放影研 RERF update
Radiation Effects Research Foundation News and Views
Hiroshima and Nagasaki, Japan
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Radiation Effects Research Foundation

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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.

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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.*

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From the Editors

Welcome back!

Cool days and evenings have returned to Hijiyama, and the RERF tennis court is quiet due to the shorter daylight hours. The employees are fitting Bonenkai into their busy end-of-the-year calendars and we all find ourselves reflecting back on highlights of the past year before we face the start of 2010.

In this issue we feature highlights of RERF's successful Open Houses held in the Hiroshima and Nagasaki laboratories. Those annual events are important "windows" to the public and the A-bomb survivors, enabling the visitors to learn more about our research activities and to afford RERF research scientists the opportunity to explain important results. We were especially pleased to see many young school-age children attending and actively participating. As in the past, the RERF staff work hard to provide interesting displays and demonstrations that communicate the RERF mission and accomplishments while acknowledging the contributions of the A-bomb survivors and the collaborating scientists. Please read more about those events in Facts and Figures.

This issue also features a scientific article by one of RERF's young research scientists, Kanya Hamasaki, who recently joined the Department of Genetics. The article reviews recent studies of chromosome instability in peripheral blood lymphocytes by Dr. Hamasaki and his collaborators.

RERF is starting a new research study of the effects of radiation on the natural aging of the immunological system. The large, five-year study involves exciting collaborations between RERF scientists and a number of scientists in research laboratories in the U.S. and Japan. With the additional funding provided by the U.S. National Institute of Allergy and Infectious Diseases, RERF scientists hope to extend the Department of Radiobiology/Molecular Epidemiology's previous findings to a new level for a better understanding of the role of immunology in the development of human diseases in an aging population. Details of the study will be described in the next issue of *Update*.

We were pleased to receive a note from Kenji Joji, a former Translation Section chief who served both ABCC and RERF (1953–1989). He said he especially was pleased to read in *Update* that the Adult Health Study had successfully completed its 50th anniversary and he remembered well the important role that Seymour Jablon had played in developing the unified study programs at ABCC. As always, drop us a line to let us know what articles you would like to read about in future issues.

Open House 2009, Hiroshima Laboratory

Ja, mata!

Evan B. Douple
Editor-in-Chief

Yuko Ikawa
Technical Editor

44th Meeting of RERF's Board of Directors Convened in Hiroshima

Two-stage Approach for Change of Status to Public-interest Incorporated Foundation Approved

The 44th meeting of the Board of Directors was held in the Auditorium at Hiroshima RERF on June 24 and 25, 2009. On behalf of the U.S. and Japanese governments, Dr. Patricia R. Worthington, Director, Office of Health and Safety, Office of Health, Safety and Security, U.S. Department of Energy and Dr. Kaoru Manabe, Deputy Director, General Affairs Division, Health Service Bureau, Japanese Ministry

of Health, Labour and Welfare, delivered opening addresses.

The participants engaged in active discussions on the handling of future research plans, an issue reviewed by RERF in response to the Senior Review Panel's recommendations made in June last year, RERF's study achievements thus far and their evaluation, and how studies at RERF should be carried out in the future. In relation to reform of the public-interest corporation system, regarding which new laws were implemented in December 2008, RERF, designated an exceptional juridical person, is aiming at completion of the transition process into a public-interest incorporated foundation within the next five years. RERF representatives explained the necessary procedures involved in the future and requested relevant advice. The visiting directors stated that coordination with the U.S. and Japanese governments and close contact among all the directors would be important. RERF's future vision, which has been discussed many times as one of the foundation's top priorities, was, together with study details, once again debated passionately at the meeting.

Dr. Toshiteru Okubo, RERF Chairman, opened the meeting with his status report for RERF, reporting on 1) the Scientific Council's review of the foundation's study program with a focus on the Department of Radiobiology/Molecular Epidemiology and the Department of Genetics, 2) initiation of re-examination of records of exposure locations and shielding status using original records including personal interview sheets, in response to the Scientific Council's support of initiation of review of issues involving individual dosimetry, 3) conduct of a staff training program initiated in November 2008 to improve staff morale/abilities and enable them to respond to the changing work environment and diversification, given the need for RERF to review its activities and reform its organization, and 4) the lack of space and funds for maintenance of biological specimens.

In terms of international collaborations, participation in international collaborative activities, acceptance of visitors from overseas for facility tours and training, and partnership activities were reported. As for public relations activities for dissemination of research-related information both in Japan and abroad, it was reported that further effort is being made to enhance such dissemination of information and establishment of friendly ties with the mass media, aiming at providing scientific information to non-RERF people in a readily understandable manner.

The FY2008 research activities report, settlement of accounts and audit reports, as well as the FY2009 research activity plans were approved as presented. The FY2009 working budget, which is almost identical to that of the previous year, was also approved.

As for responses to the Senior Review Panel's recommendations, reports were made, as suggested by the Board at its previous year's meeting, on three major items: future research plans with a focus on five-year research plans and project-type research management, review of use of biospecimens, and expansion of international collaborative projects.

As for change of status to a public-interest incorporated foundation (PIIF), an important issue related to RERF's future direction, a two-stage approach, involving application for recognition of the draft Articles of Incorporation from the competent administrative agencies by around July 2010 and subsequent application for recognition of change of status into a PIIF from the Cabinet Office, was adopted. With this, it was formally approved that an application be made to the competent administrative agencies in terms of method for selection of first councilors and that relevant procedures for the selection process be taken.

As for the personnel-reduction issue, given that maintenance of research scientists is the top-priority issue for continuation of the research program, the directors requested that RERF take actions to minimize effects of personnel reduction on research activities, by securing the maximum number of research scientists and making efforts from an international perspective to recruit young talented researchers.

On the second day, Mr. Glenn S. Podonsky, Chief Health, Safety and Security Officer, Office of the Secretary of Energy, U.S. Department of Energy, who arrived in Hiroshima the previous night, delivered a speech referring to U.S. President Obama's inauguration, appointment of DOE Secretary Chu, and continuation of financial support to RERF despite severe financial conditions in the United States. Mr. Podonsky also stated that the U.S. and Japanese governments will continue to cooperate in providing research support to the foundation. Thereafter, deliberations proceeded according to the program, and all items for deliberation and action were approved.

Lastly, the Board discussed the appointment of officers and others. The Board approved the reappointment of Chairman Toshiteru Okubo, Vice Chairman Roy E. Shore, Permanent Director Takanobu Teramoto, and Visiting Director Yasuhito Sasaki, whose four-year terms of office were due for expiration at the end of June. Dr. Shelley A. Hearne (Managing Director, Health and Human Services Policy, The Pew Charitable Trusts) was appointed as director to succeed Dr. John E. Burris. The Board approved that the term of office of Mr. David Williams, supervisor, be extended for another three years. As for scientific councilors, reappointment of

Dr. Sally A. Amundson, who had been appointed to complete her predecessor's term of office, and appointment of Dr. Kazuo Sakai (Director, Research Center for Radiation Protection, National Institute of Radiological Sciences) as successor to Dr. Ohtsura Niwa were approved.

