Message from the Chairman

Toshiteru Okubo

The Radiation Effects Research Foundation (RERF) aims to enhance its capacity as a global center of excellence while continuing to pursue its mission of conducting follow-up studies of A-bomb survivors and their children, as laid out in RERF's long-term vision, which was formulated to serve as an organizational objective into the future.

To achieve these goals and help research staff effectively obtain high-quality results by maximizing their capabilities, we have begun transitioning to a research structure based on working groups that will further promote interdepartmental, program-based studies. We are at the same time working to improve our research management and support systems for undergirding the new research structure.

The ongoing personnel reduction plan, which decreases the number of budgeted general employees by five persons annually, reduced the number of general employees, including specialists in non-research positions, to 173.6 by the end of FY2014. To cope with the impact of these reductions, we have newly hired a small number of general employees. In addition, RERF is making improvements, such as the development of a research-support system, refinements in our management of human resources and funding, and review of the reorganization of our Secretariat, with the aim of establishing an effective and fully functional administrative work structure.

RERF has, to the extent possible, addressed organizational issues independently. One outcome of these efforts was establishment of the Biosample Center in April 2013. In September 2014, we signed a contract to purchase an ultra-low-temperature robotic biorepository system, and we are currently carrying out inventory of existing samples to be stored in the biorepository, which is expected to be fully operational in October 2015. Another outcome was the dosimetry project, a series of analyses to revise individual radiation dose estimates, which began in 2009. The project was completed in FY2014, and the revised individual dose estimates are now being used for studies. We also decided to embark on re-analysis, including revision of individual dose estimates of the long-standing untoward pregnancy outcome (UPO) study of the health effects of radiation among the youngest second-generation A-bomb survivors, by enlisting new researchers in the effort.

In response to a recommendation made by the Scientific Advisory Committee in 2013, we have started a review of our cataract studies. The review led to a new research protocol in FY2014 that examined and rectified problems in previous cataract studies identified through the review. We expect to begin a new study sometime in FY2015.

For the first time, we are embarking on a new cohort study of radiation-exposed individuals other than A-bomb survivors. Following the Great East Japan Earthquake on March 11, 2011, the emergency radiation exposure dose limit for emergency workers at the Tokyo Electric Power Company (TEPCO) Fukushima Daiichi nuclear power plant was raised from 100 mSv to 250 mSv during the period between March 14 and December 16, 2011. The Ministry of Health, Labour and Welfare conducted a public invitation, ultimately selecting RERF in October 2014 as the managing research organization for conduct of a cohort study to follow the nuclear emergency workers who were at Fukushima during the aforementioned period for their lifetimes. In January 2015, RERF first sent a letter notifying all of the 20,000 eligible workers about the start of the study and later conducted a pilot study of those living in Fukushima prefecture. The full-scale study will be launched in FY2015.

As the 70th anniversary of the establishment of ABCC-RERF draws near, the entire staff of RERF feels a strong responsibility to join together in pursuing our mission and fortifying our legacy to ensure that it can be carried on by the next generation. To achieve that end, we request the continued support of the A-bomb survivors, local communities, Japanese and overseas researchers, as well as all those concerned in the U.S. and Japanese governments.

Message from the Vice Chairman and Executive Director

Roy E. Shore

The RERF epidemiologic studies on mortality and cancer incidence among A-bomb survivors (Life Span Study [LSS] and *in utero* cohorts) and their children (F_1 generation studies) have long been a primary basis for national and international estimates of the risks of cancer and other diseases from exposure to ionizing radiation. The LSS study plays the primary role in risk assessment worldwide because it is based on a very large, general population of all ages at exposure, with a wide range of well-documented exposure levels, long high-quality follow-up, and comprehensive data on mortality and cancer incidence. Importantly, the LSS is complemented by other RERF studies. Clinical examinations and biosamples in the Adult Health Study (AHS, a subsample of the LSS) and the clinical study of the F_1 generation (children of A-bomb survivors) provide more detailed information on important health conditions and opportunities to study the biological basis of those conditions in relation to radiation exposure. Our basic-science group utilizes the biosamples to further address the nature and extent of genetic and molecular changes associated with the health risks. Hence, the RERF studies uniquely provide a valuable window into both epidemiological and biological aspects of radiation risk. Such knowledge is crucial because of the many uses of radiation in today's world.

To highlight a few of the more significant accomplishments during the year:

- *Updated cancer incidence:* The LSS provides the principal comprehensive assessment of lifetime cancer risk from radiation exposure. To that end, extensive work is underway on an analysis of an 11-year update through 2009 of the radiation risk for cancer incidence, in collaboration with the U.S. National Cancer Institute (NCI). It includes detailed analyses of total solid cancers and a number of individual tumor sites, focusing on the shape of the dose-response curves, low-dose risk, and risks among those young at exposure. Another feature of the new risk estimates is that the joint roles of radiation and lifestyle risk factors are being examined.
- *Low-dose workshop:* Much public interest focuses on low-dose exposures because of Fukushima and medical exposures (e.g., CT examinations). A report based on the RERF international workshop on low-dose radiation risk will soon be published. Among the topics considered are low-dose risk estimation and uncertainties; the impact of other risk factors on low-dose studies; examination of various cancer sites separately, since the molecular pathways of cancer induction vary across sites; and strategic use of biosamples to address gaps in our mechanistic understanding of radiation risks.
- *Thyroid cancer:* The thyroid gland is one of the most radiosensitive organs, and information on lifetime thyroid cancer risk is important, e.g., for Chernobyl and Fukushima risk estimation. Thyroid examinations in the AHS showed that both thyroid cancer and other thyroid nodules had approximately linear associations with radiation dose (Imaizumi et al., *JAMA Internal Medicine* 2015), and risk is continuing even 60 years after exposure.
- *Are radiation-CVD mortality results confounded by the healthy survivor effect?:* We collaborated with researchers from the Helmholtz Institute (Munich, Germany) and found no evidence that a healthy survivor effect had distorted the radiation dose-response curve for CVD effects (Schöllnberger et al., *Radiat Prot Dosim* 2015).
- *Echocardiographic screening:* Because associations of radiation exposure with mortality from heart failure, hypertensive heart disease, and valvular heart disease have been reported in the LSS, we are aiming to confirm and evaluate these disease risks in the AHS and develop mechanistic insights. To obtain early indicators of these types of disease, we have begun a study using echocardiography and

related pre-clinical biomarkers.

