放影研 RERF update
Radiation Effects Research Foundation News and Views
Hiroshima and Nagasaki, Japan
Volume 19, Issue 1, 2008

60TH ANNIVERSARY OF ABCC-RERF

This 380 year-old Japanese white pine was donated to the American people in 1976 by the late Japanese bonsai master, Masaru Yamaki. It was selected as the symbol for the Sixth Annual Gilbert W. Beebe Symposium which commemorated the 60th Anniversary of ABCC-RERF on December 12, 2007 at the National Academy of Sciences in Washington, DC. On August 6, 1945, this bonsai was in the yard and collection of Masaru Yamaki who lived in Hiroshima about three kilometers from the atomic bomb's hypocenter. Both the Yamaki family and the bonsai were survivors and this Yamaki Pine is a testament to peace, beauty, and survival. Inside this issue of *Update*, please read more about this bonsai and the 60th Anniversary of ABCC-RERF.

Table of Contents

This newsletter is published by the Radiation Effects Research Foundation (formerly the Atomic Bomb Casualty Commission), established in April 1975 as a private, nonprofit Japanese foundation. It is supported by the government of Japan through its Ministry of Health, Labour and Welfare and that of the United States through the National Academy of Sciences under contract with the Department of Energy.

RERF conducts research and studies—for peaceful purposes—on the medical effects of radiation on humans with a view toward contributing to the maintenance of the health and welfare of atomic-bomb survivors and to the enhancement of the health of all mankind.

Editor-in-Chief: *Evan B. Douple, Associate Chief of Research*
Technical Editor: *Yuko Ikawa, Public Relations & Publications Office*

Editorial Policy

Contributions to Update *receive editorial review only and do not receive scientific peer review. The opinions expressed herein are those of the authors only and do not reflect RERF policies or positions.*

Contact: *Mailing address: RERF Public Relations & Publications Office, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815 Japan*
Telephone: 81-82-261-3131; Facsimile: 81-82-263-7279
Internet: www.rerf.jp

From the Editors

Haikei!

We are once again trying to catch up on our reporting of RERF's various research activities. The Editor in Chief of last year's *Update* Volume 18, 2007 helped set a high standard by making what we believe to be significant improvements in the quality and interest-level of the articles and reporting. However, Tom Seed has retired to his home in the United States. Only half of our editorial team (nakama) is new but, as we worked on preparing Volume 19, we realized that Tom left big footsteps to fill!

The year 2007 was a very special year for the Foundation since it marked the 60th anniversary of the founding of the Atomic Bomb Casualty Commission (ABCC). So it should not be surprising that in this issue we have highlighted the National Academy of Sciences' symposium that was held December 12, 2007 to commemorate this historic landmark. We have also included a very interesting and timely science article.

We hope that you enjoy this volume and don't hesitate to drop us a line and let us know how we might improve our reporting of RERF's many activities.

Sincerely,

Evan B. Douple
Editor in Chief

Yuko Ikawa
Technical Editor

Report on the 34th Scientific Council Meeting

The 34th Scientific Council meeting, co-chaired by Dr. Ohtsura Niwa (Kyoto University and National Institute of Radiological Sciences) and Dr. Joel Bedford (Colorado State University) was convened on March 5–7, 2007 in Hiroshima to review the scientific program of RERF. Besides the annual review of departmental research activities and short-range plans, the Scientific Council's charge was broadened this year to review two additional issues, the long-term Future Plans of RERF, and the results and future directions of the F_1 Clinical Study, so extended presentations were made of these.

Summary of General Recommendations by the Scientific Council:

The Scientific Council emphasized the important role that RERF plays world-wide in radiation risk research through its exemplary design and conduct of studies of the health effects of radiation in A-bomb survivors. They also recognized the generous support by the Japanese and U.S. governments, the U.S. National Academy of Sciences (NAS), and especially the benevolent collaboration of the survivors and their families. The principal general recommendations were:

- There is a vital need to fill key vacancies created by the recent and impending loss of leading scientists at RERF through mandatory retirement. This is made more difficult by the reduction in personnel mandated by the Japanese government.
- RERF should strive to maintain its strength and focused mission, since there is still much to be done even after 60 years of research. One reason for this is that nearly half of the A-bomb survivors' lifetime, radiation-associated cancer and non-cancer disease is projected to occur in the future. RERF's existence and continuation at current levels of support are crucial, not only to both nations supporting it, but to the entire world.
- The role of NAS in this research should be continued and strengthened, as it has lent additional credibility and scientific expertise to the efforts.
- With additional support over and above current levels, RERF can be expanded in two directions: the globalization of RERF's mission and the augmentation of its role in education and training.
- Consideration of more direct partnering with other international organizations would enhance the profile of RERF and showcase its mission and expertise. The new "Partnership" between RERF and the University of Washington and Kurume University is a good example of the benefits of such partnering.
- Every effort should be made to exploit the expertise and resources accumulated in RERF to obtain more and better knowledge about the mechanisms and extent of radiation health effects. To achieve maximum potential from the stored blood and other archival samples, an

expert panel should be assembled to recommend appropriate approaches and technologies. Introduction of high-end technologies will require collaborations with other groups outside RERF and additional sources of funding.
- Possibilities should be carefully evaluated for garnering additional outside funding to support expansion of activities while fully maintaining the efforts of our current mission. Any increased funding should be used for hiring staff and postdoctoral fellows.
- In order for RERF to continue its research mission at the highest level, including introduction of contemporary research tools, an updating and renovation of current facilities or a move to a new campus may be required.

Recommendations regarding the F_1 epidemiological and clinical studies:
- The only current opportunity to evaluate the human health effects upon offspring of radiation-exposed parents, in a dose range where some effects might be seen, lies in studies based on the children of atomic-bomb survivors. This opportunity should not be missed and the study should be pursued.
- The Scientific Council sees great merit in transforming the current cross-sectional F_1 clinical study into a longitudinal investigation. It would be a unique biomedical research resource.

Recommendations regarding RERF's long-term future plans:
- The Scientific Council is pleased to see extensive future plans which are crucial to the continuation and further extension of RERF's service to risk research communities and to the welfare of mankind. The plans describe the detail of projects which current research staff would like to conduct in the future. The Council would like to see a further reevaluation of scientific strengths and accomplishments, accumulated resources and administrative structures, as these factors should bear on the ways future contributions are planned and implemented.

Highlights of a few of the numerous recommendations to departments:
- The Scientific Council was impressed by the dose-response curves for non-cancer disease deaths in the Life Span Study (LSS). Basic studies to clarify the mechanisms of radiation effects on non-cancer diseases are encouraging, and should be further developed in order to better understand those effects, the impact of covariates, and the biological mechanisms. This work will require continued collaboration among departments and with other institutions that have sufficient infrastructure and expertise.
- The efforts to mount a new mail survey of LSS participants are commendable. The collection of biological samples from LSS participants can also be an important adjunct.
- The efforts should be continued to expand the Adult Health Study (AHS) cohort and to increase the number of younger survivors. This increase is particularly important for non-cancer risk estimation with higher precision and also for the collection of biospecimens for further basic analyses.
- The large number of paired samples collected from survivors and their progeny is an important resource which merits careful protection and also the development of collaborative projects between RERF staff and the scientific community in general.
- The efforts in immunophenotyping are an important line of research. We believe increased work is appropriate on the relationships of inflammation, cancer and altered immune function.
- We encourage continued work on the relationship between infection and cancer and how such risk is modified by radiation exposure, including additional cancer sites that have a known infectious component.
- Worldwide efforts to delineate the genetic determinants of adult diseases need to be followed closely in order to help interpret findings and differentiate disease endpoints.
- The development of methods for quantitative risk estimation and clinical data analysis, augmented by new collaborations with outside universities, should be continued. Causal modeling is a promising new direction for radiation risk assessment of cancer and non-cancer outcomes in the AHS.
- The biological dosimetry should be applied in a pilot study to evaluate the likelihood of these techniques making a relevant change to physical dose estimates and their statistical uncertainties.

RERF Scientific Councilors

Dr. Ohtsura Niwa, Professor, Radiation Biology Center, Kyoto University, *Co-chairperson*

Dr. Joel S. Bedford, Professor, Department of Radiological Health Sciences, Graduate Faculty of Cellular and Molecular Biology, Colorado State University, *Co-chairperson*

Dr. Teruhiko Yoshida, Chief, Genetics Division, National Cancer Center Research Institute

Dr. Yoshiharu Yonekura, President, National Institute of Radiological Sciences

Dr. Katsushi Tokunaga, Professor, Department of Human Genetics, Graduate School of Medicine, The University of Tokyo (Absent)
Dr. Takashi Yanagawa, Professor, The Biostatistics Center, Kurume University
Dr. Theodore L. DeWeese, Professor and Chair, Department of Radiation Oncology and Molecular Radiation Sciences, The Johns Hopkins University School of Medicine
Dr. Marianne Berwick, Professor and Chief, Division of Epidemiology, Head, Epidemiology and Cancer Prevention, University of New Mexico
Dr. John J. Mulvihill, Director, Program of Human Genetics and Professor of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center
Dr. David G. Hoel, Distinguished University Professor, Department of Biostatistics, Bioinformatics and Epidemiology, Medical University of South Carolina

The 42nd Board of Directors Meeting in Nagasaki

The 42nd meeting of the Board of Directors was held at the Nagasaki RERF on June 20 and 21, 2007. This was the first Board meeting held in Nagasaki in eight years, since 1999.

In their opening remarks, representatives of the U.S. and Japanese governments highly commended the scientific program of RERF and assured their continued active commitment to the program. Then, in his status report for RERF, Dr. Toshiteru Okubo, RERF Chairman, reported on the steady progress of the Foundation's studies over the past one year. Dr. Okubo reported that the health effects study of the children of A-bomb survivors, initiated in 2000, was completed with final reviews made at the end of February 2007, and that the chairs of the Scientific and Ethics Committees submitted a study report in April. He also reported on publication of a DS02-based, cancer incidence study report as part of the Life Span Study (LSS). Dr. Okubo thus emphasized the solid achievements of research at RERF. His report also touched on the Senior Review Panel on Future Planning for RERF. Dr. Okubo stated that the panel met in December 2006 and May 2007 and that it would submit a final report to the U.S. and Japanese governments in 2008.

In conjunction with the Senior Review Panel's deliberations, the current Board meeting had in attendance the U.S. and Japanese chairs of the panel, who explained the panel's roles and presented a progress report on its deliberations and solicited the directors' opinions regarding RERF's future plans. Reports were also made on the Agreement on Cooperation in Education and Research, concluded with Hiroshima University and Nagasaki University for enhancing comprehensive cooperation in research, as well as on the updated RERF promotional video.

In the course of the meeting's discussions, after reports on the background, study details and results of the health effects study of the children of A-bomb survivors, it was confirmed that the Senior Review Panel would be asked to provide opinions regarding possible involvement of the U.S. side in the study and that this matter would be dealt with in a constructive way through negotiations with those concerned. As for the government's plan for personnel reduction, it was suggested by the directors that the uniqueness of RERF as a research institution should be considered because reduction in the numbers of research scientists and general employees would bring about serious problems for RERF in terms of securing young and talented research scientists. In response, it was reported that new systems have been introduced at RERF in terms of recruitment and contract renewal for research scientists.

Additionally, research activities reports and settlement of accounts for FY2006, as well as research activities plans and working budget for FY2007, were discussed and approved. Of the four directors, one supervisor and two scientific councilors whose terms of office were due to expire, three directors, one supervisor and one scientific councilor were reappointed. Appointment of Mr. James W. Ziglar as successor to Dr. Paul L. Ziemer, who acted as director for four years, and Dr. Michael N. Cornforth as successor to Dr. Joel S. Bedford, who acted as scientific councilor for five years, was approved.

At the last Board meeting, it was agreed that the health effects study of the children of A-bomb survivors, which ended in February 2007, should be continued for follow-up of study results, as recommended by the Scientific Council. Continuation of the study is an important decision that could greatly impact RERF's future. While we will continue our coordination efforts with the authorities concerned in terms of budget, we have to wait for the final recommendations of the Senior Review Panel.

It was decided that the next Board meeting would be held in Washington, D.C., U.S., for three days beginning June 18, 2008.

List of Participants

Directors:
Dr. Toshiteru Okubo, Chairman
Dr. Roy E. Shore, Vice Chairman and Chief of Research

Mr. Takanobu Teramoto, Permanent Director
Mr. Masaaki Kuniyasu, Former Ambassador Extraordinary and Plenipotentiary to the Republic of Portugal
Dr. Yasuhito Sasaki, Director General, Radiology Center, International University of Health and Welfare
Dr. Senjun Taira, Permanent Director, Japanese Association of Quarantine Inspection Hygiene
Dr. Paul L. Ziemer, Professor Emeritus, Purdue University
Dr. James D. Cox, Professor and Head, Division of Radiation Oncology, University of Texas M.D. Anderson Cancer Center

Supervisor:
Dr. Tomio Hirohata, Professor Emeritus, Faculty of Medicine, Kyushu University

Co-chairmen Senior Review Panel on Future Planning for RERF:
Dr. Sadayoshi Kitagawa, Director General, Japan Public Health Association
Dr. Paul Gilman, Director, Oak Ridge Center for Advanced Studies

Co-chairman Scientific Council:
Dr. Ohtsura Niwa, Deputy Director, Research Center for Charged Particle Therapy, National Institute of Radiological Sciences

Representatives of Supporting Agencies:
Mr. Osamu Okabe, Director, General Affairs Division, Health Bureau, Ministry of Health, Labour and Welfare (MHLW)
Dr. Takeshi Sasaki, Deputy Director, General Affairs Division, Health Bureau, MHLW
Mr. Kazuhiro Kanayama, Deputy Director, General Affairs Division, Health Bureau, MHLW
Mr. Glenn S. Podonsky, Chief Health, Safety and Security Officer, Office of the Secretary of Energy, U.S. Department of Energy (DOE)
Mr. Michael A. Kilpatrick, Deputy Chief for Operations, Office of Health, Safety and Security, DOE
Mr. Dean C. Hickman, Project Manager, Office of Health, Safety and Security, DOE
Dr. Joseph F. Weiss, Japan Program Manager, Office of International Health Studies, Office of Health, Safety and Security, DOE
Mr. Thomas W. Wolf, Science and Technology and Health Affairs Officer, Environment, Science and Technology Affairs, Embassy of the United States of America
Dr. Kevin D. Crowley, Director, Nuclear and Radiation Studies Board, Division on Earth and Life Studies, National Research Council (NRC), National Academy of Sciences (NAS)
Dr. Evan B. Douple, Scholar, Nuclear and Radiation Studies Board, Division on Earth and Life Studies, NRC, NAS
Ms. Laura Llanos, Financial and Administrative Associate, Nuclear and Radiation Studies Board/ RERF Program, Division on Earth and Life Studies, NRC, NAS

RERF:
Mr. Eiji Akimoto, Chief of Secretariat
Dr. Thomas M. Seed, Associate Chief of Research
Dr. Nori Nakamura, Chief Scientist
Dr. Kazunori Kodama, Chief Scientist
Mr. Douglas C. Solvie, Associate Chief of Secretariat

The Sixth Annual Gilbert W. Beebe Symposium
Sixty Years of ABCC–RERF: Major Contributions and Future Studies

As the theme of its Sixth Annual Gilbert W. Beebe Symposium, the National Academies elected to commemorate the 60th anniversary of the founding of the Atomic Bomb Casualty Commission (ABCC) that became the Radiation Effects Research Foundation in 1975. The site of the special symposium—named after the distinguished epidemiologist who helped to establish ABCC and who was instrumental in the design of the ABCC's most important research studies—was the National Academy of Sciences Auditorium on Constitution Avenue in Washington, DC, and the date was December 12, 2007. An RERF delegation consisting of current directors, former chairman Dr. Itsuzo Shigematsu, and current RERF scientists, joined a number of former ABCC-RERF employees who gathered for the symposium from across the U.S. and renewed old friendships.