The two-day meeting was concluded with the decision that the next meeting will be held in Nagasaki over the three days of June 21–23, 2010.

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, Executive Director, Japan Radioisotope Association
Dr. Senjun Taira, Permanent Director, Japanese Quarantine Association
Mr. James W. Ziglar, Former Sergeant at Arms of the United States Senate
Dr. James D. Cox, Professor and Head, Division of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center
Dr. John E. Burris, President, Burroughs Wellcome Fund

Supervisors:

Mr. Takashi Kohno, CPA/licensed Tax Accountant, Hiroshima General Law/Accounting Office
Mr. David Williams, Senior Financial Advisor, National Academy of Sciences

Co-chairman Scientific Council:

Dr. Katsushi Tokunaga, Professor, Department of Human Genetics, Division of International Health, Graduate School of Medicine, The University of Tokyo

Representatives of Supporting Agencies:

Mr. Kenji Okayama, Director, Office of Guidance and Investigation, General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare (MHLW)
Dr. Kaoru Manabe, Deputy Director, General Affairs Division, Health Service Bureau, MHLW
Dr. Yukako Hinohara, Deputy Director, General Affairs Division, Health Service Bureau, MHLW
Mr. Kazuhiro Kanayama, Deputy Director, General Affairs Division, Health Service Bureau, MHLW
Mr. Glenn S. Podonsky, Chief Health, Safety and Security Officer, Office of the Secretary of Energy, U.S. Department of Energy (DOE)
Dr. Patricia R. Worthington, Director, Office of Health and Safety, Office of Health, Safety and Security, DOE
Mr. Dean C. Hickman, Program 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. Ronald C. Cherry, Energy Attaché and Director, DOE Tokyo Office
Dr. Warren R. Muir, Executive Director, Division on Earth and Life Studies, National Research Council (NRC), National Academy of Sciences (NAS)
Dr. Kevin D. Crowley, Director, Nuclear and Radiation Studies Board, Division on Earth and Life Studies, NRC, NAS

Participants of the 44th Board of Directors Meeting

Dr. Daniela Stricklin, Program Officer, Nuclear and Radiation Studies Board, Division on Earth and Life Studies, NRC, NAS

RERF:
Mr. Eiji Akimoto, Chief of Secretariat
Dr. Evan B. Douple, Associate Chief of Research
Dr. Nori Nakamura, Chief Scientist
Dr. Kazunori Kodama, Chief Scientist
Mr. Douglas C. Solvie, Associate Chief of Secretariat

Staff News

As of 17 June, 2009, **Susan M. Geyer** resigned as an Associate Senior Scientist in the Department of Statistics. Dr. Geyer returned to the U.S. where she accepted a position of Associate Professor in the Department of Internal Medicine in the Ohio State University College of Medicine, and Senior Biostatistical Scientist in the university's Center for Biostatistics. Drs. **Jun-ichi Asakawa**, **Fumiyoshi Kasagi**, and **Kiyohiro Hamatani** reached mandatory retirement age on 30 June 2009 and were re-employed 1 July 2009 as Fixed-term Research Scientists in the Departments of Genetics, Epidemiology, and Radiobiology/Molecular Epidemiology, respectively. Dr. **Nobuo Nishi**, Assistant Chief in the Department of Epidemiology, resigned effective 30 September 2009 and took a position of Project Leader, Center for Collaboration and Partnership at the National Institute of Health and Nutrition.

Dr. **N. Pillip Ross** resigned as Chief, Department of Statistics, effective 13 October 2009. Dr. **Harry M. Cullings**, former Assistant Department Chief, was promoted to Acting Department Chief effective 14 October 2009. Dr. **Norio Takahashi** was re-employed with the title of Fixed-term Research Scientist in the Laboratory of Biochemical Genetics effective 1 November 2009.

Dr. **Ritsu Sakata**, Research Scientist in the Department of Epidemiology, spent eight months as a visiting scientist at the U.S. National Cancer Institute. We have asked her to write a little about her experience.

Finally, Dr. **Kanya Hamasaki** was appointed as a Fixed-term Research Scientist in the Department of Genetics effective 1 September 2009. We also have asked Dr. Hamasaki to write a little about himself and his interest in the work of RERF (see also his scientific article on page 14).

Ritsu Sakata

I am very appreciative that I was given an opportunity to study at the Radiation Epidemiology Branch of the U.S. National Cancer Institute (NCI) for the eight-month period between December 2008 and August 2009. At the Radiation Epidemiology Branch, Drs. Kiyohiko Mabuchi, Charles Land, and Elaine Ron, who have visited RERF many times, helped me in many ways to make me feel comfortable during my stay. Under the direction of Dr. Peter Inskip, I was mainly involved in a reanalysis of mortality data on women undergoing radiation treatment for benign gynecological diseases and am currently putting the finishing touches on a related manuscript.


Ritsu Sakata, Research Scientist

NCI had in its basement a gym complete with showers, and many people used the facility at times when they were off from work. I joined a running team and often jogged through the lush residential area neighboring NCI during my lunch breaks. After running, I would take a shower and resume my afternoon work schedule feeling quite refreshed.

In addition to this, since the quantity of meat and prepared dishes sold at the supermarket and restaurants was all too much for me living alone, I took to cooking my own food centered on vegetables, and this led a very health lifestyle while I was there. Thanks to that lifestyle, and maybe counter to the expectations of some of my colleagues, I did not gain any weight in the U.S., and my body fat ratio actually decreased. Back in Japan, I now feel as if I am somewhat lacking sufficient exercise.

The start of my life in the U.S. was initially helped by Dr. Kyoji Furukawa, who had already been in the country for seven months by the time I arrived. When preparing to return to Japan, I was helped by the many new friends I made while in the U.S. Even though my stay was short, I was able to accomplish a lot, experienced differences in life and work between the U.S. and Japan, and made many good friends. I close by thanking all those who helped make that valuable experience possible.

Kanya Hamasaki

Although I arrived at RERF in April of 2001 and had been working as a technician in the Department

Kanya Hamasaki, Research Scientist

of Radiobiology/Molecular Epidemiology, I was especially pleased to be employed as a Fixed-term Research Scientist in the Cytogenetics Laboratory of the Genetics Department, on 1 September 2009. In 2003, I began studies in the Graduate School of Biomedical Sciences at Hiroshima University while continuing to work at RERF. I completed and received the PhD in May 2009. The thesis of my degree was "Clonally expanded T lymphocytes from A-bomb survivors *in vitro* show no evidence of cytogenetic instability."

I would like to express my appreciation to everyone who helped me accomplish my goals, especially members of the Departments of Genetics and Radiobiology/Molecular Epidemiology. My current and future work is based on the cytogenetic techniques that I learned at RERF. I am going to participate in the projects "biological dosimetry study" and "chromosome studies in the *in utero*-exposed population." It is my great pleasure to face the challenges ahead, such as resolving issues that remain unclear. I hope to make a contribution to the many great achievements of RERF.