- *Radiation and cognitive deficits:* Increased neurocognitive impairment with aging has become a prominent public health problem due to an increased life expectancy and a growing elderly population. Past ABCC results showed early evidence of neurocognitive deficits among children exposed *in utero*, which raises the question of late cognitive effects. A paper is being published on the effects of demographic factors and radiation on changes in cognitive function between 1992 and 2011 among subjects with radiation exposure at 13 or more years of age, but no clear effect of radiation was found. We are now obtaining data on those who were *in utero* or young children at exposure, for whom neurocognitive effects are more likely than among those exposed at adolescent or adult ages.
- *Macular degeneration:* A paper was submitted on radiation effects for age-related retinal macular degeneration among AHS participants. No association with radiation was found, which suggests that the lens of the eye is the main focus of potential damage after low-to-moderate radiation exposures.
- *Mechanisms of radiation immune effects:* Dendritic cells and T cells play important roles in triggering and mounting immune defenses, respectively. A microassay system to evaluate functions of human circulating hematopoietic progenitor cells (HPCs) was established to study long-lasting radiation effects on the immune system. A study using blood samples from in-house volunteers indicated a linkage between dendritic-cell and T-cell differentiation potentials in HPCs, thus confirming the potential for this system to study mechanistic radiation effects on immune cells (Kyoizumi et al., *J Immunol* 2014).
- *T-cell profiles and obesity:* Newly produced ("naïve") T cells are crucial for adequate immune surveillance in the body. A reduction in naïve T cells was significantly associated with increased body mass index and inflammation, suggesting that obesity with enhanced inflammation may be involved in the aging of the human T-cell immune system (Yoshida et al., *PLoS One* 2014). A previous study also showed a radiation-associated decrease in the ratio of naïve to "memory" (already used) T cells.
- *F_1 epidemiologic cohort study:* Long-term studies of the F_1 cohort (children of A-bomb survivors) address the key issue of the heritable effects of radiation exposure and provide unique data, as this is the only extant radiation study with data on disease experience into mid-adult ages of the children of exposed individuals. A 14-year update through 2009 of cancer and noncancer mortality risks in the epidemiologic cohort of 77,000 F_1 offspring of A-bomb survivors has been submitted for review. No significant increase in cancer or noncancer disease mortality was seen in relation to individual paternal or maternal gonadal doses, but the offspring average only around 55 years of age and longer follow-up is required to document the more extensive disease experience at older ages.
- *Fetal chromosome aberrations:* We found that chromosome translocations were induced in rat mammary epithelial cells following fetal irradiation, whereas they were not induced in lymphocytes unless exposure occurred several weeks after birth (Nakano et al., *Radiat Res* 2014). This parallels the tissue-dependent induction of malignancies among the *in utero*-exposed A-bomb survivors, for whom an excess of solid cancers but not leukemia was found. We also observed that translocation frequencies in mouse thyroid cells irradiated as fetuses varied with fetal stage at the time of irradiation. These findings suggest that tissue-specific radiosensitivity is related to the time of anchoring of stem cells to their biological niches which is a function of the stage of fetal development,
- *A-bomb physical dosimetry:* The work on creating accurate maps and correcting location (using Geographic Information System technology) and structural shielding data of LSS study subjects has been completed. We reviewed the original records and confirmed the location at the time of the bombings, pinpointing the locations on geographically corrected maps for the LSS and *in utero* cohorts and the F_1 cohort parents. A substantially revised model of elevation and terrain shielding was applied to these cohorts. Preliminary analyses suggest these changes will make little difference in the average risk estimates, but will reduce uncertainties and increase our confidence in the dose calculations.
- *Neutron dose effects:* A report explained in detail a correct methodology to calculate the relative biological effectiveness (RBE) of neutrons for dose-varying RBE functions to estimate A-bomb risks, which some past investigators have advocated but had unknowingly calculated incorrectly. When those variable RBE functions are correctly derived, there is little difference between the constant- and variable-RBE weighted doses or risk estimates (Cullings et al., *Radiat Res* 2014).
- *Fallout rain exposure:* Reported exposure to fallout rain was obtained from early ABCC questionnaires. Because of public concerns, especially after the Fukushima accident, the fallout data reported on early ABCC questionnaires have been analyzed in relation to subsequent cancer and noncancer mortality and cancer incidence. No association was seen between reported fallout exposure and the health endpoints (Sakata et al., *Radiat Res* 2014). An analysis of fallout rain exposure and reported acute symp-

toms (e.g., hair loss) also has been conducted to address concerns about an alleged association, and a paper is submitted for publication.

- *Biosample Center:* RERF is consolidating its biosamples into a centralized storage and data-management system. To that end, a robotic freezer system is being purchased for the storage of cumulative blood and urine samples, and biosample documentation is underway. This will also facilitate the linkage of biospecimens with the epidemiologic/clinical/biological data that RERF has derived.

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 by providing realistic information about the risks from radiation exposure. Such knowledge is important because of the many applications of radiation and apprehensions about its use. 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 faithfully participated in clinical studies for many years that provide invaluable knowledge benefitting all humankind.