Opening Ceremony

The program began with an opening ceremony that included a koto concert played by **Mrs. Vera Land** who learned to play the koto when her husband, Dr. Charles Land, worked with Dr. Beebe at ABCC. **Dr. Ralph Cicerone**, President of the National Academy of Sciences (NAS), welcomed the participants on behalf of NAS and commented on the historical role and long-term commitment of NAS to this important scientific and humanitarian project. **Mr. Michael Kilpatrick**, Deputy Chief for Operations in the Department of Energy (DOE) Office of Health, Safety, and Security, gave greetings and congratulations on behalf of the U.S. government. He reminded the audience that the U.S. and the DOE have had a long-term interest in, and have provided extensive support for, the important studies of health effects in the A-bomb survivors. He thanked the many current and past employees of ABCC-RERF for their dedicated service and extended a special thank you and appreciation to the many thousands of A-bomb survivors. Without the support of both groups, RERF's valuable scientific accomplishments would not have been possible.

Mr. Kilpatrick was followed by **Mr. Masahiro Mori**, First Secretary for Health and Welfare of the Embassy of Japan, who represented the government of Japan. He honored all current and former employees for their devoted service to ABCC-RERF and for "their remarkable track record in leading the world in radiation research." He also expressed appreciation to all A-bomb survivors for their participation and cooperation in the radiation research for more than 60 years. He emphasized that "Without their understanding and contribution, the world's scientists could not understand what happened in Hiroshima and Nagasaki and could not pass on this valuable information to future generations." He confirmed that the government of Japan will continue to support the research by RERF and to improve the quality of life for A-bomb survivors. He also pointed out that the U.S.-Japan partnership and cooperation in this project is symbolic evidence of the history that the U.S. and Japan experienced as they overcame a tragedy six decades ago.

Since the "Honorary Chair" for this year's Beebe Symposium was a dedication to **all former employees of ABCC and RERF** and to **all A-bomb survi-**

A standing ovation in response to Mr. Sunao Tsuboi's message from the perspective of an A-bomb survivor

vors who have participated in the ABCC-RERF studies, **Dr. Itsuzo Shigematsu** accepted congratulations on behalf of all former ABCC-RERF employees. But it was particularly noteworthy that the final speaker of this opening ceremony was **Mr. Sunao Tsuboi**, representative of the Japan Confederation of A-bomb Sufferers Organizations, who was invited by NAS. Most participants probably would agree that his address commemorating RERF's achievements from the perspective of a survivor was a highlight of the symposium. Mr. Tsuboi told his own story of exposure to the A-bomb radiations and referred to his ardent wish for the abolition of nuclear weapons. He expressed confidence that RERF would continue to contribute to the future survival of all humanity through its research activities. His concluding remark "Never give up!" won the sympathy of the audience and elicited a spontaneous standing ovation. Despite being over 80 years of age and suffering from several ailments, it was Mr. Tsuboi's energetic, thoughtful, and motivational message that produced an outpouring of emotion which was shared by the Japanese and U.S. participants in the audience.

The History

Following the opening ceremony, the special day's program was introduced by the Vice Chairman of the National Academies' Nuclear and Radiation Studies Board (NRSB), **Dr. James Adelstein**. The program included three sessions regarding ABCC-RERF's history, major scientific contributions, and future. Dr. Adelstein introduced **Dr. William "Jack" Schull**, a former ABCC department head and a former RERF director, who served as moderator of the historical session and presented a keynote lecture: **"Hajimeru—ABCC and the early years." Dr. Robert Henshaw** then showed some of the early photographs taken by his father, Dr. Paul Henshaw, during his early visits to Hiroshima and Nagasaki as a member of the group that was responsible for some of the earliest assessments of the effects of the A-bombs in 1946. The Henshaw family has donated the photos to the archival collections of the ABCC-RERF. **Dr. Carl Tessmer**, the first director of ABCC (1948–1951) gave his greetings and congratulations in a recorded message. A film followed, in which two of ABCC's first and longest-term employees, **Mr. Michael Rappaport** and **Mr. Shizuo Inoue**, reminisced about their experiences. Mr. Rappaport helped to direct the construction of the ABCC buildings on Hijiyama beginning in 1946 and later held the position of Business Administrator until his retirement in 1988. Mr. Inoue was recruited as an ABCC Motor Pool Dispatcher in 1949 and eventually assisted Chairman Shigematsu until he retired in 1997. You may recall reading more about these two employees in *RERF Update* Volume 18, 2007.

A panel joined Dr. Schull on stage that included four of the early U.S. physicians who spoke about their recollections as NAS employees assigned to ABCC. **Dr. James Yamazaki** arrived in 1949 and was in charge of the Nagasaki Laboratory between 1949–1951. **Dr. Niel Wald** was the Senior Hematologist at ABCC from 1954–1957. **Dr. Bertrand (Randy) Brill** arrived in Hiroshima as a Public Health Service Officer in July 1957, at a time when Drs. George Darling and Beebe arrived at ABCC. He spent more than two years, mostly in Nagasaki, as a member of the ABCC Statistics and Medicine Departments. **Dr. Stuart Finch** spent a total of nine and half years as either Chief of Medicine at ABCC or Chief of Research at RERF while on leave of absence from his medical school positions. He pointed out the relatively large numbers of visiting scientists to RERF from both Dartmouth College (from which he and Dr. Beebe graduated) and Yale Medical School (where Dr. Finch served as head of the Division of Hematology for 24 years). Following the panel discussions, **Dr. James Norman**, a Visiting Statistician at RERF during 1975–1977, gave a brief account of Dr. Beebe's founding of the NAS' Medical Follow-up Agency that provided management and oversight of the RERF. **Dr. James Liverman**, formerly affiliated with the ABCC-RERF through the U.S. Department of Energy, gave a first-hand account of the transition of ABCC to RERF in

1975. The historical session concluded with **Dr. Itsuzo Shigematsu** reflecting on the major highlights and contributions of ABCC-RERF during his earlier years as an epidemiology advisor to ABCC and his 16 years as the longest-term Chairman of RERF, beginning in 1981.

Major Scientific Contributions

Attention turned to the major scientific contributions of ABCC-RERF in the next session that was moderated by the former Chairman of RERF (2001–2005), **Dr. Burton Bennett**, who served as the only U.S. Chairman of RERF. The first speaker, **Dr. Dale Preston**, served more than 20 years as a biostatistician at RERF and most of that time he was Chief of the Department of Statistics. He began his presentation **"Radiation effects on cancer risks in the ABCC-RERF Life Span Study and *in utero* cohorts"** by describing the important role that Dr. Beebe played in developing ideas for the ABCC cohort-based studies of cancer and other outcomes. He also described the impact of the NAS committee chaired by Dr. Thomas Francis that was formed to assess the early stages of ABCC research and that recommended a unified study plan and the need for sound dose estimates. He then focused on the estimates of radiation effects on cancer risks derived from the Life Span Study (LSS) that was formed in 1958 and contains 121,320 persons and the cohorts that include 3,638 persons who were exposed *in utero*.

The major questions addressed by the LSS included: "Does cancer risk increase with dose, and if so, what is the shape of the dose-response curve?" and "How does the increase in risk depend on non-dose factors such as gender, age at exposure, age at death or diagnosis (attained age or age), time since exposure, and other factors such as nutrition, smoking, reproductive history, genotype, phenotype, etc.?" He described the results of the analyses with respect to relative risk (RR, ratio to what is expected in a comparable unexposed population), excess absolute rate (EAR, difference from what is expected in a comparable unexposed population or baseline), and excess relative risk (ERR, ratio of EAR to what is expected in a comparable unexposed population or proportional increase). The number of subjects in various dose categories and their attendant cases of solid cancers are shown in Table 1, with the result that women appear to be more sensitive than men when ERR% and EAR are taken into account. The dose response is illustrated in Figure 1 in which the linear model (red line) describes the data well with a linear dose response on 0–0.15 Gy, and no indication of a threshold. The non-parametric model (dashed and bolded blue line) suggests some upward curvature on the 0–2 Gy range ($P = 0.09$).

The age-time patterns for A-bomb survivor solid cancers are shown in Figure 2 which illustrates:

- ERR higher for younger exposure ages and decreases with increasing age at diagnosis
- EAR higher for younger exposure ages and increases throughout life following exposure to radiation

Cancer incidence has also been characterized for site-specific risks as shown in Table 2 where the largest proportion of radiation-attributable cases are for breast, thyroid, and non-melanoma skin cancers.

An increase in leukemias was observed relatively soon after the A-bombs and LSS leukemia mortality is shown in Table 3, including the observations that despite smaller numbers of excess cases, a considerably larger proportion of the cases are radiation-associated than for solid cancer and the dose response appears non-linear over the low-to-moderate dose range.

Table 1. Solid cancer risks among A-bomb survivors (1958–1998)

Dose category (Gy)	Subjects	Person years	Cases	Radiation-associated	Attributable fraction (%)
<0.005	60,792	1,598,944	9,597	3	0%
0.005–0.1	27,789	729,603	4,406	81	2%
0.1–0.2	5,527	145,925	968	75	8%
0.2–0.5	5,935	153,886	1,144	179	16%
0.5–1	3,173	81,251	688	206	30%
1–2	1,647	41,412	460	196	43%
2+	564	13,711	185	111	60%
Total	105,427	2,764,732	17,448	853	11%

	women	men
ERR%*	58% per Gy	35% per Gy
EAR**	60 per Gy	43 per Gy

*ERR/Gy at age 70 following exposure at age 30
**Excess cases per 10,000 PY Gy at age 70 following exposure at age 30

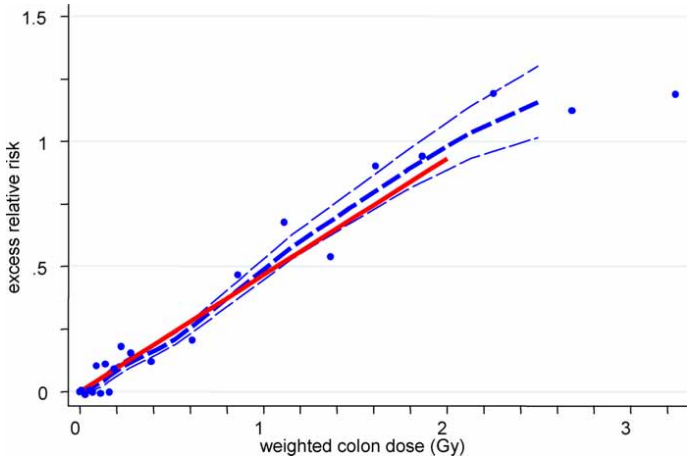

Figure 1. LSS solid cancer incidence (1958–1998) dose response.

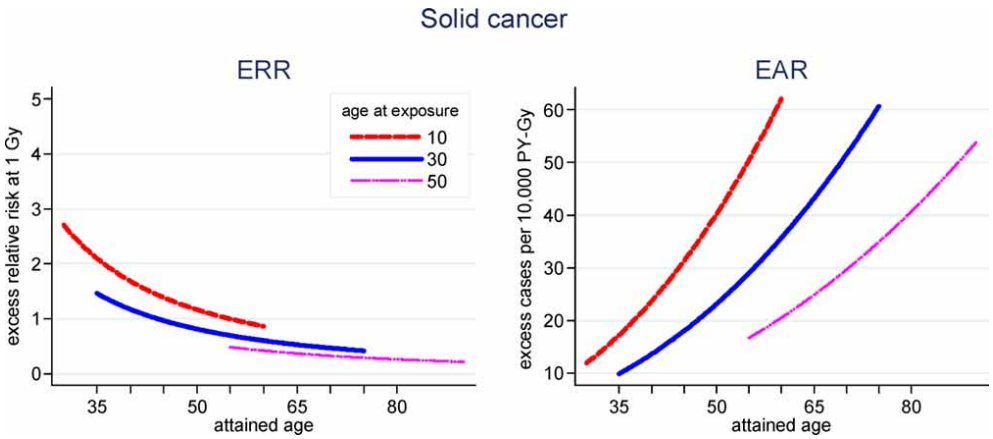

Figure 2. A-bomb survivor solid cancer age-time patterns.

Table 2. Solid cancer incidence and site-specific risks

Site	Cases	Excess cases	Attributable risk*
Stomach	4,730	151	7%
Female breast	1,073	147	27%
Remainder	3,325	126	8%
Lung	1,759	117	15%
Colon	1,516	78	11%
Thyroid	471	63	25%
Liver	1,494	54	8%
Non-melanoma skin	330	40	23%
Bladder	469	35	16%
Brain, CNS	281	19	13%
Rectum	838	14	4%
Uterus	1,162	10	2%
All solid	17,448	853	11%

*Percentage of excess cases among those with dose >5 mGy

Dr. Preston summarized by pointing out that the results of the LSS analyses provide:

- unequivocal evidence of life-long dose-related increase in cancer rates following exposure at any age;
- a linear solid-cancer dose response even into a relatively low dose range;
- temporal patterns and gender differences that provide general insight into carcinogenesis;
- characterization of site-specific solid cancer incidence rates; and
- information that serves as a primary source for quantifying risk estimates for radiation protection and risk projections which are utilized by many countries throughout the world.

The results of the leukemia risks from the *in utero* cohort studies do not show a dose response which is surprising given the striking dose-related increase following early-childhood exposure and the high childhood leukemia and other childhood cancer risks

Table 3. LSS leukemia mortality (1950–2000)

Marrow dose	Subjects	Person years	Cases	Estimated excess	AR%
<0.005	36,502	1,342,168	89	0	0%
0.005–0.1	30,898	1,135,582	69	4	6%
0.1–0.2	6,006	223,701	17	4	25%
0.2–0.5	6,993	256,584	31	13	41%
0.5–1.0	3,512	129,053	27	18	68%
1.0+	2,700	97,267	63	55	87%
Total	86,611	3,184,355	296	94	46%*

*Attributable risk % among survivors with marrow dose >0.005 Gy

reported in case-control studies of effects following pre-natal x-ray exposures.

Dr. Preston concluded by acknowledging the important contributions made by the A-bomb survivors and several ABCC-RERF scientists and staff who have been "standing on the shoulders of giants such as Gilbert Beebe, Seymour Jablon, Jim Neel, and Jack Schull." He pointed out that with more than 40% of the A-bomb survivors still alive, and most of those alive having been exposed to the radiation as children, potentially more than 40% of the LSS excess solid cancers are yet to occur and there is much to be done in the next 20 years.

After a lunch break, a film "*RERF Today*" was shown followed by a violin solo performed by **Mrs. Mayumi Pawel** and accompanied by pianist **Dr. Alejandro Hernandez-Valdez**. Mrs. Pawel lived in Hiroshima from 1992–1994 when her husband, David, was a statistician at RERF.

The scientific session continued with a presentation by **Dr. Saeko Fujiwara**, Chief of the RERF Department of Clinical Studies, titled **"The Adult Health Study: Clinical health assessments, biospecimens, and medical support for A-bomb survivors."** Dr. Fujiwara, who has been conducting clinical studies at RERF for more than 20 years, described the Adult Health Study (AHS), a subcohort of the LSS that was begun in 1958 with 20,000 study subjects. Some 17,000 individuals in the AHS, who currently number about 4,000, have had clinical examinations every two years. The participation rate in the first exam cycle in 1958–1960 was about 90% and for 50 years has remained amazingly high (85% have participated in more than 20 examinations and 60% have participated in all 24 examinations) and 4,000 (about 70%) underwent examinations in the 24th cycle in 2004–2006 when the average age of the cohort was 72 years. Blood samples obtained from the AHS participants are used for basic research and stored for future studies. Storage of serum samples began in 1969 and samples have been obtained from about 16,000 AHS subjects. Storage of blood cells began in 1990 and blood cells from about 7,000 persons have been stored.

An important finding of the AHS study has been associations between certain non-cancer health effects and radiation exposure. For example, a significant linear dose response was found for uterine myoma, thyroid diseases, and chronic liver disease. A significant quadratic dose response was found for hypertension and myocardial infarction as illustrated in Figure 3.