Visiting Scientists

While several scientists visit RERF throughout any given year, some scientists stay for several days or weeks and others stay for several months to collaborate with RERF researchers. On July 27 and 28, Dr. **Timothy E. O'Brien**, Associate Professor and Graduate Program Director of the Department of Mathematics and Statistics at Loyola University of Chicago, U.S., visited RERF and presented a series of lectures on "Applied Nonlinear Statistical Methods." Dr. O'Brien teaches a similar short-course on a regular basis in the U.S. under the auspices of the American Statistical Association. He pointed out in his lectures that while researchers often recognize that nonlinear regression models are often more applicable for modeling physical and medical processes than are linear ones, selecting an efficient experimental design, choosing, fitting, and interpreting an appropriate nonlinear model, and deriving and interpreting confidence intervals for key model parameters can present fundamental and important challenges. The course was well attended, including some researchers from Japanese universities.

This fall we were fortunate to have a former RERF Chief of Epidemiology, Dr. **Kiyohiko Mabuchi**, currently a scientist in the Radiation Epidemiology Branch of the U.S. National Cancer Institute (NCI), spend some time working on matters related to the RERF Contract with the NCI. In addition, a former Chief of Statistics, Dr. **Dale Preston**, HiroSoft Chief Scientist, and a former Senior Research Scientist, Dr. **Donald Pierce**, were also at RERF collaborating on a number of studies and providing consultation.

Visiting Student Researchers

Throughout the year there are often students from various countries visiting RERF as trainees who learn experimental techniques and conduct research. They work closely with RERF research scientists and their visit is supported by a number of fellowships or from their home country's government. During the past year, two trainees were supported by an award from the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE). HICARE's international cooperation activities include the training of medical and other technical personnel involved in the health care of the radiation-exposed worldwide, the dispatch of medical and other specialists in Hiroshima to the radiation-exposed countries/regions, and dissemination of knowledge about the medical care of the radiation-exposed people.

From 3 September until 6 November, 2009, **Liga Larmane**, from the Liga Stradins University in Latvia, and **Oleg Kovalev**, from the Federal Institution Medical Radiological Research Center (MRRC) of the Russian Academy of Medical Sciences, received training and conducted research in RERF's Department of Radiobiology/Molecular Epidemiology (RME). Since May 2008, Ms. Larmane has been working in the university's Laboratory of Biochemistry and is a student in the Doctoral Programme in the Faculty of Medicine. She has been working in the field of oxidative stress and

antioxidents, studying the effects of long-term antioxidant therapy in Chernobyl clean-up workers from Latvia. Her goal at RERF was to learn various experimental techniques that would be used in her doctoral thesis and specifically to investigate the effects of radiation on lymphocyte subset frequencies and intracellular reactive oxygen species levels in a mouse model. Mr. Kovalev is working in the Department of Radiation Biochemistry at MRRC and has been conducting genomic instability research. His goal at RERF was to learn and apply methods of immunofluorescent detection of phosphorylated histone H2AX for studying genomic instability induced by low doses of radiation. Both trainees have completed their program at RERF under the mentorship of **Dr. Tomonori Hayashi**, Chief of the RME's Immunology Laboratory.

Liga Larmane from Latvia (left) and Oleg Kovalev from Russia (center) talking with Dr. Akihiko Suyama, Chief, Nagasaki Epidemiology Department

2009 Distinguished Lecture Series

On 19 June 2009, Dr. Janko Nikolich-Zugich gave a distinguished lecture entitled "T Cell Function and Homeostasis in Immune Senescence: Causes and Consequences." Dr. Nikolich-Zugich is Chairman of the Department of Immunobiology, Co-director of the Arizona Center on Aging, and Elizabeth Bowman Professor in Medical Research in the College of Medicine, all at the University of Arizona in Tucson, U.S. He is a recognized expert in the effects of aging on the response of the immune system and is a collaborator in the new RERF study on the effects of radiation on immunosenescence.

Awards Received by RERF Scientists

Upon Receiving the 26th Tsunoo Scientific Prize

Misa Imaizumi, Chief
Division of Radiology
Department of Clinical Studies, Nagasaki

I recently received, on May 25 of this year, the 26th Tsunoo Scientific Prize. Every year, the Nagasaki University School of Medicine awards this prize to a researcher 40 years of age or younger who has made important scientific contributions to the field of medicine in Nagasaki Prefecture, in memory of the great achievements of the late Dr. Susumu Tsunoo, who contributed greatly to the development of Nagasaki Medical College. During his term as president of the college, Dr. Tsunoo was exposed to the atomic bomb on August 9, 1945, while he was working at an outpatient clinic, and passed away at the young age of 52. Receiving this prize, I newly confirmed my determination to continue studies on health effects in the A-bomb survivors.

The prize-winning research was "Study on Thyroid Diseases among A-bomb Survivors," which was conducted with cooperation from subjects of the Adult Health Study. During the period from 2000 to 2003, we jointly conducted thyroid examinations in Hiroshima and Nagasaki for the first time, and found that prevalence of not only malignant thyroid tumors, but also benign nodules, were related to radiation dose. Our study also showed that the younger the age at exposure, the greater the effects were of radiation exposure. On the other hand, no significant relationship between radiation dose and thyroid nodules was observed among survivors exposed *in utero*, although their risk ratio was similar to that among those exposed at a young age. The results showed effects of A-bomb radiation on thyroid nodules among those surviving 50 years or more after exposure.

In 2000, this research was initiated under the leadership of Drs. Tan Tominaga and Toshiro Usa,

Misa Imaizumi, Research Scientist, next to the statue of Dr. Susumu Tsunoo

my predecessors and, in 2001, I took over the project as the responsible researcher. At first, I was overwhelmed by the work and grew worried for a time, but many people in not only the Departments of Clinical Studies in Hiroshima and Nagasaki but also elsewhere, including the Departments of Statistics, Epidemiology, and Information Technology, made concerted efforts together to promote the study. While conducting this research, I have learned a great deal, including not only about the techniques and organizational resources that RERF has accumulated over the years, but also about its scientists' sincere attitudes toward research, contributions to the A-bomb survivors, and sense of mission. I now realize how wonderful it is to be able to engage in such valuable research at RERF. In the future, I would like to continue my efforts involving thyroid research in particular. Everyone's guidance and support would be truly appreciated.

Upon Receiving Education Award from the Hiroshima University Department of Molecular Internal Medicine

Yoshimi Tatsukawa, Research Scientist
Department of Clinical Studies, Hiroshima

I recently received an Education Award from the Department of Molecular and Internal Medicine (former Second Department of Internal Medicine), Hiroshima University. This prize is awarded to those who belong to that department for their achievements at universities or research institutes (excluding related hospitals).

In 1998, I obtained a medical license and, 10 years later (last year), received a doctoral degree based on the thesis for which I received the aforementioned Education Award. Looking back on the past 10 years, I feel strongly that I was able to have such success thanks to the support of many people. I gave birth to my first child just before finishing my two-year internship as a physician. Because there was not much acceptance of a female physician working in a clinical setting while raising a child, I almost gave up the idea of working as a clinician. A doctor in the university medical office, however, offered warm words of encouragement, asking whether I would be interested in joining the Second Department of Internal Medicine and working as a clinician after giving birth to my child. I therefore joined the department, and worked at related hospitals as a clinician for four years.

