Message from the Chairman

Toshiteru Okubo

On this occasion of the publication of our Annual Report FY2012, I would like to express my sincere gratitude, on behalf of the Radiation Effects Research Foundation (RERF), to the unwavering cooperation of so many people, starting with the A-bomb survivors. Their support allowed us to continue developing our research operations in FY2012 aimed at the RERF mission of scientifically assessing the health effects of radiation. With adoption at RERF of the Japanese government's continued plan to reduce personnel, however, RERF's worker numbers have decreased by several people each year over the past few years. Amid such a situation, RERF has intensified efforts internally to enhance work efficiency and fully intends through research activities to continue its contributions to society as a global center of radiation effects research. To that end, we kindly request everyone's sustained understanding and support.

The following represents my report on RERF's major activities that took place during FY2012.

[I] Major activities

1. Board of Councilors meeting

The second meeting of the Board of Councilors (BOC) of RERF was held on June 19–20, 2012, at the National Academy of Sciences (NAS) in Washington, D.C. As the first meeting after RERF's transition to a public interest incorporated foundation, the BOC confirmed the qualifications and appointment procedures for councilors, directors, auditors, scientific advisors, and local advisors, and finalized the Rules of Procedure of the Board of Councilors, which are internal guidelines for effective operation of the BOC. Other major items finalized were approval of the FY2011 financial statements, reappointment of two auditors, reappointment of Dr. Michael N. Cornforth as Scientific Advisor, and appointment of Dr. Yoichiro Gondo (RIKEN) as Scientific Advisor to replace Dr. Katsushi Tokunaga.

2. Scientific Advisory Committee meeting

The Scientific Advisory Committee held its 40th meeting on March 4–6, 2013, at Hiroshima RERF, and reviewed RERF's research progress and plans. Consisting of 10 external members and three special advisory members selected from the U.S. and Japan, the committee this year focused its review on the Department of Clinical Studies. The co-chairpersons from the U.S. and Japan will organize the preparation of formal recommendations and present them to the third BOC meeting to be held in June 2013.

3. Major personnel actions for researchers

1) As of April 1, 2012, Dr. Eiji Katsurada was appointed as Research Scientist of the Division of Health Examinations, Hiroshima Department of Clinical Studies, and his term of office expired as of March 31, 2013.
2) As of April 1, 2012, Dr. Keiko Ueda was appointed as Research Scientist of the Division of Clinical Laboratories, Hiroshima Department of Clinical Studies.
3) As of April 1, 2012, Dr. Waka Ohishi, Assistant Chief, Hiroshima Department of Clinical Studies, was concurrently appointed as Acting Chief of the same department.
4) As of May 9, 2012, the term of office of Dr. Robert D. Abbott, Senior Scientist, Department of Statistics, expired.
5) As of March 31, 2013, Dr. Masazumi Akahoshi, Chief, Nagasaki Department of Clinical Studies, retired.
6) As of September 10, 2012, Dr. Wan Ling Hsu, Associate Senior Scientist, Department of Statistics, retired.
7) As of October 1, 2012, Dr. Atsuko Sadakane was appointed as Associate Senior Scientist of the

Hiroshima Department of Epidemiology.

8) As of October 31, 2012, the term of office of Dr. Norio Takahashi, Senior Scientist, Department of Radiobiology/Molecular Epidemiology, expired.
9) As of December 31, 2012, Dr. Kazue Imai, Associate Senior Scientist, Department of Radiobiology/Molecular Epidemiology, retired due to age limit.
10) As of December 31, 2012, the term of office of Dr. Evan B. Douple, Associate Chief of Research, expired.
11) As of December 31, 2012, the term of office of Dr. Nori Nakamura, Chief Scientist, expired.