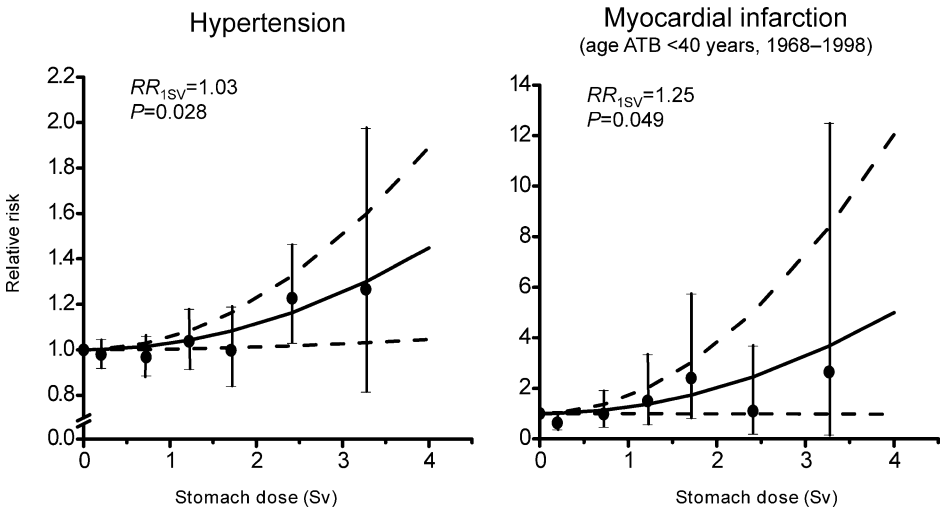

Figure 3. Dose responses for incidence of hypertension and myocardial infarction, 1958–1998. *(Yamada M et al. Radiat Res 161:622, 2004)*

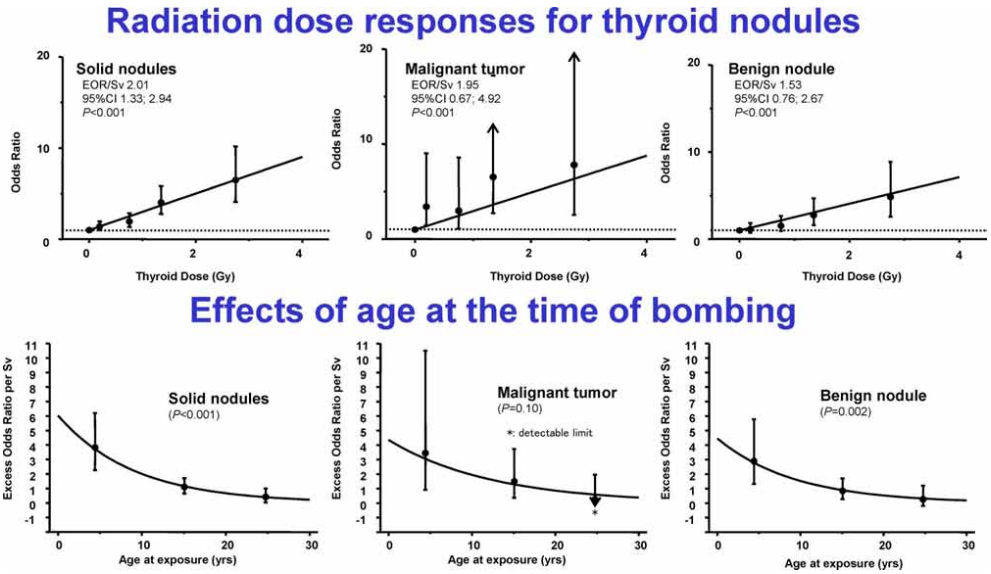

Figure 4. Radiation dose responses for thyroid nodules and effects of age at the time of bombing. *(Imaizumi M et al. JAMA 295:1011-22, 2006)*

A recent comprehensive thyroid evaluation study demonstrated a significant linear dose-response relationship for solid nodules, malignant tumors, and benign nodules (see Figure 4), with younger survivors having a higher risk than older survivors, while no significant dose response was observed for positive anti-thyroid antibodies, hypothyroidism, and Graves' Disease.

There is, so far, little or no evidence of radiation effects on risks for chronic infectious diseases, such as tuberculosis, autoimmune diseases such as rheumatoid arthritis, or common diseases associated with aging such as dementia, osteoporosis, and prostate hyperplasia. In terms of sub-clinical conditions, markers related to inflammation increased with radiation dose. Since chronic inflammatory conditions can lead to various diseases, RERF has studies underway examining inflammation as an intermediate factor in the pathways by which radiation induces non-cancer disease.

One of the early ABCC findings was that radiation-induced cataracts developed relatively early after the A-bomb exposures. RERF studies showed that cortical and posterior subcapsular opacities increased with radiation doses, whereas there was no evidence for increases for nuclear opacities. Recent studies demonstrate that clinically significant cataracts that were removed surgically increased with radiation dose compatible with a no-threshold response. Those results are illustrated in Figure 5.

The survivors who were exposed *in utero* have now reached the age of 62 years. Recent studies were conducted to examine the effects of prenatal exposure on non-cancer disease and, thus far, no increased

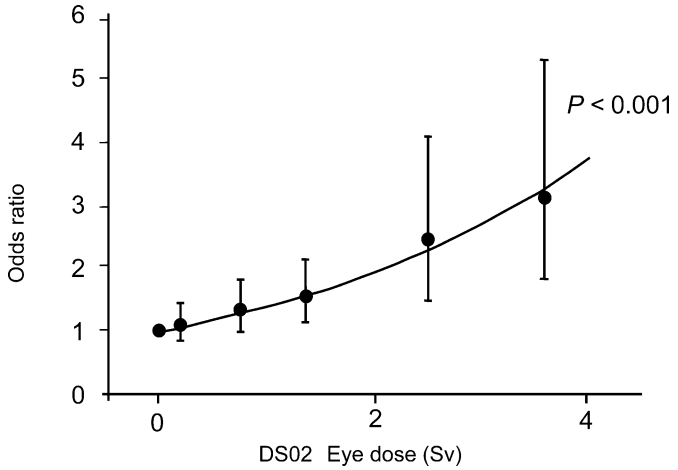

Figure 5. Dose responses for postoperative cataract. Prevalence study in 2000–2002. *(Neriishi K et al. Radiat Res 168:404, 2007)*

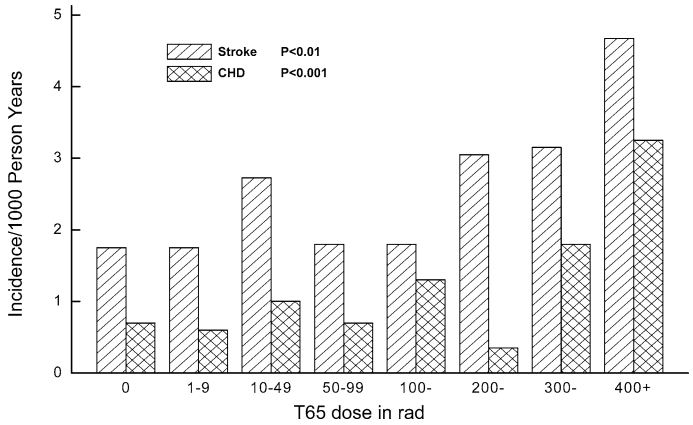

Figure 6. Age-adjusted incidence of stroke and coronary heart disease by radiation dose (AHS, 1958–1978, Hiroshima females).

risk of prenatal radiation exposure was observed for thyroid nodules, hypertension, hypercholesterolemia, or myocardial infarction and stroke.

Dr. Fujiwara acknowledged the important contributions that the A-bomb survivors have made to the AHS and pointed out that participants are informed of the examination results with health guidance, and if necessary, are referred to local physicians for further examinations and treatment. She concluded by summarizing that in addition to providing important data regarding the health effects of radiation, the AHS has contributed important biospecimens used for basic research and provides a number of beneficial services to the participants including disease prevention through early disease detection, medical consultation, health guidance, and welfare services.

Dr. Kazunori Kodama, currently a Chief Scientist at RERF, was introduced to discuss **"ABCC-RERF epidemiology: Non-cancer diseases in the LSS population, and cancer and multifactorial disease in the F_1 population."** Dr. Kodama first joined the Department of Medicine of ABCC in 1974 and has served as the Chief of both the RERF Department of Clinical Studies and later the Department of Epidemiology. In his presentation, Dr. Kodama showed the early data from 16,000 AHS subjects that suggested a dose-related increase in both stroke and coronary heart disease, especially in Hiroshima females, and most markedly in survivors who were under the age of 30 at the time of the bombing (Figure 6).

Later LSS mortality studies revealed a cause-specific dose response for non-cancer deaths from heart disease, stroke, respiratory disease, and digestive diseases as illustrated in Figure 7. Current studies continue to explore the apparent increases in non-cancer mortality associated with radiation dose, especially ischemic, hypertension, and rheumatic heart diseases, since the survivors who are alive today are entering the decades of life when these diseases become predominant causes of death.

Dr. Kodama concluded his presentation by describing the results of studies of the second-generation (offspring born to one or both parents who were A-bomb survivors). Risk estimates for multi-factorial disease in relation to parental radiation dose among the offspring in those F_1 Clinical Studies showed no evidence of an increased risk of adult-onset multi-factorial disease with parental radiation exposure. Furthermore, a series of genetic studies at ABCC-RERF over many years did not detect radiation effects for malformations, stillbirths, perinatal death, sex ratios, growth and development, chromosome aberrations, protein analyses, mortality, and cancer incidence in the F_1 generation.

The final RERF scientist speaking in this session, **Dr. Nori Nakamura**, summarized the many basic science and laboratory studies conducted over the years as **"ABCC-RERF laboratory studies: Past and future."** Dr. Nakamura joined RERF in 1984 and was Chief of the Genetics Department from 1998–2006. He is currently an RERF Chief Scientist and his presentation focused on five topics that he chose to highlight.

1. Individual radiation sensitivity. While the results of early studies demonstrated that normal skin fibroblasts showed a wide variation in radiation sensitivity, studies using blood lymphocytes generally did not.
2. Mutant cell frequencies *in vivo*. Glycophorin A (GPA) mutations were studied in red blood cells but clearly were not a suitable biomarker for radiation dose (biodosimetry). HPRT (hypoxanthine-guanine phosphoribosyl transferase) mutations showed only a weak correlation with radiation dose and T-cell receptor (TCR) mutants did not persist and disappeared with time as did dicentrics. The somatic mutation studies concluded: (a) that while bone marrow stem cells provide red blood cells for decades and can

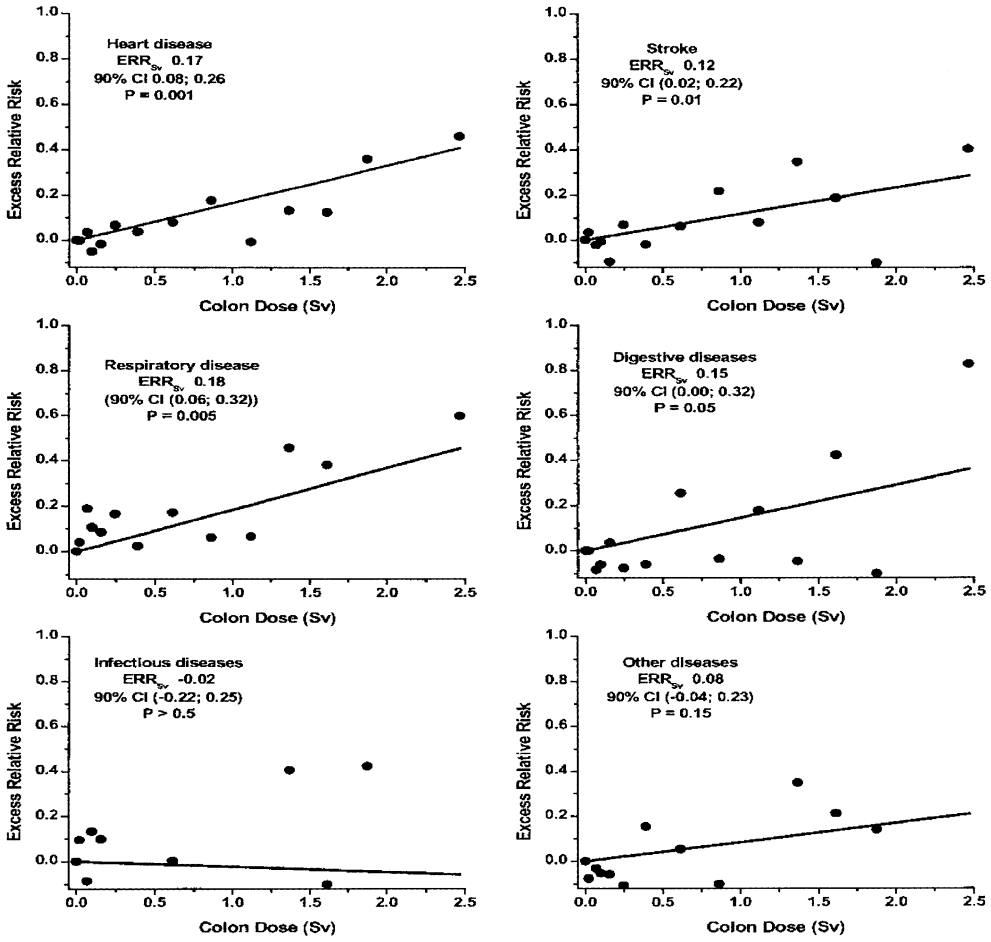

Figure 7. Cause-specific dose-response functions for non-cancer deaths, LSS, 1950–1997 *(Preston DL et al. Radiat Res 160:381-407, 2003).*

record mutations, the number of stem cells is not large; (b) some mutations in lymphocytes are negatively selected and cannot be sustained *in vivo*; and (c) although they require tedious work to score, chromosome aberrations remain one of the best biomarkers and biodosimeters for radiation exposure.

3. Genomic instability *in vivo*. Clonal cell populations marked by stable-type aberrations (translocations) were examined using techniques such as G-banding and multicolor fluorescence *in situ* hybridization (M-FISH). There appeared to be no indication that there was an increased frequency of spontaneous translocations among clonally-derived cells, and it is unlikely that the overall translocation frequency includes a large contribution from genomic instability.
4. *In utero* exposures. While it is generally believed that the fetus is hypersensitive to radiation, A-bomb survivors exposed *in utero* did not indicate a radiation dose response for translocations when examined at 40 years of age. However, when mothers who received >0.5 Gy doses were studied they did show a dose response for translocations. Therefore, the lack of a response in the *in utero* cohort is due to a biological effect. Subsequent studies in mice confirmed that irradiated fetuses do not sustain the cytogenetic damage in hemato-lymphoid cells (Figure 8) and these results appear to be related to the unexpectedly low excess risk of cancer in the survivors who were exposed *in utero*.
5. Germline mutations. Dr. Nakamura concluded by describing some of the ongoing studies that are using two-dimensional DNA gel electrophoresis (2DE) to visualize about 1,000 DNA fragments that are visualized in an autoradiogram. In mice, the mean mutation induction rate at 1,000 loci appears to be much lower than the historic mouse genetic "Russell Studies" at 7 loci. Studies using new microarray technologies (a 2,500 BAC-array) are also being used to search for alterations in DNA in the offspring of A-bomb survivors.