While I lived a busy life, examining patients and raising a child, I wondered whether to quit working as a clinician and pursue research instead. Physicians at the hospital where I worked encouraged me by advising me that, "You can work as a clinician at any time, but if you want to start research, you better do it while you are young." Another doctor of the university medical office invited me to attend university meetings to read and discuss papers, and I quickly accepted the doctor's call to participate. This eventually led to the opportunity for me to work at RERF. The paper for which I received the award was based on my first study at RERF. I feel that the Education Award has provided me a helping hand by reminding me that getting a degree is a beginning not an end.

Finally, I would like to express my sincere appreciation to the doctors in the medical office and related hospitals who have guided me along the way, and to all the staff at RERF, and the members of my family, who have always supported me. I hope to be able to continue and further my own work, and to that end, everyone's continued instruction and guidance would be truly appreciated.

Yoshimi Tatsukawa, Research Scientist, with her award

Excellent Poster Award Received from the Japanese Association of Cancer Registries

Hiromi Sugiyama, Research Scientist
Department of Epidemiology, Hiroshima

At the 18th general assembly/workshop of the Japanese Association of Cancer Registries (JACR), held on September 3 and 4, 2009, in Niigata

Prefecture, my poster presentation titled "Cancer incidence in Hiroshima Prefecture" won the award for excellence in the academic poster category. In the category introducing regional cancer registry offices, both prefectures of Hiroshima and Nagasaki also won awards (with material prepared by the Tumor and Tissue Registry Office, Department of Epidemiology, Nagasaki Laboratory), doubling the joy experienced by those concerned.

There are currently three cancer registry projects ongoing in Hiroshima Prefecture: the Hiroshima City Cancer Registry, the Hiroshima Prefecture Tumor Registry (a tissue registry), and the Hiroshima Prefecture Cancer Registry. A data-sharing agreement starting on August 1, 2009, was signed among the three projects, thereby allowing compilation of detailed incidence statistics covering the entire Hiroshima Prefecture based on information from abstracted records and pathological diagnoses, among other sources. For example, Hiroshima Prefecture has thus far observed high mortality from liver cancer and also recently found higher liver cancer incidence, compared with national levels. I hope to elucidate the background of cancer incidence in Hiroshima Prefecture by further analyzing the prefecture's cancer incidence trends, with the aim of understanding cancer incidence among A-bomb survivors.

My award-winning poster was selected in a vote cast by all participants of the general assembly/workshop, including a significant number of administrative personnel and cancer registry operators as well as researchers, and hence the decision apparently was dependent on visual impact rather than merely content. Speaking of poster presentations, visual impact is considerably important. Whenever preparing a poster, I keep in mind the following simple tips: 1) Text should be legible from over one meter away; 2) Results should be shown in the form of two-dimensional graphs if possible (the complexity of three-dimensional graphs may limit the efficient transfer of information); 3) Choice of colors should be considered carefully (red and green should be employed only sparingly together); and 4) A single sentence/phrase of key information should be shown alongside graphs. Getting a handle on these tips will greatly improve poster visuals. In the future, I hope to further develop my research activities and refine my presentation skills. Your continued support and advice to that end would be greatly appreciated.

Hiromi Sugiyama, Research Scientist, with her poster award

Dementia Study Presented ASAD Best Scientist Award and Published in World Federation of Neurology Newsletter

Michiko Yamada, Assistant Chief
Department of Clinical Studies, Hiroshima

I recently received the Best Scientist Award at the 3rd International Congress of the Asian Society Against Dementia (ASAD), held in Seoul October 11–13, 2009. I have been studying cognitive function, incidence, risk factors, and complications/prognosis in terms of dementia for the dementia study that was initiated by RERF in 1992 based on research protocol (RP) 5-92 "Study of senile dementia among the Adult Health Study," in long-term collaboration with members of the Departments of Clinical Studies, Epidemiology, Statistics, and Information Technology. As guidance from dementia experts is essential for this study, we engage in collaboration with specialists at Hiroshima International University, the Department of Clinical Neuroscience and Therapeutics of Hiroshima University, and physicians practicing at medical institutes in Hiroshima.

The award was granted to our study titled "Reaction time as a predictor of mortality and dementia." Reaction time was measured in 1970–72 as one of several physiological functions investigated to determine whether atomic-bomb radiation accelerated aging. I reported that reaction time was related to subsequent mortality and dementia development, and that risks of mortality and dementia were higher for those with slow reaction time in mid-adulthood. During the recent meeting, I was able to learn about progress being made in dementia research in Asian countries, and also obtained the latest information on basic research, diagnostic imaging, and treatment of Alzheimer's disease in Europe and the United States.

Best Scientist Award presented from the Asian Society Against Dementia

The study subjects of RP 5-92 are AHS participants at least 13 years of age at the time of bomb-

ings. Analysis results to date have not shown any indication of radiation-associated impairment of cognitive function or increased dementia incidence. A paper based on this finding titled "Incidence of dementia among atomic bomb survivors—Radiation Effects Research Foundation Adult Health Study" was published in the *Journal of the Neurological Sciences* in March 2009, and was introduced in the *Newsletter of the World Federation of Neurology* this past October.

I am truly grateful for the opportunities provided me to be involved in such important research taking place at RERF. Everyone's continued support would be greatly appreciated.

Receiving the MEXT 2009 Minister's Award—Distinguished Service for Nuclear Safety Management

Kazuo Neriishi, Assistant Chief
Department of Clinical Studies, Hiroshima

The awarding ceremony for the 2009 Minister's Award—Distinguished Service for Nuclear Safety Management—was held on November 6, 2009, at the Tokai University Club, located in the Kasumigaseki Building in Tokyo, where certificates and plaques from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) were distributed to 17 awardees, including myself, by Vice Minister Masaharu Nakagawa. The selection committee indicated that I had received the honor because I have worked on health examinations conducted among area residents after the JCO criticality accident occurred in the village of Tokaimura on September 30, 1999, and participated in the subsequent health examinations starting in 2000 and conducted every April since on a regular basis. Taking this opportunity, I would like to express what I have felt strongly throughout my experiences.

First of all, I would like to pray for the souls of the two victims of the accident and express my condolences to their families. After the accident, the national government embarked on interministerial arrangements for prevention of such disasters, and an appropriate structure has been completed to a certain extent. I do not, however, believe the current situation is satisfactory. From the viewpoint of a radiation researcher, I strongly feel that a majority of the general public, including the media and the government, misunderstand effects of radiation on human health and that more accurate information needs to be conveyed to the public. Such dissemination of accurate knowledge within government policies alone would resolve several issues. For example, radiation affects human health in the form of increased numbers of such common diseases as cancer among those exposed to radiation, compared to the non-exposed. Lacking appropriate relative risk information, however, people may worry unnecessarily about long-term heath problems, occasionally leading to serious societal crises.