4. Clinical Study of the F_1 Offspring of A-bomb Survivors

Approximately 5,100 persons participated in the health examinations of the Clinical Study of the F_1 Offspring of A-bomb Survivors for a period of two years ending in mid-2012, and the participation rate was 74.7% (76.0%, if those scheduled to undergo examination are included), which was an increase of about 7% compared with the first year. This rise was probably the result of RERF's efforts to increase participation by sending letters and contacting people by telephone, based on a proposal for improving the participation rate made at the second meeting of the Scientific and Ethics Committee for the Clinical Study of the F_1 Offspring of A-bomb Survivors. Furthermore, 99.7% of the participants have consented to continued participation in the longitudinal study in the future, providing a remarkably high rate of cooperation. Based on the data from the cross-sectional (prevalence) study conducted during the period 2002–2006, RERF also has conducted individual analyses using paternal or maternal exposure dose and parents' combined dose in terms of six multifactorial diseases including hypertension, hypercholesterolemia, and diabetes. A report of the results of analysis is scheduled to be presented at the third meeting of the Scientific and Ethics Committee for the Clinical Study of the F_1 Offspring of A-bomb Survivors to be held at Hiroshima RERF's Auditorium on April 25, 2013.

5. Research project under contract with the U.S. National Institute of Allergy and Infectious Diseases

In the five-year project related to the study of age-related decline in immune function accelerated by radiation exposure based on a contract between RERF and the U.S. National Institute of Allergy and Infectious Diseases (NIAID), a full-scale study involving samples from the Adult Health Study (AHS) population is ongoing, with cooperation from A-bomb survivors, their physicians, medical associations, and RERF's Departments of Clinical Studies, Information Technology, and Statistics. In 2011, NIAID provided $85,000 in funding for a pilot study involving autopsy thymus specimens. Based on this funding, RERF examined the storage status of the thymus specimens and considered whether to conduct pathological and molecular biological analyses involving a portion of the specimens. An annual report meeting was held with collaborating research organizations in Tokyo on July 28–29, 2012, and based on those deliberations a study report for the third year of the five-year contract was prepared, and submitted to NIAID in October.

6. Update of information processing system

On the basis of a survey conducted for each department by the Working Group to Review Information Processing Systems, RERF promoted in FY2012 the streamlining of the information-processing environment through the virtualization of its servers. For the sake of security enhancement, the PCs used at RERF were categorized into those that can be accessed by individuals or organizations outside of the foundation and those that cannot be, thereby limiting unnecessary communication with external parties. Similar measures were adopted for email communications. Concerning program specifications, it was decided that those individuals requesting the development of new systems be required to submit detailed specifications information. In addition, due to aging of the network cables installed on the premises, RERF initiated relevant replacement work.

7. Response to the Fukushima Dai-ichi nuclear power plant accident

RERF accepted visitors from Fukushima prefecture, as follows: Nine persons including assemblypersons from the town of Futaba, Fukushima prefecture, July 25; 16 persons from the Fukushima Prefecture Chamber of Commerce, August 7; two persons from the Fukushima Medical University Radiation Medical Science Center, August 21; two employees from the Health Promotion Section, Radiation Health Management Office, Fukushima City Health and Welfare Center, November 7; two employees from the Fukushima Prefecture Social Health and Welfare Department (in conjunction with the Fukushima Health Management Study), November 12; three employees from the town of Namie, two employees from the town of Futaba, Fukushima prefecture, and three accompanying persons, November 28; and five assemblypersons from the city of Kitakata, Fukushima prefecture, January 31, 2013.

[II] Government-mandated personnel reduction plan

The ongoing personnel reduction plan mandated by the Japanese national government asks RERF to reduce its employee number by five persons each year, and therefore, the number of general staff as of the end of FY2012 fell to 173.8 persons, which is less than half of the staff number at the time of RERF's establishment. Under such circumstances, RERF has started considering reorganization of the Secretariat to

establish a more functional and effective administrative system. The number of research staff as of March totaled 38.2 persons, of whom two are slated to retire on the last day of the month. There are 48 budgeted personnel slots determined by RERF for the research staff, but as several slots are consistently vacant, RERF continues its efforts to fill the positions.

[III] Future Planning for RERF

On March 15, 2013, RERF put into effect the Regulations Concerning Handling of RERF Future Plans to clarify the foundation's long-term and short-term future plans and to update these plans each fiscal year. Moreover, RERF prepared the Regulations Concerning the RERF Future Plans Drafting Committee, which was established to draft the future plans for each fiscal year, and these regulations were approved at the regular meeting of the Board of Directors held in March 2013.