So despite many avenues of research that are being explored, chromosome aberrations appear to remain an important biomarker and biodosimeter. RERF scientists are attempting to further calibrate

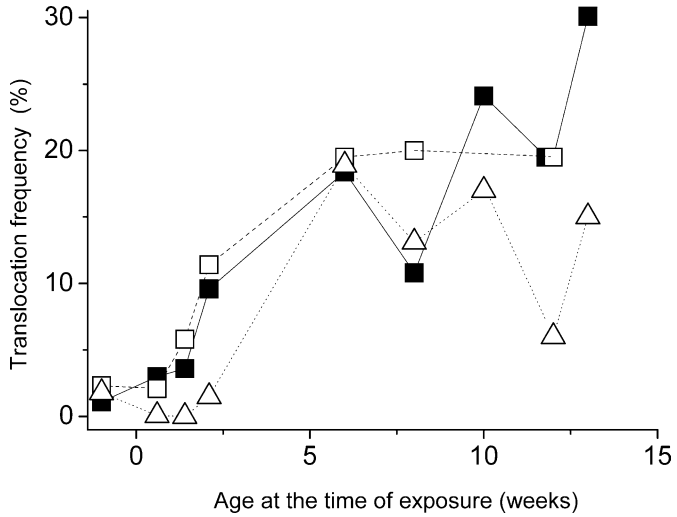

Figure 8. The frequency of translocations detected in blood lymphocytes (closed square), spleen cells (open square), and bone marrow cells (triangle), in mice exposed to 2 Gy of X rays at different ages indicated on the x axis but were all examined at 20 weeks of the age.
(Nakano M et al. Radiat Res 167:693-702, 2007)

individual doses in survivors using the technique of electron spin resonance (ESR) in tooth enamel to measure radiation dose in teeth donated by survivors. The results of this biodosimeter are being compared to calibration curves using chromosome aberrations in the same survivors.

Dr. Martha Linet, Chief of the Radiation Epidemiology Branch of the National Cancer Institute (NCI), spoke about the many contributions that RERF has made as a result of several long-standing collaborations between the NCI and RERF scientists, especially with respect to site-specific cancer risk assessments following exposure to radiation. Several NCI scientists, such as Dr. Beebe, had worked at ABCC and RERF over the years. **Dr. Burton Bennett** concluded this session by summarizing the impact of ABCC-RERF on radiation risk assessment through the contributions to bodies such as the NAS' BEIR committees, and to the work of NCRP, ICRP, and UNSCEAR. He was especially familiar with the contributions to the latter body, having served 12 years as director of the UNSCEAR secretariat in Vienna, Austria.

The Future

The final session of the symposium focused on the future of RERF and was moderated by **Dr. Charles Waldren** who served as the RERF Chief Scientist and then became the former Vice Chairman and Chief of Research. Dr. Waldren pointed out that one of the valuable resources at RERF is the large number of biospecimens that have been collected and stored. In order to exploit the potential for these samples to contribute knowledge regarding mechanisms of radiation-induced adverse health effects, RERF is challenged to employ the latest technologies of molecular biology and perhaps establish collaborations with investigators from laboratories around the world who are refining new methodologies and investigations. He introduced the final keynote speaker of the symposium, **Dr. Joe Gray**, currently the Associate Laboratory Director for Life and Environmental Sciences and Life Sciences Division Director at the Lawrence Berkeley National Laboratory whose lecture was titled **"The 'omic' revolution and epidemiology."**

Dr. Gray outlined the goal of his lecture which was to review the "omics" landscape and provide some of the technological advances that have been made. He also promised to illustrate some applications of the methodologies to epidemiological research and to summarize some of the lessons learned from those applications. He defined the scope of omic analyses at levels of DNA, RNA, proteins, and pathophysiology, and indicated that omic analyses at all levels may eventually reveal molecular events that influence disease susceptibility.

Dr. Gray first reviewed the use of various microarrays for scanning genomes for disease-associated polymorphisms and the identification of cancer susceptibility loci. He predicted that the use of numerous low penetrance, high prevalence single nucleotide polymorphisms (SNPs) are likely to contribute to a better understanding of the risks of breast cancer. He then proceeded to take the audience on a "journey" through various examples of this dynamic field of molecular biological and technological developments. Some major approaches included:

- Integration of mouse and human studies to validate functional polymorphisms;

- The use of large-scale copy number polymorphisms (CNPs) in the human genome where allele-specific copy number analyses of tumors may suggest candidate polymorphisms to be tested in epidemiological searches for susceptibility genes;
- Next-generation array technologies (such as molecular inversion probes [MIPs]) and candidate disease-associated SNPs and mutations are emerging from genome-wide sequencing efforts;
- The Cancer Genome Atlas (TCGA) Project should accelerate studies given the large number of participants at numerous institutions across the U.S.;
- Genome-scale DNA and epigenome sequencing will generate a candidate disease gene "parts list" to guide future epidemiological studies;
- Advances have been rapid as illustrated by going from 454 sequencer 100 million bases with 250 bp reads to Helicos 1 billion bases in 25–35 bp reads;
- The next generation of sequencing and high-throughput sequencing of affinity-enriched sequences will enable one to capture "all" human exons on arrays;
- Epigenomic events may be important; functional proteomics could employ reverse-phase protein lysate arrays and use protein profiling to predict mutational status; and
- Proteomic platforms should become potentially powerful tools for detection of pathway-associated molecular aberrations that may be especially suitable for detection of blood-borne disease indicators.

Dr. Gray emphasized that the manipulation of *in vitro* systems can identify molecular events associated with response phenotypes. The large collection of well-characterized lymphoblastoid cell lines at RERF might be used to facilitate discovery of a range of biomolecular associations.

Dr. Gray concluded his lecture with three observations:

- Powerful analysis tools are permitting discovery of candidate disease variants in all parts of the "ome";
- Robust technologies support analyses of variants in archival materials; and
- Well-studied RERF populations and RERF's biosample archives constitute a unique resource for a broad range of molecular epidemiologic studies.

Two relatively new initiatives were the focus of the next part of this session. **Dr. Scott Davis** is Chairman of the Department of Epidemiology at the University of Washington and he served as a Research Associate in Epidemiology at RERF from 1983–1985. Dr. Davis, along with his biostatistician colleague Dr. Kenneth Kopecky, developed a Partnership in March of 2005, with RERF, the University of Washington (UW), the Fred Hutchinson Cancer Research Center (FHCRC), and Kurume University (KU) in Japan. Supported with funds provided by DOE through the NAS, the Partnership's goals are to:

- encourage and facilitate scientific exchange and collaborations in epidemiology and biostatistics;
- provide expertise and advice to RERF from scientists at UW, FHCRC, and KU;
- augment RERF staff with students and faculty;
- assist NAS in recruiting a new generation of qualified investigators to RERF;
- develop and provide training opportunities to attract talented young investigators to careers in radiation science; and to
- provide RERF scientists with access to expertise and opportunities for training in developing areas of epidemiology and biostatistics.

Dr. Davis reviewed the current research projects of the three graduate students and the three faculty members affiliated with the UW and FHCRC component of the Partnership.

Dr. Tatsuyuki Kakuma, Professor of Biostatistics and Director of the Biostatistical Center in Kurume University, completed the presentation by describing the role of his university in the Partnership. Kurume University's School of Medicine is 80 years old and the only medical school in Japan with a federally-supported graduate program in biostatistics.

A second initiative was represented by the presentation by **Dr. David Pawel**, a statistician in the U.S. Environmental Protection Agency. Dr. Pawel was the second scientist sponsored by a Gilbert W. Beebe Fellowship, a research program administered by NAS through funding provided by DOE. The purpose of the Beebe Fellowship is to provide scientists the opportunity to spend some time working at RERF in order to become more familiar with the RERF research and to learn more about the radiation sciences while contributing to the RERF research activities. The goal is to attract new scientists into radiation statistics and epidemiology with the hope that some might even become interested in working as an NAS/RERF employee in the future or, at the very least, might develop future scientific collaborations. Dr. Pawel presented results of his studies which tested methods for sharing information among data for specific cancer types to improve site-specific radiogenic risk estimates such as improved estimates of ERR: **"Improved estimates of cancer site-specific risks for A-bomb survivors."**

The DOE's support of the RERF program resides in the Office of Health and Safety (HS) within DOE's Office of Health, Safety, and Security (HSS). The Director of HS, **Dr. Patricia Worthington**, described

the activities of a Senior Review Panel on Future Planning for RERF as **"The future of RERF: View of a funding agency."** That panel is charged with making recommendations regarding the future of RERF and to provide a vision of what RERF should look like at various time points during the next 20 years and beyond. Chaired by Dr. Paul Gilman (Oak Ridge Center for Advanced Studies) and Dr. Sadayoshi Kitagawa (Japan Public Health Association), the panel consists of a total of four U.S. scientists and four Japanese scientists and is expecting to deliver its report to DOE and the Japanese Ministry of Health, Labour and Welfare in 2008.

Dr. Toshiteru Okubo, the current Chairman of RERF, presented his **"Personal perspectives regarding RERF's future."** He began by reviewing the key characteristics of the ABCC-RERF studies which have contributed to the important RERF achievements, namely the large-scale cohorts consisting of both genders and all age groups, the long-term dedicated institutional follow-up, and the development of a dosimetry system for determining individual doses that spanned a relatively large dose range. Most importantly, he emphasized the sacrifices and the commitment to participation made by the A-bomb survivors and whose contributions inspire the resolve to never give up on the Foundation which is a symbol of the eternal desire of the Japanese and U.S. peoples for world peace and the abolition of nuclear weapons. He pointed out that RERF's future is important because the exposed population includes a large percentage with relatively low doses in the 0.005–0.1 Gy range which is an area of interest to the world's radiation protection community. Also, more than 40% of the LSS cohort members are alive today and most of them were <10 years of age at the time of the bombing. As those survivors enter their cancer-prone years, more cancers (perhaps as many as have occurred during the first 60 years of this study) are projected to occur. Furthermore, the survivors have contributed biospecimens which have the potential to contribute important information related to the processes leading to adverse health effects, such as cancer and heart disease. And finally, new technologies of modern science may provide more sensitive assessments of whether there are radiation-induced health effects in the F_1 generation. He concluded by pointing out that the RERF future should be bright provided RERF continues to: (a) build strong collaborations with international scientists; (b) accumulate reliable data; (c) contribute to world peace and the health of mankind; (d) maintain high standards and is a "Center of Excellence" for research and education; and (e) build affiliations with international organizations.

The final presentation was made by the current Vice Chairman and Chief of Research at RERF, **Dr. Roy Shore**, whose talk was titled **"Future RERF research directions: Continuity and change."** He began by pointing out how RERF's cancer mortality and incidence data are used in many ways, including:

- establishing exposure standards and risk estimations for radiation workers and the public;
- developing probability of causation assessments for workers and for compensation;
- assessing the impacts of radiation accidents;
- estimating the effects that radiation has had on special groups, such as fetuses and young children; and
- estimating potential affects of medical radiation exposures.

Dr. Shore then focused on a number of issues and challenges that remain to be resolved in RERF's future including:

- what we expect to learn about radiation and cancer in the next 20 years;
- cancer and non-cancer research in the clinical AHS;
- studies of the relationship between radiation and circulatory disorders;
- radiation and heritable diseases in the F_1 generation; and
- basic research on radiation such as susceptibility to disease and to radiogenic cancers, including genetic, immunological, and phenotypic aspects of radiation and aging, and transgenerational effects.

He concluded by emphasizing that the AHS provides a rich biospecimen resource permitting innovative studies of radiation and disease and the potential for strategic collaborations for ideas, expertise, and access to new techniques and methodologies. RERF has a unique opportunity to continue to provide essential new information on radiation risks that is vital given the world's widespread and increasing use of radiation.

Dr. Evan Douple, Scholar in the National Academies' NRSB and the Responsible Staff Officer for NAS' support role in RERF for more than 10 years, closed the symposium by thanking the speakers, the attendees, and the sponsors, including the Presidents Committee of the National Academies, the Environmental Protection Agency, and the Department of Energy—and recognized Dr. Joseph Weiss in the audience who has been the DOE's Project Manager for RERF for more than 10 years. He reminded the audience that the symposium was dedicated to all of the current and past employees of ABCC-RERF and the A-bomb survivors—such as Mr. Tsuboi—whose contributions and participation in the studies were essential to the success of ABCC-RERF. And he acknowledged the presence in the audience of **Mrs. Cathie Berkley** and **Mr. David Williams**, who have been intimately associated with the National Academy of Sciences support of the ABCC-RERF project, each for more than 40 years. Finally, he turned to

the symbol that was chosen for the banners on the stage and the symposium program cover and posters—the 380 year-old bonsai that had survived the A-bomb in Hiroshima. A delegation from RERF, including scientists, directors, and Mr. Tsuboi visited the U.S. National Arboretum in Washington the day before the symposium to view the actual tree. It stands at the entrance to the Arboretum and is a dignified testament to Japan-U.S. cooperation and to peace, beauty, and survival.

With the "Yamaki's Pine" at the U.S. National Arboretum in Washington, DC, (from left) Dr. Kazunori Kodama, Dr. & Mrs. Itsuzo Shigematsu, Mr. Sunao Tsuboi, Dr. Toshiteru Okubo, Mr. Takanobu Teramoto, and Dr. Saeko Fujiwara

RERF Chairman Meets with the U.S. Secretary of Energy

Dr. Toshiteru Okubo, RERF Chairman, paid a courtesy visit to Dr. Samuel Wright Bodman, the 11th U.S. Secretary of Energy, on December 13, 2007, the day following the Beebe Symposium. Dr. Bodman, who received a bachelor's degree in chemical engineering from Cornell University and a doctor of science degree from the Massachusetts Institute of Technology, has had a long and sincere interest in RERF's research, and dialogue between the two continued for more than ten minutes.

Dr. Toshiteru Okubo (at left) presenting Dr. Samuel Bodman with an aerial photo of RERF Hiroshima Laboratory

Arrangements for the courtesy visit were made by Mr. Glenn Podonsky, Chief Health, Safety and Security Officer, Dr. Patricia Worthington, Director for Health and Safety, and Dr. Joseph Weiss, Japan Program Manager, Office of International Health Studies, Department of Energy (DOE). This was the first visit with the DOE Secretary by an RERF chairman since the inauguration of RERF in 1975. Chairman Okubo presented Dr. Bodman with an aerial photo of RERF's Hiroshima Laboratory as a memory of the occasion, which Dr. Bodman unwrapped on the spot and hung on the wall of his office.

Staff News

The RERF scientific staff continues to evolve with new recruitments, retirements, and visiting scientists. During the period of April 2007 to March 2008 there have been three new additions to the scientific staff, along with three departures. In addition, two long-term employees retired but were rehired under new contracts of employment.

Dr. Nobuko Sera joined the Division of Internal Medicine, Department of Clinical Studies, in Nagasaki, in April 2007, as a fixed-term research scientist. She came from the Nagasaki University Graduate School of Biomedical Sciences and Mitsubishi Hospital. **Dr. Susan M. Geyer** joined the Department of Statistics in June 2007 as an Associate Senior Scientist. She had been working at the Mayo Clinic in Rochester, Minnesota and brings valuable expertise in analyzing biological data, including high-dimensional data analyses and bioinformatics. Her advice and participation in RERF research will be very important as RERF enters the 'omic revolution of bioresearch and she was instrumental in working with the Chief of Statistics, Dr. Phil Ross, and the RERF department chiefs in planning a Bioinformatics Symposium held March 24–25, 2008.

Dr. Thomas M. Seed resigned as Associate Chief of Research in December 2007 and he returned to his home in Bethesda, Maryland. Dr. Seed has had a very positive impact on RERF through his oversight of the Genetics and Radiobiology/Molecular Epidemiology Departments and chairing of the Scientific Reports Review Committee and the Biological Samples Committee (BSC). Before he left RERF he was instrumental in working with Dr. Kei Nakachi to organize a major symposium held at RERF in November 2007 in a collaboration between RERF and the U.S. National Institute of Allergies and Infectious Diseases (NIAID) on the subject of Radiation and Age-associated Immunosenescence (see meeting report on page 20). He also prepared a BSC report that summarizes the status of RERF biosamples and makes important recommendations regarding this precious RERF resource.