In consideration of this point, I have worked on both physical and mental health management for such individual residents. I have learned through the activities that I should not be so hasty to convince those who are worried about health effects of radiation otherwise. Instead it is important to be someone with whom they can discuss problems or questions at any time. In this regard, I think work of this nature contributed to my receiving the aforementioned honor.

What approaches can be adopted for the purpose of dissemination of accurate information? I hereby propose the establishment of a training system under which new findings obtained by RERF can be directly reflected in government policies. Every year RERF generates a number of new findings, rapidly updating the existing body of knowledge. I make this proposal because at least 10 years are now required for the national government to ratify international radiation standards that provide the government with scientific grounds for revision. Furthermore, it is necessary to establish a framework under which any information newly acquired by the government is continuously provided to citizens.

In closing, I would like to extend my heartfelt appreciation to the many people who supported me in the work for which I received this award.

Kazuo Neriishi, Assistant Department Chief, with MEXT award plaque and certificate

Late Health Effects of Ionizing Radiation: Bridging the Experimental and Epidemiologic Divide

Evan B. Douple, Associate Chief of Research

Despite the threat imposed by an H1N1 influenza outbreak, RERF was well represented by a delegation of six scientists at a conference held at the Georgetown University Conference Center on the historic campus in Washington, DC, May 4–6, 2009. Planned by an organizing committee that included RERF Vice Chairman and Chief of Research **Roy Shore**, the multidisciplinary conference focused on emerging data and new challenges in radiation sciences, with the aim to stimulate collaboration and synergistic interactions among the approximately 150 participants. There were 12 scientific sessions with a total of 36 invited speakers from the fields of radiobiolgy, dosimetry, epidemiology, and statistics on topics ranging from experimental biology to epidemiologic studies of radiation-exposed populations. The papers from all invited speakers, including RERF's **Kyoji Furukawa** (Interaction Effects of Radiation and Smoking on Lung Cancer Risks among Atomic Bomb Survivors), **Yoichiro Kusunoki** (Immunological Alterations in Aging A-bomb Survivors), and **Roy Shore** (Cataract Risk at Low-to-Moderate Radiation Doses: (Not) Seeing is Believing), will be published in a supplement of the journal *Radiation Research*. The conference was sponsored by the U.S. National Cancer Institute (NCI), Georgetown University Medical Center, Helmholtz Zentrum Munchen, the U.S. National Institute of Allergy and Infectious Diseases, and the U.S. Environmental Protection Agency.

Two poster sessions were included with a total of 100 posters covering a diversity of issues including effects of radiation quality, mechanistic modeling, non-targeted effects, genomic instability, biodosimetry, dose reconstruction, dose uncertainties, medical radiation and germline mutations, thyroid cancer in French Polynesia and Chernobyl, lung cancer and radiation/smoking interactions, radiation and cognitive disorders, radiation doses to interventional medical practitioners, and many other interesting topics. RERF's **Nobuo Nishi** and colleagues had a poster on "A New Mail Survey on the Life Span Study (LSS) Cohort" and **Ritsu Sakata** and her colleagues presented a poster "Effects of Other Factors in Radiation Risk Assessment of Gynecologic Cancer Incidence." **Harry Cullings** and colleagues presented a poster on "Estimated Gamma Doses to the Teeth of the Japanese Atomic Bomb Survivors." Former RERF Visiting Scientist, **David Richardson** (University of North Carolina) presented his work in collaboration with RERF scientists, "Ionizing Radiation and Leukemia Mortality among Japanese Atomic Bomb Survivors, 1950–2000."

The conference began with a comprehensive review of some of the evidence for key biological events that may play an important role in radiation health effects such as the bystander effect. Results from microbeam experiments and the contributions of studies using cultured cells, 3-D models such as tissue explants, and *in vivo* studies were described. Additional speakers described the challenge of attempting to account for such radiation-induced effects as genomic instability, bystander effects, or low-dose hypersensitivity in cancer epidemiology. **Ohtsura Niwa** (National Institute of Radiological Sciences, Chiba, and RERF Scientific Councilor) described stem cell radiobiology and provided evidence that the stem cells are a likely target for initiating some solid cancers.

The morning of the second day of the conference focused on quantifying the carcinogenic effects in radiation workers, including lymphohematopoietic malignancies and thyroid cancer in Chernobyl clean-up workers, mortality and cancer incidence following occupational radiation exposure in the third analysis of the U.K. National Registry for Radiation Workers, joint effects of radon exposure and smoking on lung cancer risk among uranium miners, cancer risks in medical radiation workers, updated results of the German uranium-miner cohort study (radon and the risk of lung and non-lung cancer), and results of a second follow-up of cancer mortality among German aircrew.

The afternoon session focused on site-specific cancers following environmental exposures. Former RERF Chief of Statistics, **Dale Preston** (HiroSoft International Corporation), pointed out that the extreme variability in the site-specific risk estimates based on studies of Mayak workers and people who lived along the Techa River is largely a consequence of the small number of excess cases. RERF's **Kyoji Furukawa** reported the results of studies of the joint effects of smoking and radiation on lung cancer risks in the LSS cohort of the A-bomb survivors. He concluded that the interaction between smoking and radiation results in an excess relative risk (ERR) that decreases with increasing age and is super-multiplicative for light smokers but additive or sub-additive for heavy smokers.

The third day included a focus on the late health effects of radiation therapy, and on radiation-related

non-malignant conditions such as cardiovascular disease, cataracts, and non-malignant thyroid diseases. A session on radiation exposure and non-malignant conditions included **Yoichiro Kusunoki**'s review (presented by **Evan Douple**) of the RERF studies of the effects of radiation on the immune system of A-bomb survivors in which many effects are similar to the normal immunosenescence seen in aging populations. In addition, RERF's results suggest that increases in plasma levels of inflammatory cytokines with increased radiation dose support the hypothesis that T-cell immunological alterations linked to an enhanced inflammatory response may lead to the development of inflammation-related diseases such as cardiovascular disease in the A-bomb survivors. **Roy Shore** described the latest evidence from RERF studies of radiation-induced cataractogenesis in which a clear dose-response is seen for cataract surgery incidence and with a suggestion that the dose threshold may be lower than previously thought. Those results, coupled with similar observations in other studies, have instigated reassessments of the guidelines for exposure of the lens of the eye by various radiation protection bodies.

The final session included two keynote lectures. The first by David Brenner (Columbia University, New York) reviewed the risks and benefits associated with the rapidly growing use of one of medicine's higher radiation dose procedures, the CT scan. The annual number of CT scans is rapidly increasing in Japan and the U.S. (approximately 70 million in the U.S.; Japan leads the world in numbers of CT scans per capita), CT scans are now producing about half of the annual radiation exposure from medical procedures, and many of the scans include pediatric patients. He concluded that while CT risks are small, a small risk multiplied by many millions of scans might translate into a public-health concern some years in the future, particularly from pediatric CTs.