[IV] Liaison with local communities and related organizations

1. Local Liaison Councils

The 18th meeting of the Hiroshima Local Liaison Council was held at Hiroshima RERF's Auditorium on September 13, 2012, with 22 council members and observers in attendance. Subsequently, the 21st meeting of the Nagasaki Local Liaison Council was held in the 3rd floor conference room of the Nagasaki Laboratory on October 11, 2012, attended by 22 council members and Secretarial Committee members. At both meetings, RERF reported on its present status, recent study results, clinical study of second-generation A-bomb survivors, status of the collaborative study with NIAID, and the foundation's PR activities.

2. Council of Radiation Effects Research Organizations

The Council of Radiation Effects Research Organizations, which was established to promote mutual understanding and partnership among radiation research organizations, held its seventh meeting at the Fukushima View Hotel on December 19, 2012. RERF's Chairman Okubo and Chief Scientist Kazunori Kodama attended the meeting, at which the council's future support system for the Fukushima accident and other topics were discussed.

In addition, under the sponsorship of the council, the seminar titled "Epidemiological Training Workshop for Biologists," designed to provide training about epidemiological approaches from a multidisciplinary perspective regarding radiation risk, was held at Hiroshima RERF on August 20–21, 2012, following previous seminars in 2010 and 2011. The seminar was attended by about 30 researchers from throughout Japan.

3. Hiroshima International Council for Health Care of the Radiation-exposed

On June 20, 2012, Chairman Okubo succeeded the late Shizuteru Usui (former President of the Hiroshima Prefectural Medical Association) as President of the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE), with a term of office of two years.

4. International collaboration

In FY2012, RERF accepted 99 overseas trainees through its own means or through collaboration with HICARE, the Nagasaki Association for Hibakushas' Medical Care (NASHIM), and the Japan International Cooperation Agency (JICA), thus successfully making a contribution at the international level.

[V] Preparation for establishment of the Biosample Center

RERF has made do with securing space for deep freezers at the Hiroshima Laboratory by moving materials and adopting other makeshift measures. However, since such measures are not adequate to the requirements, the Preparatory Committee for Establishment of the Biosample Center was established in July 2012, with a view to establishing such a center sometime in FY2013. The preparatory committee, which consists of the chairman (RERF Chairman Okubo), two vice chairmen, eight committee members, and one secretary, established working groups to review matters such as drafting internal regulations; determining the scope of samples to store, location for housing the samples, and number of center employees; and designing the information systems. The review results, which were initially made into the working groups' reports, were later compiled into a final report. This final report was submitted to the RERF Executive Committee in February 2013, and the RERF Board of Directors approved the establishment of the Biosample Center in March. The Biosample Center started operations on April 1, 2013, and preparations are now being made to begin full operations in one year's time.

[VI] Public relations activities

1. Television coverage by Tokyo Broadcasting System Television and RCC Broadcasting

Tokyo Broadcasting System Television (TBS) and its local affiliate RCC Broadcasting nationally broadcast a news program titled "First-ever coverage of the unknown reality of the Radiation Effects Research Foundation" at 17:30, July 28, 2012 (Saturday). This program appeared to misinform viewers regarding RERF's research program. Using such language as "the serious darkness that connects to Fukushima," the narration first gave the impression that the program's chief aim was to entertain, but it instead added to the anxiety felt among

those who are suffering the most. RERF sent a formal letter of protest to TBS and RCC on July 31. Although TBS sent RERF a reply on August 13, there was no mention in it about producing a corrected version of the program. RERF therefore submitted a formal objection to the broadcasting human rights committee and the broadcasting ethics review committee of the Broadcasting Ethics & Program Improvement Organization (BPO) on October 19.

2. Open House events

RERF held its 18th and 16th Open House events on August 5–6 in Hiroshima and August 8–9 in Nagasaki, respectively. With the theme "Useful knowledge about radiation and health sciences," the events this year featured programs aiming at widely informing the public of accurate knowledge about radiation. In Hiroshima, Chairman Okubo delivered a lecture titled "Atomic bomb radiation health risks and Fukushima," in commemoration of the 65th anniversary of ABCC-RERF. With continued intense public interest in radiation due to the Fukushima Dai-ichi nuclear power plant crisis, this year's Open House events included a special exhibit about low-dose radiation exposure and a specialist's Q&A corner, in addition to the regular exhibits of the foundation's latest research results. The two-day events drew enthusiastic visitors, including families, totaling 964 and 326 persons in Hiroshima and Nagasaki, respectively.

