomb radiation is 339, or 7 percent. For those LSS survivors receiving between 5 mSv and 200 mSv, 63 of 3,391 cancer deaths, or 2 per cent, may be attributable to radiation exposure. These are very low numbers. It is vital that the RERF staff increase its efforts to educate the public about the relative hazards of exposure to ionizing radiation. This is also especially true with regards to radiation-induction of non-cancer diseases.

National Council on Radiation Protection and Measurements
7910 Woodmont Avenue, Suite 400, Bethesda, Maryland 20814-3095
Voice (301) 657-2652 Ext. 19 • Fax (301) 907-8768 • http://ncrponline.org • e-mail: tenforde@ncrponline.org

April 28, 2007
(07.743)

To: Dr. Sadayoshi Kitagawa and Dr. Paul Gilman
RERF Senior Review Panel Chairmen

From: Dr. Thomas S. Tenforde
President, NCRP

Subject: Views on importance of work by Radiation Effects Research Foundation

---

Dear Dr. Kitagawa and Dr. Gilman:

I am pleased to respond to your request for my views on behalf of the National Council on Radiation Protection and Measurements (NCRP) on issues related to planning for future activities of RERF.

Our overall perspective is that RERF is a unique international resource providing information on radiation effects on humans. All international programs that evaluate radiation risks and provide guidance on limitations of public and occupational radiation exposure rely on the evolving database of information being obtained by RERF on A-bomb survivors. The recent extensions of the database to include information on cancer incidence (in addition to cancer mortality) and non-cancer effects has been extremely important, and should be continued as part of the future RERF program.

In your March 15 letter, you asked me to respond to five specific questions related to the planning of future RERF activities. The following are my responses submitted on behalf of NCRP:

1) Continuing Life Span Study. As stated above, the data being obtained from the LSS is a unique resource and must be continued until most of the A-bomb survivors are deceased.
2) Adult Health Study. The data being acquired on the cohort of A-bomb survivors who were less than 10 years of age when exposed will be of considerable value to NCRP in an expected future study on radiation risks. Understanding the age dependence of risk to incidence and mortality from radiogenic disease is a very important component of the overall evaluation of human radiation risks.
3) Non-cancer Risks. The recent work by Preston *et al.* at RERF in quantitating non-cancer risks in the A-bomb survivor population has been very informative, and must be continued. The magnitude of non-cancer risks is significant, and a determination of the dose-response characteristics will be of great value to organizations such as NCRP, ICRP, and others.

National Council on Radiation Protection and Measurements
7910 Woodmont Avenue, Suite 400, Bethesda, Maryland 20814-3095
Voice (301) 657-2652 Ext. 19 • Fax (301) 907-8768 • http://ncrponline.org • e-mail: tenforde@ncrponline.org

4) F_2 Cohort Studies. The LSS provides a unique opportunity to study radiation-induced genetic effects that are transmissible to progeny. The issue of genetic transmission of heritable radiation-induced defects is of great interest to NCRP. The F_2 study should definitely be continued.
5) Other RERF Research Activities. It would be of great value for RERF to expand its activities in characterizing both genetic and epigenetic signatures of radiation damage. I would strongly encourage increased funding for RERF activities by the Japanese and United States governments to utilize modern genomic and proteomic approaches to characterizing biomarkers of radiation damage and their relationship to human health defects.

I hope that the above views on the RERF programs will be useful in your review of future planning for RERF. NCRP remains a strong supporter of the research programs being conducted at RERF and the future expansion of these programs.

Sincerely,

Thomas S. Tenforde

Thomas S. Tenforde, Ph.D.
President, NCRP

Appendix 3 - REFERENCES

IARC. *Cancer Incidence in Five Continents*. Lyon, France, International Agency for Research on Cancer (WHO), 2002.

Preston D, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, Kamada N, Dohy H, Matsui T, Nonaka H, Thompson D, Soda M, Mabuchi K. Cancer incidence in atomic bomb survivors. Part III: Leukemia, lymphoma and multiple myeloma, 1950-1987. *Radiat Res* 137:S68-S97, 1994.

Thompson D, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, Sugimoto S, Ikeda T, Terasaki M, Izumi S, Preston D. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958-1987. *Radiat Res* 137:S17-S67, 1994.

Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. Solid cancer incidence in atomic bomb survivors: 1958-98. *Radiat Res* Submitted2006.

Sharp GB, Mizuno T, Cologne JB, Fukuhara T, Fujiwara S, Tokuoka S, Mabuchi K. Hepatocellular carcinoma among atomic bomb survivors: significant interaction of radiation with hepatitis C virus infections. *Int J Cancer* 103:531-537, 2003.

Yonehara S, Brenner AV, Kishikawa M, Inskip PD, Preston DL, Ron E, Mabuchi K, Tokuoka S. Clinical and epidemiologic characteristics of first primary tumors of the central nervous system and related organs among atomic bomb survivors in Hiroshima and Nagasaki, 1958-1995. *Cancer* 101:1644-1654, 2004.

Kishikawa M, Koyama KM, I, Kobuke T, Yonehara S, Soda M, Ron E, Tokunaga M, Preston DL, Mabuchi K, Tokuoka S. Histologic characteristics of skin cancer in Hiroshima and Nagasaki: background incidence and radiation effects. *Int J Cancer* 117:363-369, 2005

Ron E, Ikeda T, Preston DL, Tokuoka S. Male breast cancer incidence among atomic bomb survivors. *J Natl Cancer Inst* 97:603-605, 2005.