The second keynote lecture, by Julian Preston (U.S. Environmental Protection Agency), focused on radiation risk perception, communication, and policy. He reminded the audience that there are really two bridges to cross; the first is from the environmental observations to epidemiology, while the second is bridging the gap from science to risk management and to the public. It is very difficult to put risks in proper perspective because any number projecting adverse health effects, regardless of how small, is likely to be viewed as unacceptable by a public that is generally risk averse and favoring "zero risk" which is often unrealistic, expensive, or unattainable.

The conference concluded with observations by a panel of experts, including RERF's **Roy Shore**. The panelists were asked to select their two most important "gaps of information" that they felt should be a focus for future research and needed to be filled. New techniques for cancer therapy, such as intensity-modulated radiation therapy (IMRT; delivering the radiation so that the beam enters the body from many different angles to get to the tumor with pinpoint accuracy) and stereotactic radiation surgery (SRS; destroying diseased tissue with an intense, highly-focused beam) are changing the way radiation therapy is applied and will involve large radiation doses delivered in small numbers of treatments with some scatter of radiation to normal tissues. Other panelists (a) encouraged development of better models for estimating doses, including models that actually work and that will integrate internal and external doses, (b) called for improved biodosimetry and methods for pooling data, (c) suggested a focus on certain tumors for which radiation-associated risks have not been well characterized such as cancers of the GI tract, and (d) improved biomarkers and biologically-based dose response models.

The continuous rainy weather throughout the conference did not dampen the spirits of the six RERF scientists who felt they received important

Dr. Kyoji Furukawa presenting his paper on interaction effects of radiation and smoking on lung cancer risk

Dr. Ritsu Sakata explaining her poster on ERRs with adjustment for factors possibly associated with gynecologic cancer

information regarding the status of the radiation epidemiologic studies of some of the world's major radiation-exposed cohorts. This was an especially important conference for RERF's Chief of Epidemiology, **Kotaro Ozasa**, whose first visit to Washington, DC, included valuable discussions with the international radiation scientists and a visit to the Radiation Epidemiology Branch of the U.S. NCI in Rockville, Maryland. While some of the study cohorts described are impressively large (such as 240,000 Chernobyl "liquidators," 116,000 "evacuees" from the Chernobyl area, and 5,000,000 exposed to <555 KBq/m^2 of Cs-137 from Chernobyl), most studies are plagued by one or more limiting factors such as large dosimetric uncertainties, healthy-worker effects, relatively short follow-up, low mean radiation doses, confounding factors (known and unknown), and small numbers of excess cases. We were all reminded on several occasions during the conference of the continued importance of, and interest in, the results of the studies underway at RERF. It was clear that there is a strong need for improved biophysical and mechanistic understandings before scientists are able to bridge the gap between basic science and epidemiology—and that there is great potential benefit if mankind is able to do so.

Dose Uncertainty Workshop

Harry M. Cullings, Acting Chief
Department of Statistics

A one-day workshop was held on May 8, 2009, at the Georgetown University Conference Center in Washington, DC, entitled "Impact of Uncertainty in Dose to the Dose Response." The workshop was organized by Dr. Andre Bouville of the Radiation Epidemiology Branch of the National Cancer Institute (NCI). The workshop was held in conjunction with the "Late Health Effects of Ionizing Radiation Conference" previously described. The purpose of the workshop as defined by the organizers was "to explore how uncertainties in individual dose estimates affect the statistical power and shape of the dose response in epidemiologic investigations and to review strategies that are in use today to try and account for the impacts of dose uncertainty." The workshop was a successor to a similar one held in 1997 by NCI.

The workshop began with a statement of the problem from the points of view of a dosimetrist, a statistician, and an epidemiologist. The last perspective was presented by RERF's Vice Chairman and Chief of Research, **Roy Shore**. Three case studies were examined of major populations exposed to ionizing radiation: the A-bomb survivors; the children exposed to I-131 fallout from the Chernobyl accident; and the people of Kazakhstan exposed to the fallout from the nuclear tests conducted there. Each case study had three presentations including: (1) quantification and organization of the uncertainties; (2) assessment of the dose response; and (3) possible improvements. RERF's (then) Assistant Chief of Statistics, **Harry Cullings**, spoke on the quantification and organization of dose uncertainties for the A-bomb survivors. Eight of the program speakers were scientists who formerly spent time working at RERF. The program concluded with a panel discussion led by an eminent Bayesian statistician from Johns Hopkins University, Tom Louis. Owen Hoffman of SENES/Oak Ridge has been working with Dr. Bouville to document the discussions and a consensus paper is expected.

International Symposium Based on Radiation Research Partnership

Kotaro Ozasa, Chief
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An international symposium based on the Radiation Research Partnership was held on September 14–15, 2009. With the objectives of encouraging radiation health effects research conducted by young researchers in the areas of epidemiology and statistics and promoting personnel exchange, the University of Washington (UW), Kurume University Biostatistics Center, and RERF have been carrying out the partnership program since 2006. The theme of this symposium was "Confounding and modification of radiation effects by lifestyle and other factors/utilization of mail survey data." The symposium was held with the support of RERF's International Exchange Program, and its objectives were to present summary reports of relevant studies and to review future research directions. On the morning of September 14, Kazunori Kodama (Chief Scientist, RERF), Scott Davis (Professor, UW), and Tatsuyuki Kakuma (Professor, Kurume University) presented summaries and future challenges of the partnership program from their perspectives. Their presentations were followed by keynote speeches by Dr. Davis, Kenneth Kopecky (Professor, UW), and Dr. Kakuma from their theoretical/methodological viewpoints regarding the symposium theme.

In the afternoon of the same day, symposium participants made presentations on studies of radiation-related cancer risks, as follows:

- study on bladder cancer by Eric Grant (Associate Senior Scientist, Department of Epidemiology, RERF);
- two studies on second primary cancers by Nobuo Nishi (Assistant Chief, Department of Epidemiology, RERF) and Christopher Li (Research Assistant Professor, UW);
- studies on colon cancer and breast cancer by Erin Semmens and Jean McDougall (PhD students, UW);
- study on dose-response risk model by Yoshisuke Nonaka (Visiting Research Fellow at the Department of Epidemiology from Kurume University); and
- study on causal models by Wan-Ling Hsu (Research Scientist, Department of Statistics, RERF).

Papers reporting the results of these studies are scheduled to be published in the future.

On September 15, active discussions were held on future perspectives of research based on the summaries presented on day 1. As a part of a personnel exchange program with Kurume University, Ritsu Sakata was hired as a research scientist by the Department of Epidemiology in Hiroshima, and Dr. Nonaka is currently engaged in his research work as a visiting research fellow at the Department of Epidemiology in Hiroshima. Partnership activities are ongoing. From UW, the above-mentioned two PhD students and other researchers have produced research results on radiation health effects based on RERF data. The UW members also said that, in addition to using RERF data, they had an opportunity to feel what the A-bombed city of Hiroshima has experienced through their stay at the Hiroshima Laboratory as a part of the exchange program. RERF research staff members have regularly visited UW to conduct research discussions, and Mr. Grant has had an opportunity to study epidemiology as a PhD student at UW. The three organizations agreed that it would be worthwhile to try to obtain research funding to continue the partnership program. It was noted that one example of collaborative projects to be promoted would be to analyze confounding and modification of radiation health effects by lifestyle and other factors based on information collected from past mail surveys, which was also a theme of this symposium. RERF needs to make systematic analyses in this area of research, which will be appropriate training of PhD students. Further development of the partnership program is eagerly anticipated.