Dr. Seed was replaced in January 2008 by **Dr. Evan B. Douple**. Dr. Douple had been directly involved in the RERF for more than 10 years, with responsibility for the National Academy of Sciences (NAS) role in supporting RERF, most recently as a Scholar in the National Academies, and prior to that, as director of the Board on Radiation Effects Research with involvement in the most recent BEIR studies. While he had visited RERF several times and was quite familiar with RERF research and scientists, he is now pleased to be able to help provide support as an RERF employee living here in Japan. Prior to joining NAS in 1992, Dr. Douple had been a radiobiologist and Professor of Medicine at Dartmouth Medical School for more than 20 years.

During this past year long-term RERF employee **Dr. Kazunori Kodama** retired as Chief of the Department of Epidemiology to focus on his role as Chief Scientist. **Dr. Fumiyoshi Kasagi** was appointed Acting Chief. In addition, **Dr. Jun-ichi Asakawa** was appointed Acting Chief of the Genetics Department in December 2007, replacing **Dr. Norio Takahashi** who faced mandatory retirement in June 2007 but who was reemployed.

Other departures included **Dr. Frederic A. A. Lagarde** who had been employed in the Department of Statistics since June 2003 and who resigned in October 2007 and returned to his native country of France. **Dr. Hidetaka Eguchi** resigned from the Department of Radiobiology/Molecular Epidemiology in September 2007 where he had been contributing important work in the area of molecular biological studies since July 2001 (see his excellent review article on the molecular features of colorectal cancer in the *Update* Volume 18). Dr. Eguchi has joined the faculty of Saitama Medical University.

Student Researchers

While RERF scientists have been involved every year with training students and short-term visitors, two students have spent several weeks in 2008 in the RERF Department of Statistics working on their Ph.D. dissertations. **Carmen D. Tekwe** is from the Department of Biostatistics in the School of Public Health and Health Professions at the State University of New York at Buffalo. She is working with her advisor, Professor Randy L. Carter (a former RERF scientist in the 1980s) on the application of generalized multiple indicators multiple causes measurement error (G-MIMIC ME) models to dose uncertainties in RERF data. **Guangquan "Philip" Li** is from the Department of Epidemiology and Public Health, at the Imperial College London Faculty of Medicine, St. Mary's Campus. He is working with his advisor Dr. Mark P. Little on a Bayesian approach to modeling of measurement error using RERF data.

Gilbert W. Beebe Fellows

The Gilbert W. Beebe Fellowships were established in order to provide an opportunity for scientists to work at RERF in order to become more familiar with RERF's research and to explore the fields of radiation epidemiology and statistics. The Fellowships are supported by the National Academy of Sciences in collaboration with the U.S. National Cancer Institute's Radiation Epidemiology Branch using funds provided by the U.S. Department of Energy. During the past year, two Beebe Fellows were supported and conducted research at RERF. **Dr. Dino Samartzis**, from Chicago, Illinois, used the Life Span Study (LSS) cohort to estimate the excess relative risk per gray of ionizing radiation exposure in the development of bone sarcomas. **Dr. Byron S. Kennedy** continued a long tradition of scientists from Yale University working at RERF since he had received an M.P.H. and Ph.D. in Chronic Disease Epidemiology and an M.D. from Yale. He came to RERF after completing a Postdoctoral Fellowship in Cardiovascular Epidemiology at Stanford University and an Internship in Family Medicine at Georgetown University's Providence Hospital. At RERF he is working on the patterns and predictors of risk of esophageal and gastric cancers in the RERF LSS cohort.

2008 Distinguished Lecture Series

RERF initiated a new Distinguished Lecture Series and was fortunate to have its first two lecturers in 2008. In addition to delivering lectures, the distinguished scientists spend time visiting with RERF scientists and they receive briefings regarding the latest results of RERF research. **Dr. Andre Bouville**, Senior Radiation Physicist, Chornobyl Research Unit, Division of Cancer Epidemiology and Genetics, U.S. National Cancer Institute, visited January 21, 2008. He delivered a lecture "Radiation dosimetry for use in epidemiologic studies: Current research program at the U.S. National Cancer Institute."

On February 12, **Dr. John D. Boice, Jr.** visited RERF and delivered a lecture entitled "Genetic consequences of cancer treatments: An international study of the children of cancer survivors." Dr. Boice is from the International Epidemiology Institute and is also a Professor of Medicine at Vanderbilt University Medical Center and the Vanderbilt-Ingram Cancer Center.

Honors and Awards Received by RERF Scientists

Poster Prize at the Fifth International Congress on Vascular Dementia

Michiko Yamada, Assistant Chief
Department of Clinical Studies, Hiroshima

The Fifth International Congress on Vascular Dementia was held in Budapest, Hungary, November 8-11, 2007. I participated in this congress to make a presentation titled "Incidence and risks of dementia in Japanese women: Adult Health Study," which was awarded second prize for posters. Modern society is populated with increased numbers of elderly, which has made them important subjects in terms of public-health research into the possibilities of early diagnosis, treatment/care, and prevention of dementia. The congress is held biennially, and with each meeting, the number of participants increases. At this latest congress, there were increased numbers of participants from China, South Korea, and Thailand, presenting a good opportunity to learn about relevant studies in the Asian region. Japanese participants, however, represented a minority, at about 20 individuals in total.

My presentation at the above congress can be summarized as follows: "Analytical result of risk factors for dementia supports usefulness of blood-pressure control and physical strength improvement in preventing dementia." We have been studying dementia within the RERF's Adult Health Study based on Research Protocol 5-92 since 1992. In RERF's study on dementia, we examine cognitive abilities like memory and orientation (ability to understand time and place), and for persons suspected of declining cognitive abilities, neurologists provide a more detailed examination for determining status of dementia incidence. Diagnosing dementia requires many data based on cognitive ability examinations, interviews with caregivers, neurologists' diagnoses, CT/MRI data, and so on. This study has been made possible with support from physicians of Hiroshima University's Third Department of Internal Medicine

and other researchers at other medical organizations, in addition to support from RERF employees. I would like to take this opportunity to express my sincere thanks to my co-presenter Yasuyo Mimori of Hiroshima University, in particular, and other related individuals.

Finally, I think the layout and coloring of the presentation materials were important factors in the poster prize evaluation. Please let me conclude this article by adding that support from Ms. Hiromi Tsuji, a staff member of the Department of Clinical Studies, was indispensable in our receiving the prize.

Young Investigator Award from the Japan Epidemiological Association

Nobuo Nishi, Assistant Chief
Department of Epidemiology, Hiroshima

I had the honor of receiving the Young Investigator Award at the 18th annual scientific meeting of the Japan Epidemiological Association, held in Tokyo on January 25 and 26, for a study titled "Regional differences in stroke mortality using multilevel modeling." The award is intended to encourage continued work by promising young and middle-aged researchers who conduct excellent research in epidemiology, but awardees must be under the age of 45 at the time of the application deadline (June 30). I consider myself very fortunate that I did not miss my last chance to win this award, since I will turn 45 this coming May.

At the awards ceremony, a professor at Nagoya University, another winner of the award, and I each received a certificate and a commemorative gift from Dr. Kazunori Kodama, trustee head of the association. In fact, as chief of secretariat of the association, I was responsible for choosing the new commemorative gift last year, when the secretariat office was relocated to RERF. I eventually became the first winner of this gift, an acrylic plaque of very sophisticated design, although that might sound as if I am blowing my own horn.

The research for which I received the award elucidated regional differences in stroke mortality by population size using multilevel modeling based on the study NIPPON DATA (participants of which are aged 30 years or older and selected from 300 regions throughout Japan, both of which were randomly selected). I hope that younger research scientists win this award in the future for research based on RERF's Life Span Study, Adult Health Study, and other study cohorts.

I reported in the last issue of the *RERF Update* published in 2007 that I was awarded a poster prize at the 28th annual meeting of the International Association of Cancer Registries held in November 2006. Now that I have received prizes from both international and national associations, I guess my next goal is to win a Hiroshima local prize. I would like to conclude this report by asking for your continuous support and guidance.

RERF–NIAID Workshop: Radiation and Age-associated Immunosenescence

27–29 November 2007, Hiroshima Laboratory

Yoichiro Kusunoki, Assistant Chief
Department of Radiobiology/Molecular Epidemiology

Various changes in the immune system become apparent with aging, and many of these changes are related to predisposition of aged people to a wide variety of diseases. For example, reduction in the number and function of T lymphocytes with aging causes decrease in resistance to pathogenic microbes and exacerbation of infectious diseases and chronic inflammation. One of the impending issues in medical care of aged people is how immunological function reduced in the aging process can be recovered and how such recovery can lead to prevention and treatment of infectious diseases. Currently, there are concerns about emerging infectious diseases, such as new types of influenza, and infection from multidrug-resistant pathogenic bacteria, and therefore strong demand exists for studies on mechanisms of immunological aging and ways to recover immune function so that effective measures can be established to protect the elderly from such disease. These studies are also expected to help reduce the risk of infectious diseases among patients whose immune systems have been compromised due to radiotherapy and chemotherapy.

In view of the above, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) has been inviting research institutes throughout the world to participate in collaborative studies to promote research on immunological aging. On the other hand, RERF studies have shown reduction in function and number of blood T lymphocytes and increase in inflammatory protein levels with increase of A-bomb radiation dose, suggesting the possibility that immunological aging in A-bomb survivors has been accelerated by radiation exposure. Dr. Thomas Seed, former Associate Chief of Research, who resigned from RERF in December 2007, planned this workshop to gauge the possibility of promoting RERF studies on immunological aging through collaborative studies with other research institutes. RERF invited to the workshop three researchers from NIAID, five researchers from other U.S. research institutes, and two researchers from within Japan.

Following presentations of RERF's overall research by RERF directors, the associate chief of research, chief scientists, and department chiefs, outlines of ongoing collaborative studies at NIAID, and prospects for studies on immunological aging were presented by Drs. Richard Hatchett, Joseph Kaminski, and Francesca Macchiarini (all from NIAID). Our honest reaction at that point of the workshop was to wonder what would be expected of RERF's researchers, who have promoted immunological studies on A-bomb survivors on their own, if RERF were to embark on such international collaborative studies. Presentations were then made by Drs. Nancy Manley (University of Georgia), Yoko Hirabayashi (Japanese National Institute of Health Sciences), and Koji Yasutomo (Tokushima University) on "hematopoiesis and T-cell development," Drs. Nan-ping Weng (U.S. National Institute on Aging), Janko Nikolich-Zügich (Oregon Health and Science University), and Yoichiro Kusunoki (RERF) on "breakdown and reconstitution of the immune system," and Drs. Gregory Sempowski (Duke University) and Marcel van den Brink (Sloan-Kettering Cancer Center) on "molecular approaches to enhancing immune response," which were followed by discussion. Vigorous debate continued thereafter on mechanisms of immunological aging and reconstitution, indicating great interest in this topic. The discussion mainly focused on factors involved in reduction of T-cell mediated immune competence with aging and medical procedures for enhancement of this competence. We believe that the discussion prompted participants to understand and support our studies that have been carried out based on the assumption of immunological aging in A-bomb survivors.

This was followed by a proposal put forth by the Department of Radiobiology/Molecular Epidemiology regarding collaborative studies on the issue of radiation and immunological aging, the main focus of this workshop. First, Department Chief Kei Nakachi explained the research framework of that department. Next, Assistant Department Chief Kusunoki proposed research studying hematopoietic stem cells and dendritic cells. Because it has been suggested that genetic instability is involved in age-related reduction in function of hematopoietic stem cells, the producers of various kinds of immune cells, genetic instability of hematopoietic stem cells induced by radiation is considered to be one of the possible factors in immunological aging among A-bomb survivors. Thus, it was considered necessary to conduct studies on this possibility. Dendritic cells are known to play important roles at the begin-

ning of T-cell mediated immune response and in the mechanism of controlling this response. Therefore, the importance of studying the relationship between these cells and aging of T-cell immunity in A-bomb survivors was emphasized. Further, Dr. Tomonori Hayashi, Chief of the Immunology Laboratory, proposed development of a comprehensive scoring system for immune competence. His proposal represents an attempt at risk estimation of infectious and inflammatory diseases on an individual basis. Such risk estimation would be possible by collecting data on various immunological parameters based on results of cross-sectional and longitudinal studies of RERF Adult Health Study (AHS) subjects and stored biological samples and by conducting comprehensive evaluation of changes in immune response on the basis of radiation exposure status and aging. We obtained agreement from the workshop participants that the three research projects proposed at this workshop would be studies incorporating the newest information on immunobiology and genomic science based on the AHS results and immunological studies conducted at RERF.

Following the proposals by the Department of Radiobiology/Molecular Epidemiology, Dr. Seed explained RERF's stored biological specimens, and Drs. Yoshiaki Kodama, Jun-ichi Asakawa, and Norio Takahashi from the Department of Genetics introduced the molecular genetic techniques used at RERF. In addition, workshop participants were briefed on research projects at each department and taken on a tour of the facilities to ensure that they would have a better understanding of RERF's overall research activities. Lastly, the participants were divided into groups for discussion of details relating to the three research projects proposed for collaborative studies on radiation and immunological aging ("hematopoietic stem cells," "dendritic cells," and "comprehensive scoring system for immune competence"). Results of these group discussions were then summarized at a general session. Through these discussions, opinions based on specialized fields were exchanged vigorously concerning technical problems and possible directions for the respective research projects, and ideas for the development of plans aiming at collaborative studies were strongly supported. In addition to these research projects, several researchers proposed a new project to assess immune response to flu vaccinations in AHS participants. For any of these research projects, the cooperation and support of both RERF directors and many RERF researchers will be necessary. We hope to conduct further discussion in the future.

Lastly, we would like to express appreciation to the RERF directors who provided the opportunity for holding this workshop, the researchers who made such valuable research presentations and participated in the workshop discussion, and the staff members who cooperated in organizing this workshop.

Ophthalmologic Studies in Atomic-bomb Survivors

Kazuo Neriishi,[a] Tomoko Yokoyama,[b] Michiya Takamatsu,[b] Takeshi Kumagami,[c] Masafumi Uematsu,[c] Eiko Tsuiki,[c] Atsushi Minamoto,[d] Yoshiaki Kiuchi,[b] Takashi Kitaoka,[c] Eiji Nakashima,[e] Ayumi Hida,[f] Saeko Fujiwara,[a] Masazumi Akahosh,[f] Roy Shore[g]

Departments of [a]Clinical Studies (Hiroshima), [e]Statistics, and [f]Clinical Studies (Nagasaki), and [g]Vice Chairman, Radiation Effects Research Foundation; [b]Department of Ophthalmology and Visual Sciences, Graduate School of Biomedical Sciences, Hiroshima University; [c]Department of Ophthalmology and Visual Sciences, Graduate School of Biomedical Sciences, Nagasaki University; [d]Minamoto Eye Clinic

Synopsis: Until now, the radiation protection community has assumed that only high doses of 2 Gy or more cause cataracts, but new data from the atomic-bomb (A-bomb) survivors suggest that the dose threshold for both minor opacities and vision-limiting cataracts may be below 1 Gy. That important finding is causing major risk assessment groups to consider re-evaluating their guidelines for permissible occupational and medical exposures to the eye.