Crow JF, Kaplan HS, Marks PA, Miller RM, Storer JB, Upton AC, Jablon S. Report of the Committee for Scientific Review of ABCC. *ABCC Technical Reports*. Hiroshima**:** 23 pp., 1975.

Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *Radiat Res* 160:381-407, 2003.

Yamada M, Wong FL, Fujiwara S, Akahoshi M, Suzuki G. Noncancer disease incidence in atomic bomb survivors, 1958-1998. *Radiat Res* 161:622-632, 2004.

Yamaoka M, Kusunoki Y, Kasagi F, Hayashi T, Nakachi K, Kyoizumi S. Decreases in percentages of naïve CD4 and CD8 T cells and increases in percentages of memory CD8 T cell subsets in the peripheral blood lymphocyte populations of A-bomb survivors. *Radiat Res* 161:290-298, 2004.

Grote K, Drexler H, Schieffer B. Renin-angiotensin system and atherosclerosis. *Nephrol Dial Transplant* 19:770-773, 2004.

Rocha R, Stier CT, Kifor I, Ochoa-Maya MR, Rennke HG, Williams GH, Adler GK. Aldosterone: a mediator of myocardial necrosis and renal arteriopathy. *Endocrinol* 141:3871-3878, 2000.

Keidar S, Kaplan M, Pavlotzky E, Coleman R, Hayek T, Hamoud S, Aviram M. Aldosterone administration to mice stimulates macrophage NADPH oxidase and increases atherosclerosis development: a possible role for angiotensin-converting enzyme and the receptors for angiotensis II and aldosterone. *Circul* 109:2213-2220, 2004.

Lebaron-Jacobs L, Wysocki J, Griffiths NM. Differential qualitative and temporal changes in the response of the hypothalamus-pituitary-adrenal axis in rats after localized or total-body irradiation. *Radiat Res* 161:712-722, 2004.

Szmitko PE, Wang C-H, Weisel RD, Jeffries GA, Anderson TJ, Verma S. Biomarkers of vascular

disease linking inflammation to endothelial activation, Part II. *Circulation* 108:2041-2048, 2003.

Neriishi K, Nakashima E, Delongchamp RR. Persistent subclinical inflammation among A-bomb survivors. *Int J Radiat Biol* 77:475-482, 2001.

Hayashi T, Morishita Y, Kubo Y, Kusunoki Y, Hayashi I, Kasagi F, Hakoda M, Kyoizumi S, Nakachi K. Long-term effects of radiation dose on inflammatory markers in atomic bomb survivors. *Am J Med* 118:83-86, 2005.

Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet* 14:353-362, 1962.

ICRP. 1990 Recommendations of the International Commission on Radiological Protection. *Ann ICRP* 21 (Publication 60):1-201, 1991.

Minamoto A, Taniguchi H, Yoshitani N, Mukai S, Yokoyama T, Kumagami T, Tsuda Y, Mishima HK, Amemiya T, Nakashima E, Neriishi K, Hida A, Fujiwara S, Suzuki G, Akahoshi M. Cataract in atomic bomb survivors. *Int J Radiat Biol* 80:339-345, 2004.

Nakashima E, Neriishi K, Minamoto A. A reanalysis of atomic-bomb cataract data, 2000-2002: a threshold analysis. *Health Phys* 90:154-160, 2006.

Schull WJ, Otake M. Effects on intelligence of prenatal exposure to ionizing radiation. RERF Tech. Rpt. 7-86, Hiroshima, Radiation Effects Research Foundation1986.

Otake M, Schull WJ, Lee S. Threshold for radiation-related severe mental retardation in prenatally exposed A-bomb survivors: a re-analysis. *Int J Radiat Biol* 70:755-763, 1996.

Yamada M, Sasaki H, Mimori Y, Kasagi F, Sudoh S, Ikeda J, Hosoda Y, Nakamura S, Kodama K. Prevalence and risks of dementia in the Japanese population: RERF's Adult Health Study Hiroshima subjects. Radiation Effects Research Foundation. *J Am Geriatr Soc* 47:189-195, 1999.

Yamada M, Sasaki H, Kasagi F, Akahoshi M, Mimori Y, Kodama K, Fujiwara S. Study of cognitive function among the Adult Health Study (AHS) population in Hiroshima and Nagasaki. *Radiat Res* 158:236-240, 2002.

Schull WJ, Nishitani H, Hasuo K, Kobayashi T, Goto I, Otake M. Brain abnormalities among the mentally retarded prenatally exposed atomic bomb survivors. Hiroshima, Japan, RERF (Radiation Effects Research Foundation)1991.

Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. *Radiat Res* 123:275-284, 1990.

Ohtaki K, Kodama Y, Nakano M, Itoh M, Awa AA, Cologne J, Nakamura N. Human fetuses do not register chromosome damage inflicted by radiation exposure in lymphoid precursor cells except for a small but significant effect at low doses. *Radiat Res* 161:373-379, 2004a.

Ogawa T, Hayashi T, Kyoizumi S, Kusunoki Y, Nakachi K, MacPhee D, Trosko J, Kataoka K, Yorioka N. Anisomycin downregulates gap-junctional intercellular communication via the p38 MAP-kinase pathway. *J Cell Sci* 117:2087-2096, 2004.

Ogawa T, Hayashi T, Tokunou M, Nakachi K, Trosko J, Chang C, Yorioka N. Suberoylanilide hydroxamic acid enhances gap junctional intercellular communication via acetylation of histone containing connexin 43 gene locus. *Cancer Res* 65:9771-9778, 2005.