Participants of the international symposium based on Radiation Research Partnership held at Hiroshima Laboratory

Chromosome Instability in Peripheral Blood T Lymphocytes from A-bomb Survivors—*In Vivo* and *In Vitro* Studies*

Kanya Hamasaki and Yoshiaki Kodama

Department of Genetics, Radiation Effects Research Foundation (RERF)

*This article is based on the following publications:

Ref. 1. Kodama Y, Ohtaki K, Nakano M, Hamasaki K, Awa AA, Lagarde F, Nakamura N. Clonally expanded T-cell populations in atomic bomb survivors do not show excess levels of chromosome instability. *Radiat Res* 164:618–26, 2005.

Ref. 2. Hamasaki K, Kusunoki Y, Nakashima E, Takahashi N, Nakachi K, Nakamura N, Kodama Y. Clonally expanded T lymphocytes from atomic bomb survivors *in vitro* show no evidence of cytogenetic instability. *Radiat Res* 172:234–43, 2009.

INTRODUCTION

In 1992, Kadhim *et al*.[3] reported that elevated levels of non-clonal *de novo* chromosome aberrations (mainly chromatid-type aberrations) occur in *in vitro* culture of mouse hematopoietic stem cells many generations after exposure to α particles *in vivo*. This event was defined as radiation-induced delayed genomic instability, which is distinguishable from the immediate effects of radiation. Many biologists have considered that such instability may play an important role in radiation carcinogenesis. It is now recognized that instability can be studied by not only chromosome alterations as a marker but also by other end points such as gene mutations and cell death.[4–8] While there are many reports using cultured cells *in vitro* or mouse cells *in vivo*, few studies on genomic instability have been done with normal human cells. In fact, it remains to clarify whether chromosome instability occurs *in vivo* in humans, especially in A-bomb survivors who were exposed to radiation many years ago.

In the Cytogenetics Laboratory (Department of Genetics, RERF), we have continued the efforts to examine the frequency of chromosomal aberrations in the lymphocytes of A-bomb survivors in order to either validate, or demonstrate biases in, the individual radiation dose estimates made by physical measurements. In this study, the stable type chromosome aberrations, such as translocations and inversions were examined, because unstable type aberrations, such as dicentrics and rings, have disappeared from the body during the long post-irradiation period. The problem for detecting the chromosome instability in A-bomb survivors is that there is no good way to distinguish the chromosome aberrations that were induced immediately after exposure in 1945 and the aberrations that occurred later as a result of genomic instability. Two methods were selected to resolve the issue. One is *in vivo* examination using clonal chromosome aberrations occasionally observed in peripheral blood T lymphocytes of A-bomb survivors[1] and the other is *in vitro* study using long-term cultured T-lymphocyte colonies obtained from survivors.[2]

IN VIVO STUDY

Clonal chromosome aberrations

Clonal chromosome aberrations, occasionally observed in the lymphocytes of A-bomb survivors, were defined as the identical aberrations detected in more than three cells in each blood examination. Such clonal chromosome aberrations are exclusively stable-type aberrations, mainly translocations and inversions. It was thought that the clonal aberrations originated from the stem cells that could survive a severe depletion of hematopoietic stem cells caused by radiation exposure. The frequencies of the cells with clonal chromosome aberrations were varied from case to case, up to 50% in the highest case. It was also reported that such clonal expansions probably occurred primarily in the first few years after the exposure.[9]

If new *de novo* chromosome aberrations can be shown to appear cell generations after irradiation in clonal cell populations, such aberrations are thought to be the consequence of genomic instability in the cell proliferations after irradiation (Figure 1). Therefore, we have collected the cells with clonal

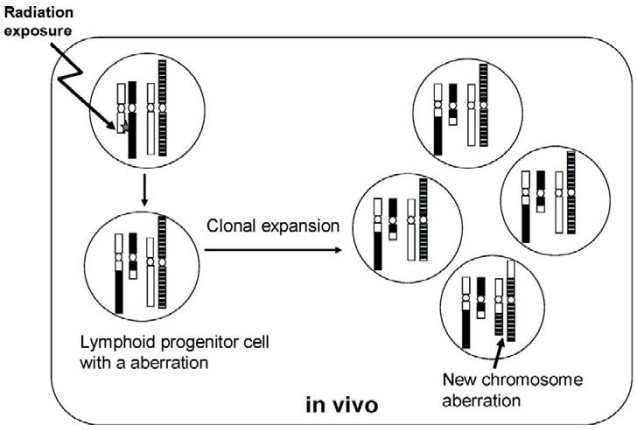

Figure 1. A lymphoid progenitor cell with a chromosome aberration (mainly translocations) caused by radiation expands clonally *in vivo* and these clonal cells can comprise a part of the total T-lymphocyte population. Additional subsequent *de novo* translocations generated in the clonal cell population are thought to be the consequence of genomic instability in later cell generations.

chromosome aberrations in the lymphocytes of A-bomb survivors and examined the newly induced chromosome aberrations in those cells.

Materials and Methods

G-band method

Peripheral blood lymphocytes were collected in the 1980s (41 years after the exposure, on average) from 50 A-bomb survivors whose estimated doses were more than 1 Gy. Blood samples were obtained from each of the subjects during periodic health examinations (every two years), for a total of three to six samples. After two days blood culture, chromosome slides were prepared by conventional air-drying methods. The total number of metaphases scored per donor averaged 760 (38,000 cells were examined in total). Only clones which can be seen in more than 10 cells were selected for the study.

mFISH method

Three survivors, who are known to carry large clonal populations from a previous study, were examined with multicolor FISH (mFISH) analysis (two of the survivor samples overlap with the G-band study subjects). The blood samples were obtained between 2000 and 2002. After 48 h blood culture, chromosome slides were prepared by conventional methods. mFISH was performed with Spectra Vision DNA probes (Vysis, Downers Grove, IL) according to the manufacture's protocol. Acquisition and analysis of mFISH images was performed using a CytoVision ChromoFluor System (Applied Imaging, Newcastle upon Tyne, UK). More than 100 clonal cells were scored for each sample. None of the blood donors (including the next *in vitro* study) had a medical history of cancer before blood drawing.

Results

G-band analysis

The results showed that 22 clones (952 cells in total) were detected from 18 survivors with G-band analysis (Table 1A). The average estimated dose of the 18 survivors was 2.5 Gy (0.8–3.6 Gy). Following the careful examination of the 952 cells, we found seven additional translocations. Since two of seven were found in the same subject (subject 3) and were identical translocations [t(7;14)], we counted these subclonal clones as a single event. Thus, the frequency of newly induced *de novo* translocations was 0.6% (6/951).

mFISH analysis

As shown in Table 1B, six clones were detected from three survivors (subjects 2 and 4 overlap with the G-band study). Eventually, we could observe four additional translocations in 333 clonal cell populations with mFISH (1.2%).