A well-known deterministic effect of ionizing radiation exposure to the eye is the formation of opacities of the lens, cataracts. At the Atomic Bomb Casualty Commission (ABCC), and later at the Radiation Effects Research Foundation (RERF), three major cataract studies based on ophthalmoscopic and slit-lamp examinations were conducted. During 1963–1964, Nefzger and colleagues found a significant radiation dose response for posterior subcapsular cataracts,[1] as did Choshi and colleagues in a later study in 1978–1980.[2] Otake and Schull reported evidence for a dose threshold,[3] based on the Nefzger study.[1] In 2000–2002, Minamoto and colleagues found a statistically significant radiation dose response for posterior subcapsular and cortical cataracts with no clear evidence of a dose threshold.[4] This article describes the recent reanalysis of the ABCC-RERF data with a focus on the issue of whether there is evidence for a dose-effect threshold and, if so, the estimated threshold dose.[5]

Slit-lamp examinations were performed on A-bomb survivors based upon an RERF Research Protocol (RP 3-00).[6] Results from the examination of 837 A-bomb survivors during 2000–2002 revealed a significant radiation dose response for posterior subcapsular cataract, cortical cataract, and retinal arteriosclerosis.[4] Furthermore, in the reanalysis of 730 A-bomb survivors, threshold estimates were 0.6 Sv (90% confidence interval [CI], <0.0 Sv–1.2 Sv) and 0.7 Sv (90% CI, <0.0 Sv–2.8 Sv) for cortical cataract and posterior subcapsular opacity, respectively, which are not significantly different from 0 Sv ($p > 0.30$) but were also compatible with a dose threshold of >1 Gy (Table 1). Detailed analyses applying a no-threshold model showed no dose responses ($p > 0.40$) for nuclear color and nuclear opacity. Cortical cataract showed a significant dose effect ($p = 0.002$) with an odds ratio (OR) at 1 Sv of 1.30 (95% CI, 1.10–1.53) with no dose-effect modifiers. Posterior subcapsular opacity showed a significant dose effect ($p < 0.001$), with an OR at 1 Sv of 1.44 for an age at exposure of 10 years (95% CI, 1.19–1.73). That dose effect decreased significantly with increasing age at exposure ($p = 0.02$). The results of re-analysis in this study are quite similar to that of the original study.[4] No dose response was observed for survivors exposed *in utero* ($p >$ 0.20), though this study had quite limited statistical

Table 1. Thresholds in studies in A-bomb survivors

Type of study	Threshold dose (Gy)	90% CI
Slit-lamp examination	0.6 for cortical cataract	<0.0–1.2
	0.7 for posterior subcapsular cataract	<0.0–2.8
Postoperative cataract cases	0.1	<0–0.8

power because of the small number of study members with high doses.

Similar evidence has been reported from studies of cohorts other than A-bomb survivors. A study of children living in the vicinity of the Chernobyl accident reported a subsequent excess of cataracts.[7] A Swedish follow-up study of infants treated with radium plaques for hemangiomas, reported an OR at 1 Gy of 1.49 (95% CI, 1.07–2.08).[8] A study of 295 astronauts participating in NASA's longitudinal study of astronaut health reported that relatively low doses of space radiation might predispose crew to an increased incidence and early appearance of cataracts.[9] A recent study of Chernobyl clean-up workers reported significant risk estimates very similar to the one in the present study (OR at 1 Gy of 1.42 for Stage 1 posterior subcapsular cataracts and 1.51 for Stage 1 cortical cataracts), and also found estimates of the dose threshold that were statistically inconsistent with values over 0.7 Gy.[10] The 2007 ICRP publication numbered 103[11] summarizes that "… the lens of the eye may be more radiosensitive than previously considered. In particular, among both A-bomb survivors (Minamoto *et al*., 2004) and a group of children treated for skin hemangioma (Hall *et al*., 1999), there is evidence of excesses of both cortical and posterior subcapsular cataract at doses somewhat lower than expected."[11]

However, none of the above studies reported evidence of radiation effects on vision-impairing cataracts, because they were based on slit-lamp microscope examinations and they excluded many of the cataract cases of greatest interest, namely, the most severe cases in whom lenses had been removed. Therefore, we evaluated evidence regarding the radiation dose response for clinically significant cataracts, namely, those that were surgically removed, on the assumption that the lensectomies in most cases represent vision-impairing cataracts.[12] We conducted a logistic regression analysis to estimate the dose response and used a likelihood profile procedure to determine the best-fitting threshold model among 3,761 A-bomb survivors who underwent medical examinations during 2000–2002, for whom radiation dose estimates were available. These data included 479 operative cataract cases. The analyses indicated a statistically significant dose-response increase in the prevalence of operative cataracts (OR, 1.39; CI, 1.24–1.55) at 1 Gy, with no indication of upward curvature in the dose response. (Please see Figure 5 of Dr. Saeko Fujiwara's presentation on the Adult Health Study in the article of the Sixth Annual Gilbert W. Beebe Symposium, page 10 in this issue of *Update*.) The dose response was suggestive when the restricted dose range of 0 to 1 Gy was examined. A non-significant dose threshold of 0.1 Gy (95% CI, <0–0.8) was found (Table 1). The prevalence of postoperative cataracts in A-bomb survivors increased significantly with A-bomb radiation dose. The best estimate (0.1 Gy) and upper bound (0.8 Gy) of the dose threshold for operative cataract prevalence was much lower than the threshold of 2–5 Gy usually assumed by the radiation protection community and was statistically compatible with no threshold at all.

Why did we observe results different from previous ones? Otake and Schull[3] had conducted analyses of A-bomb cataract data that have often been cited as showing a dose threshold. They reported that dose linearity provided an inadequate fit to their data, while a model incorporating separate dose thresholds for gamma and neutron doses provided a good fit. Specifically, the estimates of the dose thresholds were 0.73 (95% CI, 0–1.39) Gy for gamma and 0.06 (95% CI, 0–0.16) Gy for neutrons. There are a few possible explanations for the apparent dose response and threshold differences between the current study and theirs. Their analyses were based on data collected in the early 1960s,[1] about 20 years after the bombings, and used the older DS86 dosimetry system that was available in 1990. Conceivably, the types of early cataract observed in the 1960s differed from those observed in this study. Although it is not possible to determine which types of cataract were present then, visual impairment in the elderly is caused mainly by posterior subcapsular or cortical cataracts, and these showed significant dose responses in our recent study.[5]

Another possibility is that age at exposure may relate to the magnitude of a dose threshold; the persons developing cataracts in the 1960s study were mainly those who were relatively old at the time of the bombing (ATB), whereas the present study subjects are primarily those who were young ATB since the older cohort members have died. Other possible differences include improvements over time in the dosimetry[13] and statistical methodology. On the other hand, the Otake estimates of dose thresholds were also compatible with no threshold (i.e., the CI included zero dose). Although Otake's interpretation of a threshold for cataracts in A-bomb survivors has been widely accepted,[14] the evidence in the Minamoto study, which used an ophthalmologic slit-lamp examination with adequate pupil dilation and the more sophisticated LOCS II diagnostic classification system,[15] is more consistent with the results generated in the study of more severe (postoperative) cataracts.

However, there are many unanswered questions. Some examples of questions to be addressed include: (1) Is the dose response in the LOCS II classification identical with that in a radiation-specific classification? (2) Does the association of cataract formation with radiation dose progress with time? (3) Is there any predictive and mechanistic factor(s) in the radiation-associated cataract formation? (4) Does

radiation have transgenerational effects on the lens? (5) Is there any relationship with other ophthalmologic findings such as arteriolosclerosis and macular degeneration?

As for radiation-specific cataract classification, we are using the Merriam-Focht method, which is believed to be radiation specific,[16] and stored lens images, to re-evaluate RERF data. Stored lens images of A-bomb survivors have great potential in cataract research, not only for the above-mentioned re-evaluation and/or follow-up of the cases, but also for standardization of analyses in training new ophthalmologic researchers. As for possible progression of the cataracts, Klein *et al*. have shown that small posterior subcapsular cataracts observed in middle age dramatically increase the need for lens implants at later ages.[17] We tried to analyze the impact of radiation exposure on cataract latency using incident cases of cataract surgery. However, information on cataract incidence was available only for 1988–2000. The results indicated a 0.18-year acceleration of cataract surgery per Gy which was non-significant (p = 0.30). A longer observation period and additional aging of the potentially most sensitive population (the youngest survivors were only 55 years old in 2000, while the average age of cataract surgery was 72.9) may provide more meaningful data on cataract acceleration by radiation.

In addition, we have a plan to conduct a follow-up study on cases who were examined with a slit-lamp microscope during 2000–2002 by comparing those stored lens digital images with new ones we obtain. This study would also provide information on several risk factors indicative of predictive and mechanistic factor(s). As for genetic predisposition, a study on ATM mutations, in which differential radiosensitivity has been observed in mice,[18,19] is under way in A-bomb survivors. Furthermore, we are starting a project to collect and store lens tissues removed from A-bomb survivors for future use, because postoperative cases among A-bomb survivors showed a strong association with A-bomb radiation,[12] and the removed cataract tissues are likely to have important information on molecular biological change in radiation cataractogenesis.[20] We were very fortunate to obtain generous cooperation from ophthalmologist groups in universities and ophthalmologist associations in Hiroshima and Nagasaki, respectively. As for possible transgenerational effects of radiation on the lens, cataract studies on children of the A-bomb survivors (RP 8-02)[21] conducted during 2002–2006 also are being analyzed.

As for other ophthalmologic findings, retinal arteriolosclerosis has been recognized to have an association with radiation dose in A-bomb survivors[4] as well as in other radiation-exposed populations.[22,23] Quantitative analysis of retinal arteriolosclerosis and macular degeneration is being planned because radiation-associated arteriosclerosis has great potential influence on retinal function, including the optic nerve[24] and macula.[25] A glaucoma prevalence study (RP 1-05)[26] started in 2006 will finish examinations by September 2008 and will then be analyzed.

In conclusion, recent cataract studies in A-bomb survivors have revealed new findings, such as a dose response in cortical cataract and, perhaps more importantly, results suggesting a possibility for a lower threshold, both in cortical and posterior subcapsular cataract, compared to previous estimates. We also expect more mechanistic and predictive findings in new studies in the near future.

References

1. Nefzger MD, Miller RJ, Fujino T. Eye findings in atomic bomb survivors of Hiroshima and Nagasaki: 1963–1964. *Am J Epidemiol* 89:129-38, 1969.
2. Choshi K, Takaku I, Mishima HK, Takase T, Neriishi S, Finch SC, Otake M. Ophthalmologic changes related to radiation exposure and age in the Adult Health Study sample, Hiroshima and Nagasaki. *Radiat Res* 96:560-79, 1983.
3. Otake M, Schull WJ. Radiation-related posterior lenticular opacities in Hiroshima and Nagasaki atomic bomb survivors based on the DS86 dosimetry system. *Radiat Res* 121:3-13, 1990.
4. 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* 80:339-45, 2004.
5. Minamoto A, Taniguchi H, Mishima HK, Amemiya T, Nakashima E, Neriishi K, Hida A, Fujiwara S, Suzuki G, Akahoshi M. Ophthalmologic study of atomic bomb survivors. RERF Research Protocol 3-00, Radiation Effects Research Foundation, 2000.
6. Nakashima E, Neriishi K, Minamoto A. A reanalysis of atomic-bomb cataract data, 2000–2002: A threshold analysis. *Health Phys* 90:154-60, 2006.
7. Day R, Gorin MB, Eller AW. Prevalence of lens changes in Ukrainian children residing around Chernobyl. *Health Phys* 68:632-42, 1995.

8. Hall P, Granath F, Lundell M, Olsson K, Holm LE. Lenticular opacities in individuals exposed to ionizing radiation in infancy. *Radiat Res* 152:190-5, 1999.

9. Cucinotta FA, Manuel FK, Jones J, Iszard G, Murrey J, Djojonegro B, Wear M. Space radiation and cataracts in astronauts. *Radiat Res* 156:460-6, 2001.

10. Worgul BV, Kundiyev YI, Sergiyenko NM, Chumak VV, Vitte PM, Medvedovsky C, Bakhanova EV, Junk AK, Kyrychenko OY, Musijachenko NV, Shylo SA, Vitte OP, Xu S, Xue X, Shore RE. Cataracts among Chernobyl clean-up workers: Implications regarding permissible eye exposures. *Radiat Res* 167:233-43, 2007.

11. International Commission on Radiological Protection. 2007 Recommendations of the International Commission on Radiological Protection. *Ann ICRP* 37 (Publication 103):168-9, 2007

12. Neriishi K, Nakashima E, Minamoto A, Fujiwara S, Akahoshi M, Mishima HK, Kitaoka T, Shore RE. Postoperative cataract cases among atomic bomb survivors: Radiation dose response and threshold. *Radiat Res* 168:404-8, 2007.

13. Young RW, Kerr GD, ed. Reassessment of the Atomic Bomb Radiation Dosimetry for Hiroshima and Nagasaki—Dosimetry System 2002. Radiation Effects Research Foundation, 2005.

14. National Council on Radiation Protection and Measurements. Guidance on Radiation Received in Space Activities. *NCRP Report No. 98*, 1989.

15. Chylack LT, Leske C, Mccarthy D, Khu P, Kashiwagi T, Sperduto R. Lens opacity classification system II (LOCS II). *Arch Ophthalmol* 107:991-7, 1989.

16. Worgul BV, Merriam GR Jr, Medvedovsky C. Cortical cataract development—An expression of primary damage to the lens epithelium. *Lens Eye Toxic Res* 6:559-71, 1989.

17. Klein BE, Klein R, Linton KL. Prevalence of age-related lens opacities in a population. The Beaver Dam Eye Study. *Ophthalmology* 99:546-52, 1992.

18. Worgul BV, Smilenov L, Brenner DJ, Junk A, Zhou W, Hall EJ. Atm heterozygous mice are more sensitive to radiation-induced cataracts than are their wild-type counterparts. *Proc Natl Acad Sci USA* 99(15):9836-9, 2002.

19. Kleiman NJ, David J, Elliston CD, Hopkins KM, Smilenov LB, Brenner DJ, Worgul BV, Hall EJ, Lieberman HB. Mrad9 and atm haploinsufficiency enhance spontaneous and X-ray-induced cataractogenesis in mice. *Radiat Res* 168(5):567-73, 2007.

20. Chang PY, Bjornstad KA, Rosen CJ, Lin S, Blakely EA. Particle radiation alters expression of matrix metalloproteases resulting in ECM remodeling in human lens cells. *Radiat Environ Biophys* 46(2):187-94, 2007.

21. Minamoto A, Kumagami T, Yoshitani N, Mishima HK, Amemiya T, Nakashima E, Neriishi K, Hida A, Fujiwara S, Suzuki G, Akahoshi M. Ophthalmologic study of children of atomic bomb survivors (Addendum to RP 1-02). RERF Research Protocol 8-02, Radiation Effects Research Foundation, 2002.

22. Peiretti E, Slakter JS, Wu S, Iranmanesh R, Yannuzzi LA. Late effect of external eye irradiation on choroidal circulation. *Eur J Ophthalmol* 16(4):637-40, 2006.

23. Robertson DM, Buettner H, Gorman CA, Garrity JA, Fatourechi V, Bahn RS, Petersen IA, Stafford SL, Earle JD, Forbes GS, Kline RW, Bergstralh EJ, Offord KP, Rademacher DM, Stanley NM, Bartley GB. Retinal microvascular abnormalities in patients treated with external radiation for graves ophthalmopathy. *Arch Ophthalmol* 121(5):652-7, 2003.

24. Flammer J, Orgul S, Costa VP, Orzalesi N, Krieglstein GK, Serra LM, Renard JP, Stefansson E. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res* 21(4):359-93, 2002.

25. Metelitsina TI, Grunwald JE, DuPont JC, Ying GS, Brucker AJ, Dunaief JL. Foveolar choroidal circulation and choroidal neovascularization in age-related macular degeneration. *Invest Ophthalmol Vis Sci* 49(1):358-63, 2008.

26. Minamoto A, Tsukamoto H, Yokoyama T, Tsuiki E, Uematsu M, Ogawa T, Mishima HK, Kitaoka T, Nakashima E, Neriishi K, Hida A, Fujiwara S, Akahoshi M. Glaucoma study in atomic bomb survivors. RERF Research Protocol 1-05, Radiation Effects Research Foundation, 2005.

In Remembrance of Dr. Howard Hamilton (1918–2007)

Akio Awa, Former Associate Chief of Research

On the afternoon of April 30, 2007, Dr. Dale Preston, who lives in California, left a message for me at my office at the Oak Ridge Associated Universities (ORAU). I called him back and found that Dr. Howard Hamilton had passed away on April 27 in Falls Church, Virginia, where he had lived since leaving Japan in 1986.