3. RERF's public lecture series

Following last year's series, RERF held its second public lecture for Nagasaki citizens at a hall in the Nagasaki A-bomb Museum on July 21 (Saturday), 2012. More than 110 people attended the event and enthusiastically listened to the talks titled "Considering low-dose radiation exposure" by Dr. Nori Nakamura, Chief Scientist, and "Methods of evaluating radiation doses" by Dr. Asao Noda, Assistant Chief, Department of Genetics.

In Hiroshima, on December 1 (Saturday), RERF held its third public lecture for citizens at the Memorial Hall in the basement of the Hiroshima Peace Memorial Museum's East Building, drawing about 150 people. The talks titled "Long-term health effects of radiation" and "Mechanistic study of health effects of radiation" were delivered in a readily understandable manner by Dr. Kotaro Ozasa, Chief, Department of Epidemiology, and Dr. Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology, respectively.

With cooperation from the A-bomb survivors and understanding by the public, RERF has been able to solemnly carry out its research program, informing the A-bomb survivors and the general public of the foundation's research results through events such as the Open House and public lectures. RERF resolves to continue adhering to this approach by informing the A-bomb survivors and the public of the enormous amount of invaluable data collected by ABCC-RERF, the long history of the organization's research program, and its globally reliable research results.

Message from the Vice Chairman and Executive Director

Roy E. Shore

Epidemiologic data on mortality and cancer incidence among A-bomb survivors (Life Span Study [LSS]) and their children (F_1 generation studies) continue to be the basis for most national and international estimates of the risks of cancer and other diseases from exposure to ionizing radiation. However, the RERF research activities extend well beyond that. Clinical examinations and biosamples in the Adult Health Study (AHS, a subsample of the LSS) provide more detailed information on health conditions of interest, especially radiation-related noncancer conditions, and opportunities to study the pathogenesis of those conditions. Similarly, the F_1 Clinical Study provides more detailed information on health conditions among the offspring of A-bomb survivors. Our basic science groups utilize the biosamples to further address the nature and extent of genetic and molecular changes associated with the health risks. Hence, the RERF studies provide a unique window into both epidemiological and biological aspects of radiation risk.

To highlight a few of the more important papers published during the year:

- The data on leukemia risk in the LSS were updated to extend more than 55 years after the bombings. A small radiation risk of leukemia is still seen, mainly of the acute myeloid cell type, and is not limited to those who were exposed in childhood. The dose-response curve shows upward curvature with increasing dose. There was a small excess of non-Hodgkin lymphoma among males but none among females, and there were no radiation-related excesses of Hodgkin lymphoma or multiple myeloma.
- An update of the radiation thyroid cancer data shows that there is a large risk for exposed children but no clear evidence of excess risk from exposures after age 20. The excess thyroid cancer radiation risk is evident even at low doses and has persisted for over 50 years, so it likely will continue for the lifetime.
- The LSS data have shown a strong risk for urothelial cancers (mostly bladder cancers), but there was a question as to whether some of the imputed risk might actually be attributable to variations in other risk factors: smoking, alcohol consumption, diet, or occupational factors. A more detailed analysis examining these possible co-factors showed that the strong radiation risk is virtually unchanged by those risk factors.
- Regarding breast cancer risk, a paper showed that radiation dose is associated with alterations in estrogen levels, which in turn may mediate radiation-associated breast cancer. Further analyses are underway to test that hypothesis.
- Since DNA damage that is unrepaired is believed to be a central feature of radiation-induced cancer, a study is being conducted to identify unique protein or biochemical signatures of unrepaired DNA double-strand breaks. Preliminary results were published, and further characterization of unrepaired DNA damage is underway.
- The role of genetic variation is being studied in relation to radiation-associated papillary thyroid cancer. We reported the first finding that *EML4-ALK* gene rearrangements are implicated in a fraction of radiation-associated thyroid cancers.
- We reported a significant association between radiation dose and risk of hemorrhagic stroke, but not ischemic stroke, although the degree of risk at lower doses requires further study.
- A relationship was found between radiation exposure and kidney dysfunction. Further analyses will determine the degree to which kidney dysfunction is an intermediate variable in the association between radiation and cardiovascular disease.