Dr. Hamilton joined ABCC in 1956 and worked at ABCC and RERF until 1983 when a mandatory retirement age was introduced for RERF researchers. Following his formal retirement he worked as a full time consultant to RERF until leaving Hiroshima and returning to Falls Church, a suburb of Washington, DC.

For most of his 30 years in Hiroshima, Dr. Hamilton served as chief of the Department of Clinical Laboratories and devoted considerable attention to improving the accuracy and maintaining the quality of hematological tests for Adult Health Study participants. He paid particularly close attention to insuring the consistency of the measurements from the Hiroshima and Nagasaki laboratories.

In addition to his managerial activites, Dr. Hamilton was an active researcher with an interest in molecular structural alterations in blood hemoglobin. He detected many molecular variants in study participants and published the findings in several international scientific journals. Dr. Hamilton also made substantive contributions to many other important ABCC-RERF research projects.

From Hokkaido University, I joined the Cytogenetics Laboratory, which was newly established at ABCC, in January 1967, more than 10 years after Dr. Hamilton had first begun to live in Hiroshima. I worked for him from the beginning, and collaborated closely with him for almost 20 years. I am still grateful for his presence in Hiroshima over that period. Most of the department chiefs at ABCC came to Hiroshima from the U.S. on two-year contracts. One disadvantage of that arrangement was that, every time a new department chief came, a new managerial system was introduced. On the other hand, since Dr. Hamilton lived in Japan permanently, researchers who worked under him were able to develop long-term perspectives, which was a great merit. I was fortunate to be able to engage in research under such circumstances. Dr. Hamilton contributed to the development of not only the Cytogenetics Laboratory but also the Biochemical Genetics Laboratory,

Dr. Howard Hamilton receiving the Hiroshima Governor's Cup after winning the 26th Hiroshima Tennis Competition (May 3, 1972)

which was jointly managed by Professor James Neel, who came from the University of Michigan. Dr. Hamilton's contribution to the Biochemical Genetics Laboratory should be given high marks as one of his unheralded achievements.

Dr. Hamilton's hobbies were varied (some say they were his main occupation). Many already have heard about them, so I will not cover his activities in detail here, but his performance of Kita-style Noh drama is widely known. I have heard that he once fell from the stage because he was so focused on his dancing. His collection of "Kumadori" (Kabuki actors' makeup printed on silk), which he obtained immediately after performances, was wonderful. That collection was only possible because he had been a friend of the performers for many years and thus had free entry to their dressing rooms. He also amassed an impressive collection of hand-carved noh-masks, many of which were created by living national treasures. I was really pleased that he published a book on Noh and Kabuki after he returned to the U.S. Dr. Hamilton was not only well versed in cultural arts but was also an excellent tennis player.

After he returned to the U.S., I visited him at his home many times in Falls Church, and sometimes stayed overnight. Until recently, I had been communicating with him by the Internet, but our communication stopped in the fall of 2006. In the meantime, Dr. Preston told me that Dr. Hamilton was sick.

I am in deep mourning since receiving the news

of the death of Howard, my supervisor and friend, who was a master of cultural arts and sports. I close this memorial note with hands clasped in prayer for the repose of his soul.

Editor's note: Dr. Dale L. Preston, former chief of RERF Department of Statistics, who knew Dr. Howard Hamilton well, conveyed his sincere condolences to us on the occasion of Dr. Hamilton's death. We would like to introduce below a part of his condolence message since it clearly reveals Dr. Hamilton's personality and his deep affection for Japanese traditional culture.

After his retirement and return to the U.S., Howard maintained a strong interest in Japanese culture. His home was filled with stunning traditional and contemporary Japanese arts and crafts, and he created a living space that captured the essence of the traditional Japanese culture he loved so much: a tatami room with hand-painted byobu, a soothing tokonoma, and exquisite shoji that opened to reveal a beautiful small garden that echoed some of Howard's beloved Kyoto gardens.

Howard's collections of Kumadori and Noh masks reflected his passion for and involvement in the world of Japanese traditional theater and dance. Howard's passion for these Japanese arts grew out of his earlier interest in opera and dance. Prior to coming to Japan, Howard had studied modern dance with Martha Graham and was a member of a choir organized by the renowned 20th century composer Paul Hindemith. In the late 1950s and throughout much of the 1960s, Howard traveled to Tokyo and Kyoto almost every month to see the latest Kabuki and Noh programs. He developed close ties to the leading actors and was allowed to photograph the performances. He amassed a collection of more than 10,000 carefully cataloged slides and carefully preserved all of the programs. In recent years Howard scanned these slides and developed a computer database that contains information on the play, actors, roles, theater, and performance date for each of these photos.

Until the end of his life, Howard maintained a strong interest in science in general and RERF research in particular while carrying on a lively correspondence with his many friends in the worlds of science and art around the world. I feel privileged and honored to have known Howard as a colleague and a friend for more than 20 of his remarkable 89 years. Even now, more than one year after his death, I often recall his impish grin and curmudgeonly wit.

Dr. Howard Hamilton performing a Noh dance at the RERF 10th Anniversary in April 1985

In Memory of Dr. Koji Takeshima (1917–2007)

Hideya Tamagaki, M.D.
Former ABCC Department of Medicine

When the Atomic Bomb Casualty Commission (ABCC) came into existence in 1947, the first department to be established was the Department of Genetics. The latter, like the Commission itself, began in borrowed space in the Hiroshima Red Cross Hospital in Senda-machi, where the damage from the atomic bombing still remained. However, as soon thereafter as possible the majority of the Commission's staff and activities moved to the Gaisenkan and a newly constructed clinic in Ujina, although the genetics program continued at the Red Cross Hospital. The genetics study to examine every newborn baby in Hiroshima and Nagasaki, the first major project by ABCC, was initiated in 1948. Direction of this program fell to a number of American scientists, the first being Dr. James V. Neel, who was followed by Dr. Ray C. Anderson, then Dr. William J. Schull, and finally Dr. Duncan McDonald. However, from the work perspective, the unifying force was not the American supervisors but Dr. Koji Takeshima, who had been engaged in this work from its beginning. He was fluent in Japanese and English and as a consequence he served as an intermediary between the American and Japanese staffs and as a good consultant for us, the young physicians, nurses, and secretaries involved in the examination of newborn babies.

His experience and career were ideal for that role. His parents, Hosui and Toyo Takeshima, migrated to Hawaii in 1909 at the urging of the Japanese Buddhists living in Olaa, a small community in the Puna district of the "big island." Koji, the third child, was born in Hawaii in 1917, and so were his two sisters, Kasumi (1911) and Ayame (1914). (His younger brother died in the A-bombing of Hiroshima.) He received his early education through the public schools in Hawaii and at the "terakoya" where his father and mother taught. Koji and his family returned to Saijo in Hiroshima Prefecture, his parents' ancestral home, when he was 13 years old. He received his medical education at Kyoto Prefectural Medical School from which he graduated in 1942. As a physician he was drafted into military service during the latter conflict, but he was not sent abroad. After the war, his affiliation with the Department of Surgery at the Hiroshima Red Cross Hospital was perhaps the start of his relationship with ABCC's Department of Genetics.

Collaborative relationships with outside individuals and organizations were essential if the aim of examining all of the newborns in Hiroshima and Nagasaki was to succeed. The cooperation of the midwives was especially important in this regard since, at that time in Japan, a midwife took care of an expectant mother for the duration of her pregnancy, and thus full-scale collaboration with the midwives' association was mandatory if this project, aimed at examination of 100% of newborn babies, was to succeed. The success the project achieved owed much to the warm personality and gentle demeanor of Dr. Takeshima, who often participated in general meetings with the several hundred midwives then practicing in Hiroshima. More often still he was a central figure in discussions with the officers of the association, particularly their diminutive president, Mrs. Setsuko Yamamoto, regarding issues that arose in the day-to-day interactions of the midwives with the genetics doctors. Sometimes, he had to translate English into Japanese, and when this occurred his Japanese more than met the standards of the most demanding linguist. It was neither lacking in appropriate honorifics nor overly deferential and unquestionably helped to establish relationships of trust. His skill as a mediator was not limited to the relationship with the midwives association; he was familiar with Japanese medical practices and could act as a facilitator in negotiations with the local medical and paramedical organizations. His ability was shown in the discussions seeking cooperation from the city government, the city and prefectural medical associations, and especially from obstetricians, with the goal of obtaining necessary information to be registered in mother-child handbooks and recorded in notifications of child delivery.

Dr. Koji Takeshima in 1990

Our initial health examinations were performed in the home, at which time we presented each family with a bar of "Lux" soap and a towel, which were well received and thus helpful in performing our work. These gifts were the warm-hearted idea of the

department chief and Dr. Takeshima, who appreciated the difficulties mothers were experiencing in child rearing in those times of scarcity.

I joined the department in 1949. I was pleased to find that the atmosphere of the workplace into which I was enrolled was very positive and the environment very lively. There were always about 20 young physicians, nurses, and secretaries, engaged in the study, and working there was truly enjoyable. Dr. Takeshima was our supervisor, and was in charge of reviewing our reports and providing us with guidance and instruction. He was a phenomenal mentor—simultaneously demanding but sensitive and understanding, which I suppose was one of the major reasons I enjoyed working there.

When the clinical study of pregnancy terminations in Hiroshima and Nagasaki ended in the Spring of 1954, Dr. Takeshima moved to ABCC's Department of Medicine, and I moved to the same department soon after. Shortly thereafter, it was decided that members of ABCC's Department of Medicine should join the U.S. survey team examining the crewmembers of a fishing vessel, the Lucky Dragon 5 (Daigo Fukuryu Maru), exposed to radiation from a hydrogen bomb test at Bikini Atoll. After the first survey team was dispatched, Dr. Takeshima and I were chosen to be members of the second team. I remember vividly flying in the cargo compartment of a military airplane, a DC-3, from Iwakuni to Haneda with him.

Subsequently, Dr. Takeshima studied at Duke University for three years for training in anesthesiology. He returned to Hiroshima to start his own medical and surgical practice in Saijo, had a hospital constructed, and later served as chairman of the nursing home for the elderly that was established on the property of his hospital. All of this was accomplished while he continued to maintain his father's temple until a suitable priest could be found.

Dr. Koji Takeshima receiving the ABCC Medallion presented to those who provided essential services to ABCC. (from left) ABCC Associate Director Hiroshi Maki, Dr. Howard Hamilton, Dr. Joseph Belsky, Dr. Koji Takeshima, ABCC Director George Darling, and Dr. Yasuyoshi Nishimaru (July 8, 1969)

Several years ago, I visited Dr. Takeshima in Saijo with Dr. Schull, a former chief of the Department of Genetics, who had been invited to be a speaker at the event commemorating the 30th anniversary of the establishment of RERF, ABCC's successor organization. It was a heart-warming occasion; the first time in several decades the three of us were together. We found Dr. Takeshima frail, but he was very alert, still spoke English easily, and was well informed on Buddhism, U.S.-Japan issues, and the economic and personnel problems private hospitals in Japan are currently obliged to address. I still remember him waving to us with tears in his eyes when we left his house. In November last year, he suddenly toppled over due to a heart attack as he worked, and passed away several days later at the age of 91.

In retrospect, it is clear that Dr. Takeshima was not only responsible for the clinical activities of the Department of Genetics but he was also extremely helpful in establishing an environment conducive to the success of the department's various projects. He never made much of this achievement; indeed he generally sought to keep it in the background and not clearly visible, but actually I feel that his efforts helped to establish an important framework for all of ABCC's programs, not merely those in genetics. He also contributed to the establishment of cooperative relationships with outside organizations, which was one of ABCC's most important goals in its early days. In my view, his contributions made possible many if not all of the research programs RERF would inherit almost thirty years after his employment.

He is survived by his wife, Reiko, two daughters, Yoshimi and Akemi, and two sons, Yuji and Yasuji. The family is engaged in the management and operation of their hospital and nursing home. His older sister, Ayame, who also worked at ABCC, returned to America and is in good health at present.

Editor's note: Dr. Hideya Tamagaki, who is 85 years old, was a physician in the Departments of Genetics and Medicine at the Atomic Bomb Casualty Commission (ABCC), the predecessor of the Radiation Effects Research Foundation (RERF), for 16 years starting in 1949. His mother died and his younger sister was seriously injured by the atomic bombing of Hiroshima. He survived only because as a medical student he had been evacuated to Tsuruoka City, Yamagata Prefecture in the northern part of Japan. His father, who ran a medical clinic near his house located 1.3 km from the hypocenter, worked desperately to provide medical care to the A-bomb survivors, despite suffering from broken bones and acute radiation symptoms. Dr. Tamagaki with Dr. Takeshima contributed to ABCC's studies in the organization's early days.

It's a Small World—With a Strong Link Between Hiroshima and Texas

When the National Academy of Sciences recruited Dr. James Cox as a nominee for a Member of the Board of Directors of the Radiation Effects Research Foundation, it was clear that a qualified and distinguished physician recognized world-wide as a leader in the radiation oncology community had been selected. But nearly six decades ago, a young Japanese woman would not yet know about Dr. Cox who had not yet begun his distinguished career or earned his impressive credentials.

Ritsuko Komaki was born in Amagasaki City, Hyogo Prefecture and moved with her family to Hiroshima City at the age of four after World War II. When she was ten years old and a fifth-grade student, she transferred to Nobori-machi Elementary School, becoming a classmate of Sadako Sasaki. Ritsuko still remembers how impressed she had been by Sadako's speed after seeing her run at a school athletic meet. But ten years after the atomic bombing, just prior to her graduation from elementary school, Sadako developed leukemia. That fall, at the age of 12, Sadako died. She had made many paper cranes in her bed at the hospital in the belief that she would recover from her disease when she finished a thousand origami cranes. The following year, Ritsuko, who was then a second-year middle-school student working as the student council president, discussed at the student council the wish to preserve Sadako's memory. She worked with Sadako's older brother and classmates to create "The Sadako Memorial Statue" and joined them in collecting donations on Hiroshima's streets for funding a memorial statue honoring the children who were victims of the atomic bombings.

The idea of building a monument to mourn the deaths of children due to the atomic bombings quickly gathered momentum, with donations arriving from throughout Japan. In 1958, three years after Sadako's death, the "Children's Peace Monument" was erected in the Peace Memorial Park in Hiroshima. On May 5 of that year, children from all over Japan attended the new monument's unveiling ceremony. This year marks the 50th anniversary of the monument's establishment. Every year, many millions of origami cranes are sent from all over the world in honor of Sadako's legacy.

The death of Sadako had a profound effect on Ritsuko who vowed to dedicate her life to helping people who suffered from cancer like her friend, and she would become a cancer researcher and physician in the years to follow. Ritsuko went on to graduate from Hiroshima University School of Medicine, spent a year working at ABCC, and came to the United States for further medical training, thanks to a mother and father who valued education highly. She chose the Medical College of Wisconsin for residency and fellowship training in radiation oncology. And she credits her excellent teachers at the Medical College of Wisconsin for developing her skills and knowledge. Over the course of her professional career, Dr. Komaki would receive numerous awards, including the Marie Sklodowska-Curie Award in 2005 from the American Association for Women Radiologists, the Business Professional Women of Texas Award in 2005, and the 2006 Alumna of the Year Award from the Medical College of Wisconsin/Marquette Medical Alumni Association.

Today, Ritsuko is Doctor and Professor Komaki and the Gloria Lupton Tennison Distinguished Endowed Professor for Lung Cancer Research at one of America's largest cancer hospitals, the M.D. Anderson Cancer Center at the University of Texas, in Houston. In 2006, Dr. Komaki was instrumental in helping introduce a new era in cancer care at the

Children's Peace Monument at the Peace Memorial Park in Hiroshima City

M.D. Anderson Cancer Center when she was involved in the planning of the Proton Therapy Center. The Center is one of only three institutions in the United States offering proton therapy to patients. Dr. Komaki helped M.D. Anderson navigate the complex logistics associated with importing the proton-generating radiation equipment to Houston, which ironically was manufactured in Japan and by a company whose CEO just happened to attend the same high school in Hiroshima as Dr. Komaki.