- We reported that the risk for surgical removal of cataracts was increased in a radiation dose-response fashion among A-bomb survivors. Our best estimate of a dose threshold was 0.5 Gy. Based in substantial part on the RERF data, the International Commission on Radiological Protection (ICRP) has now recommended a reduction in the dose limit to the eye from the conventional 5 Gy to 0.5 Gy.
- Since many diseases besides cancer have a strong genetic component, a unique study was developed to establish whether there are radiation-associated inherited risks for common adult noncancer diseases. Approximately 12,000 offspring of atomic-bomb survivors—children conceived after the bomb—have participated in a health examination to evaluate the possible association between parental radiation exposure dose and the prevalence of various common diseases in the offspring (such as heart disease, stroke, hypertension, and diabetes). A paper on the prevalence of various diseases among those offspring in relation to parental radiation doses was published. The second round of examinations is underway, with plans to repeat examinations every four years to determine whether development of subclinical and clinical disease in offspring is related to parental dose.

This year marked progress on a number of important activities at RERF. The DS02 dosimetry data for the LSS subjects has been improved by undertaking a number of steps, including improving the maps of Hiroshima and Nagasaki that were used to identify locations of study subjects, reviewing and recoding the old paper records on exact survivor geographic locations, and using an electronic geographical information system (GIS) to provide more accurate locations for study subjects. Those steps have been completed, and development of programs to provide more accurate terrain shielding is underway.

In response to public health concerns about the possibility that radiation exposure from "black rain" fallout may have had some impact on mortality and cancer incidence, we compared the health outcomes among those who had reported exposure to rain after the bombings with those who reported no exposure (based on surveys conducted in the 1950s and early 1960s). The results were essentially negative except for one positive result related to solid cancer mortality in Nagasaki. However, the fact that cancer incidence data did not reveal a comparable difference and that other results (e.g., for leukemia) were negative suggests this result was probably due to chance. We released results to the media and explained them in a public forum.

Recent reports of the LSS have suggested a small association between radiation and the broad diagnostic category of nonmalignant respiratory disease. In order to clarify whether that association is genuine or artifactual, analyses were undertaken to determine whether the nominal associations might occur because of misdiagnoses or co-morbidity with cancer or cardiovascular disease. We also examined this for more specific categories of nonmalignant respiratory disease. The analyses showed that much of the apparent association was due to misdiagnosis of cancer-related deaths, but some possible association still remained for the category of pneumonia/influenza, which, if real, might be associated with a radiation-related reduction in immune competence.

A program is underway to learn more about the biological basis for how radiation compromises immune function and the evidences for decreased immune competence. One project aims to determine the mechanisms—how radiation affects the stem cells, dendritic cells, and thymus—that give rise to or activate the mature immune cells. A second project is developing a broad-based set of biological markers of variations in immune competence in relation to radiation exposure, and another is examining whether radiation exposure decreases the immune response to influenza vaccination.

A workshop was held at RERF this year on radiation effects upon cardiovascular disease risk at low-to-moderate doses. The suggestions from the international set of experts provided a number of new insights that will help guide our cardiovascular research in the future. A summary paper of that meeting is being prepared for publication.

Another international workshop was held on potential uses of DNA sequencing to study radiation effects. Out of this workshop came some collaborative studies and a better understanding of future directions in this area of research.

The RERF research provides benefits to A-bomb survivors in terms of early disease detection and informs both the survivors and the world at large about the risks from radiation exposure. Such knowledge is important because of the many uses of radiation in today's world. We want to thank our sponsors, the Japanese Ministry of Health, Labour and Welfare and the U.S. Department of Energy, who strongly support our research on the health effects of atomic radiation. We especially want to thank the many A-bomb survivors and their children who have selflessly participated in studies for many years that provide invaluable knowledge benefiting all humankind.