Oh—and Dr. James D. Cox? He just happened to coincidently be a faculty member at the Medical College of Wisconsin who Dr. Komaki met when she arrived in the United States and with whom she would form a relationship that, beginning in 1980, grew into a 28-year marriage. They would eventually move to Houston together where Dr. Cox is Professor and Head of Radiation Oncology. Now serving as an RERF Visiting Director, he will be attending his third RERF Board of Directors Meeting in Washington this June.

(Evan B. Douple, RERF Associate Chief of Research)

Research Protocols Approved in 2007

RP 1-07 Estimation of Genetic Risk of Radiation on Immature Oocytes of Rats by Using Two-dimensional DNA Analysis: An Animal Model for Human Female Exposure

Asakawa J, Kamiguchi Y, Nakamura N, Katayama H, Cullings HM

It is well recognized that mouse immature oocytes are extremely sensitive to radiation exposure and more than 90% are killed following exposure to 0.5 Gy of X rays. Therefore, mouse mutagenesis study using several Gy of X or γ rays have not been possible. In contrast, it has been recognized that rat immature oocytes are not as radiosensitive as those in mice, and we confirmed it on our own. We then came to think that the analysis of rat DNA by two-dimensional electrophoresis should be a unique animal model for the risk estimation of human female exposure. In the present research proposal, we will measure the mutation induction rate by examining F_1 rats derived from immature oocytes irradiated with 2.5 Gy of γ rays. We will use 750 F_1 animals each for the exposed and the control groups. Since we found from preliminary experiments that approximately 1,500 loci per animal could be screened, the study plan makes it possible to search for germline mutations at 1,125,000 loci in total in each group. Based on our previous data on the spontaneous mutation rate in female mice obtained by two-dimensional DNA analysis technique, we think it unlikely that the spontaneous mutation rate in female rats exceeds $0.5–1.0 \times 10^{-5}$/locus/generation. In addition, also based on our own data in male mice, it seems unlikely that the mutation induction rate is higher than $0.5–1.0 \times 10^{-5}$/locus/Gy. Under these conditions, it is expected that we will detect 5–11 mutations or less in the control group and 19–39 mutations or less in the exposed group. The molecular characterization of the detected mutations will further reveal the spectrum of radiation-induced mutations occurring in immature oocytes. The results to be obtained by this proposal will be the first data in the world on the estimation of genetic risk of radiation in immature oocytes.

RP 2-07 Study on Genetic Effects of Radiation by Array Comparative Genome Hybridization (Array CGH) Method—Validation of Ability of the Methodology for the Genetic Study

Takahashi N, Satoh Y, Kodaira M, Katayama H, Kodama Y, Cologne JB

The microarray-based comparative genome hybridization (array CGH) method was introduced to effectively identify "radiation-induced *de novo* large deletion type mutations" to the Biochemical Genetics Laboratory. The results of the pilot study revealed that our array CGH system could detect the copy number changed variation. In this proposal, by array CGH method using slide glasses with about 2,500 Bac clones, we will examine genomic DNA of 225 offspring born to parents exposed to relatively high radiation doses. From this research protocol (RP), we anticipate the following two outcomes. First, we will try to assess whether the frequency of large deletion type mutations observed in gametes from the exposed parents is higher than that in those from unexposed parents. Even if we do not obtain any significant results, we will be able to estimate an upper confidence bound for the induction rate in humans. Next, with the information from this RP, some assessment should be possible as to whether using denser array CGH systems in the future is likely to yield useful information for studies on the genetic effects of atomic-bomb radiation.

RP 3-07 Clinical Health Study for Expanded Group of Younger A-bomb Survivors

Akahoshi M, Yamada M, Hida A, Ohishi W, Nishi N, Kasagi F, Suyama A, Furukawa K, Ross NP, Hayashi T, Nakachi K, Kodama Y, Katayama H, Kodama K, Nakamura N, Fujiwara S

The Adult Health Study (AHS) of A-bomb survivors has been invaluable in determining the association of radiation with risk for conditions that cannot be identified through mortality studies. Many of the older members of the AHS cohort have died, however, and reviewers at the meeting of the International Blue Ribbon Panel (1996) and the 31st and 32nd meetings of the Scientific Council (2004 and 2005) recommended that we expand the AHS cohort by adding more younger survivors (who are considered highly sensitive to radiation) for radiation risk research purposes. Accordingly, we will identify younger survivors willing to participate in clinical health examinations in a mail survey conducted by the Department of Epidemiology on the Life Span Study (LSS) in 2007. We hope to add to the AHS cohort about 2,300 people who were <10 years old at the time of the bombing, bringing the cohort to about 3,000. The added 2,300 subjects will also undergo health examinations biennially.

RP 4-07 Pathology Study of Malignant Tumors of Soft Tissue and Bone among A-bomb Survivors, 1957–2003

Yonehara S, Hayashi T, Daimaru Y, Ikeda T, Tokuoka S, Nishi N, Soda M, Suyama A, Kodama K, Mabuchi K, Ron E, Preston DL

The excess risk of sarcomas of the soft tissues and bones associated with high therapeutic doses of radiation has been known for some time but epidemiological data on the risk associated with radiation exposure at relatively low doses are very limited. The latest analysis of solid cancer incidence data of

the Life Span Study (LSS) cohort of the Radiation Effects Research Foundation (RERF) provided, for the first time in this cohort, evidence of a significant dose response for broadly-classified sarcomas using the tumor registry-based incidence data. We propose to conduct a detailed, standardized pathology review of sarcomas in order to investigate the association between estimated radiation dose (DS02) and risk of sarcomas by histological types and sub-types. Soft-tissue and bone sarcomas occurring between 1957 and 2003 in the LSS cohort will be identified through the Hiroshima and Nagasaki tumor registries and supplemented by additional information based on autopsy and surgical pathology records at RERF and major medical institutions in both cities, and death certificates. A panel of pathologists will review cases of soft-tissue and bone sarcomas as reported to the tumor registries and other sources indicated above together with cases with diagnoses to which soft-tissue and bone sarcomas may have been misclassified. The panel will provide consensus diagnoses by histological types, which will be classified using the World Health Organization (WHO) Classification of Tumours of Soft Tissue and Bone (2002). Analyses will be performed to assess the radiation-related risk of sarcomas using a Poisson regression model and to evaluate modifying effects, if any, of age, gender, and other factors.

Recent Publications

(Japanese): the original article is in Japanese.

Asakawa J, Nakamura N, Katayama H, Cullings HM. Estimation of mutation induction rates in AT-rich sequences using a genome scanning approach after X irradiation of mouse spermatogonia. Radiation Research 2007 (August); 168(2):158-67. (RERF Report 15-06)

Egbert SD, Kerr GD, Cullings HM. DS02 fluence spectra for neutrons and gamma rays at Hiroshima and Nagasaki with fluence-to-kerma coefficients and transmission factors for sample measurements. Radiation and Environmental Biophysics 2007 (November); 46(4):311-25.

Hamasaki K, Imai K, Hayashi T, Nakachi K, Kusunoki Y. Radiation sensitivity and genomic instability in the hematopoietic system: Frequencies of micronucleated reticulocytes in whole-body X-irradiated BALB/c and C57BL/6 mice. Cancer Science 2007 (December); 98(12):1840-4. (RERF Report 8-07)

Hayashi I, Morishita Y, Imai K, Nakamura M, Nakachi K, Hayashi T. High-throughput spectrophotometric assay of reactive oxygen species in serum. Mutation Research 2007 (July 10); 631(1):55-61. (RERF Report 17-06)

Heidenreich WF, Cullings HM, Funamoto S, Paretzke HG. Promoting action of radiation in the atomic bomb survivor carcinogenesis data? Radiation Research 2007 (December); 168(6):750-6.

Izumi S, Ohtaki M. Incorporation of inter-individual heterogeneity into the multistage carcinogenesis model: Approach to the analysis of cancer incidence data. Biometrical Journal 2007 (September); 49(4): 539-50.

Kodama K, Kasagi F, Nishi N. Cohort study at Radiation Effects Research Foundation in Hiroshima and Nagasaki. Cardiac Practice 2007; 18(2):151-6. (Japanese)

Kusunoki Y, Hayashi T. Long-lasting alterations of the immune system by ionizing radiation exposure: Implications for disease development among atomic bomb survivors. International Journal of Radiation Biology 2008 (January); 84(1):1-14. (RERF Report CR1-07)

Masunari N, Fujiwara S, Nakata Y, Nakashima E, Nakamura T. Historical height loss, vertebral

deformity, and health-related quality of life in Hiroshima cohort study. Osteoporosis International 2007 (November); 18(11):1493-9. (RERF Report 13-06)

Matsumura M, Arita K, Takada Y, Suyama A, Nishi N, Ishida K, Hirabayashi A, Kato H, Kato M, Yoshida S, Hyoudou M, Egawa M, Taniguchi A, Watanabe T, Ogasawara Y, Soramoto E, Mukai M, Nishioka Y, Sakatani K, Yamaguchi Y, Tamura R, Usui S. Report on the results of the sixteenth medical examination of atomic bomb survivors resident in North America. Hiroshima Igaku [Journal of the Hiroshima Medical Association] 2008 (March); 61(3):161-85.

Moriya M, Seto S, Yano K, Akahoshi M. Two cases of short QT interval. Pacing and Clinical Electrophysiology 2007 (December); 30(12):1522-6. (RERF Report 4-07)

Nagano J, Mabuchi K, Yoshimoto Y, Hayashi Y, Tsuda N, Land CE, Kodama K. A case-control study in Hiroshima and Nagasaki examining non-radiation risk factors for thyroid cancer. Journal of Epidemiology 2007 (May); 17(3):76-85. (RERF Report 10-05)

Nakamura N. Dose evaluation of A-bomb survivors by means of electron spin resonance using tooth enamel. Electron Spin Science 2007 (October); 5(9):106-13. (Japanese)

Nakano M, Kodama Y, Ohtaki K, Nakashima E, Niwa O, Toyoshima M, Nakamura N. Chromosome aberrations do not persist in the lymphocytes or bone marrow cells of mice irradiated *in utero* or soon after birth. Radiation Research 2007 (June); 167(6):693-702. (RERF Report 6-06)

Nakashima E, Akahoshi M, Neriishi K, Fujiwara S. Systolic blood pressure and systolic hypertension in adolescence of atomic bomb survivors exposed *in utero*. Radiation Research 2007 (November); 168(5): 593-9. (RERF Report 5-07)

Nakashima E, Fujii Y, Imaizumi M, Ashizawa K. Finite mixture models in assessing anti-thyroglobulin antibody positivity as a marker of chronic thyroiditis. Japanese Journal of Biometrics 2007 (November); 28(2):79-90. (RERF Report 9-06)

Neriishi K, Nakashima E, Minamoto A, Fujiwara S, Akahoshi M, Mishima HK, Kitaoka T, Shore RE. Postoperative cataract cases among atomic bomb survivors: Radiation dose response and threshold. Radiation Research 2007 (October); 168(4):404-8. (RERF Report 1-06)

Nishi N, Kodama K. Cohort studies in the Radiation Effects Research Foundation of Hiroshima and Nagasaki. Igaku no Ayumi [Journal of Clinical and Experimental Medicine] 2008 (January 12); 224(2):157-61. (Japanese)

Nishi N, Sugiyama H, Kasagi F, Kodama K, Hayakawa T, Ueda K, Okayama A, Ueshima H. Urban-rural difference in stroke mortality from a 19-year cohort study of the Japanese general population: NIPPON DATA80. Social Science & Medicine 2007 (August); 65(4):822-32.

Nishi N, Sugiyama H, Kodama K, Ninomiya M, Kuwabara M, Hiramatsu K, Umehara M, Okuno H, Kishimoto A. Current situation and challenges of Hiroshima City Cancer Registry. Hiroshima Igaku [Journal of the Hiroshima Medical Association] 2008 (March); 61(3):186-9. (Japanese)

Noda A, Kodama Y, Cullings HM, Nakamura N. Radiation-induced genomic instability in tandem repeat sequences is not predictive of unique sequence instability. Radiation Research 2007 (May); 167(5):526-34. (RERF Report 5-06)

Ohishi W, Chayama K. Guidelines for management of hepatitis B. Shindan to Chiryo [Diagnosis and Treatment] 2008 (March 1); 96(3):481-7. (Japanese)

Ohishi W, Fujiwara S, Suzuki G, Chayama K. Validation of the use of freeze-dried sera for the diagnosis of hepatitis B and C virus infections in a longitudinal study cohort. Research Advances in Microbiology 7. Mohan RM (edit). Kerala: Global Research Network 2007 (June), pp 1-9. (RERF Report CR2-07)

Bib#3606
Okubo T(Edit). Report of Atomic Bomb Disease Research Project, FY2006 MHLW Grants 2007 (April 1), 57 p. (Japanese)

Osaki Y, Okamoto M, Kaetsu A, Kishimoto T, Suyama A. Retrospective cohort study of smoking and lung cancer incidence in rural prefecture, Japan. Environmental Health and Preventive Medicine 2007 (July); 12(4):178-82.

Pawel DJ, Preston DL, Pierce DA, Cologne JB. Improved estimates of cancer site-specific risks for A-bomb survivors. Radiation Research 2008 (January); 169(1):87-98.(RERF Report 9-07)

Pierce DA, Vaeth M, Shimizu Y. Selection bias in cancer risk estimation from A-bomb survivors. Radiation Research 2007 (June); 167(6):735-41.

(RERF Report 9-05)

Preston DL, Cullings HM, Suyama A, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K, Kasagi F, Shore RE. Solid cancer incidence in atomic bomb survivors exposed in utero or as young children. Journal of the National Cancer Institute 2008 (March 19); 100(6):428-36.(RERF Report 15-07)

Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiation Research 2007 (July); 168(1):1-64. (RERF Report 8-06)

Sasaki H, Kasagi F, Yamada M, Fujita S. Grip strength predicts cause-specific mortality in middle-aged and elderly persons. American Journal of Medicine 2007 (April); 120(4):337-42. (RERF Report 17-04)

Shimizu W, Matsuo K, Kokubo Y, Satomi K, Kurita T, Noda T, Nagaya N, Suyama K, Aihara N, Kamakura S, Inamoto N, Akahoshi M, Tomoike H. Sex hormone and gender difference—Role of testosterone on male predominance in Brugada syndrome. Journal of Cardiovascular Electrophysiology 2007 (April); 18(4):415-21.

Sogon T, Masamura S, Hayashi SI, Santen RJ, Nakachi K, Eguchi H. Demethylation of promoter C region of estrogen receptor α gene is correlated with its enhanced expression in estrogen-ablation resistant MCF-7 cells. Journal of Steroid Biochemistry & Molecular Biology: Elsevier 2007 (June); 105(1-5):106-14.

Suyama A. Introduction of IREP, US computer software for determining the probability of causation. Gen-ankyo Dayori [Tidings of Nuclear Safety Research Association] 2007 (June 25); 218:3-7. (Japanese)

Suzuki G, Cullings HM, Fujiwara S, Hattori N, Matsuura S, Hakoda M, Akahoshi M, Kodama K, Tahara E. Low-positive antibody titer against *Helicobacter pylori* cytotoxin-associated gene A (cagA) may predict future gastric cancer better than simple seropositivity against *H. pylori* cagA or against *H. pylori*. Cancer Epidemiology, Biomarkers and Prevention 2007 (June); 16(6):1224-8. (RERF Report 12-06)

Yano M, Hamatani K, Eguchi H, Hirai Y, MacPhee DG, Sugino K, Dohi K, Asahara T. Prognosis in patients with hepatocellular carcinoma correlates to mutations of p53 and/or hMSH2 genes. European Journal of Cancer 2007 (April); 43(6):1092-100.

Yoshida MA, Hayata I, Tateno H, Tanaka K, Sonta S, Kodama S, Kodama Y, Sasaki MS. The chromosome network for biodosimetry in Japan. Radiation Measurements 2007 (August); 42(6-7):1125-7.