Comparison of in vivo data with the frequency of spontaneous aberrations

In this study, most of the blood samples were obtained about 40 years after radiation exposure and the mean age at the examination of the blood donors was about 61 years old. It was also known that the spontaneous frequency of translocations in blood lymphocytes increases with an increase in donor age.[10] Therefore, under the present conditions, it would be most appropriate to use the translocation data for unexposed individuals who were about 40 years old for comparison. Since spontaneous translocation rates increase with increasing donor age with upward curvature,[10] the increasing level of base-line translocation frequency among those of age 40 (irradiated soon after birth) is lower than those of

age 60 (irradiated at about age 20). Thus, we decided to use our own data with the G-band method which is based on 181 survivors in our *in utero*-exposed cohort with estimated doses of <5 mGy,[11] because the mean time span between the radiation exposure and the time when the blood samples were obtained for the G-band study in 1985 was 41 years. That study provided a value of 1.2% (219 translocations in a total of 17,878 cells scored). As shown in Table 1, compared with this spontaneous frequency of 1.2%, the frequency of additional translocations among clonal cell descendants was not higher: 0.6% with the G-band method and 1.2% with the mFISH method. Thus, chromosome instability with elevated frequency of additional translocation by past radiation exposure was not detected in this study.

IN VITRO STUDY

In the next study, we tried to evaluate the frequency of additional chromosome aberrations in clonally expanding T lymphocytes from A-bomb survivors with mFISH. This study was intended to provide information whether long-term *in vitro* forced cell proliferation can increase opportunities to obtain new *de novo* chromosome aberrations in culture (Figure 2).

Materials and Methods

Peripheral blood lymphocytes were obtained from four female A-bomb survivors. Among them, two were proximally exposed survivors whose estimated doses were 1.2 Gy (subject 2) and 2.0 Gy (subject

Table 1. Frequency of additional translocations among *in vivo* clonal cells examined

Subject no.[a]	Clonal chromosome aberration	No. of clonal cells [fraction of clonal cells (%)][b]	No. of clonal cells with additional translocations[c]	Additional translocations
A. G-band analysis				
1	t(3;4)	10 (1.4%)	0	
2	t(2;4)	48 (10%)	1	t(1;13)
			1	t(12;19)
3	t(2;12)	336 (14%)	2 (1)	t(7;14)
4-1	t(4;6),t(5;13)	62 (5.8%)	1	t(2;10)
4-2	t(1;2),t(2;15)	10 (0.9%)	0	
5	t(X;2)	20 (2.9%)	0	
6	t(1;6)	24 (4.0%)	0	
7	t(X;1),inv(2)	13 (1.8%)	0	
8	t(2;18)	34 (4.0%)	0	
9	t(X;5)	11 (2.0%)	0	
10	t(X;2)	16 (1.8%)	0	
11-1	t(6;9)	54 (6.3%)	1	t(5;18)
11-2	t(X;16)	40 (4.7%)	0	
11-3	t(14;15)	12 (1.4%)	1	t(7;14)
12	t(10;17),t(20;11)(11;22)	14 (1.8%)	0	
13	t(5;21),t(8;10)	72 (6.1%)	0	
14	t(13;15)	32 (4.4%)	0	
15	t(4;5)	10 (1.1%)	0	
16	t(X;15)	41 (7.0%)	0	
17-1	t(2;4)	18 (2.5%)	0	
17-2	t(1;2),del(5)	11 (1.5%)	0	
18	t(6;10),t(11;17),del(5)	64 (8.8%)	0	
	Total	952 cells (6.2%)	7 cells (6 events)	0.6%
B. mFISH analysis				
2	t(2;4)	101 (51%)	1	t(1;11)
			1	t(1;16)
			1	t(1;17)
4-1	t(4;6), t(5;13)	65 (12%)	0	
4-2	t(1;2), t(2;15)	31 (5.5%)	0	
4-3	t(16;20)	26 (4.7%)	0	
4-4	t(4;8)	10 (1.8%)	0	
19	inv(1), del(5)	100 (38%)	1	t(1;5;14)
	Total	333 cells	4 cells	1.2%

[a] Subjects with hyphens indicate multiple clones from the same cases.
[b] The fraction of clonal cells is expressed as the number of clonal cells divided by the total number of cells examined.
[c] Numbers in parentheses indicate the number of events.
t = translocation, inv = inversion, del = deletion

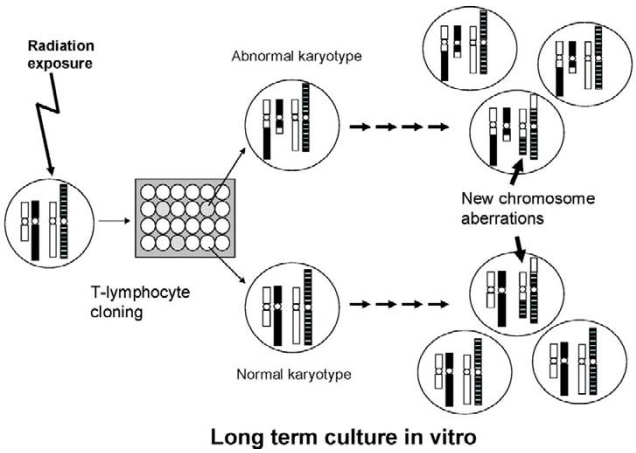

Figure 2. T lymphocytes from A-bomb survivors were clonally expanded *in vitro* to determine whether chromosome instability can develop during long-term cell culture.

4), respectively. Both are known to carry clonal chromosome aberrations *in vivo* with a high frequency (10–50%), and are overlapped with the *in vivo* study in the previous section. Such clonal aberrations in the two cases were also detected in the present study (described below). The other two survivors (subjects 20 and 21, whose estimated doses are less than 5 mGy) were age- and gender-matched controls to subjects 2 and 4, respectively.

T-lymphocyte cloning

T-lymphocyte cloning was conducted with conventional methods[2] and the cells were cultured until 10^6–10^7 cells were available for chromosome tests. For subjects 2, 20, and 21, the average culture time was approximately four weeks, and the number of population doublings was 23 to 25. In subject 4, T-cell colonies that had been cloned previously and cryopreserved[12] were thawed and cultured in a 24-well plate under the same culture conditions.[2]

mFISH analysis

Chromosome slides were prepared after 2 h colcemid treatment by conventional air-drying methods. One hundred cells were scored for each clone. The mFISH protocol is the same as described in the *in vivo* study.

Results

T-lymphocyte clones obtained from A-bomb survivors

In this study, a total of 66 clones were established from two highly exposed survivors (subjects 2 and 4) and two control individuals (subjects 20 and 21).

Subject 2. Twenty-two clones were obtained including eight clones with normal karyotype, eight with the clonal translocations [t(2;4)], five with other structural aberrations, and one with an aneuploid karyotype.

Subject 4. Fourteen clones were investigated. They consisted of four clones with normal karyotype, five with the double clonal translocations [t(4;6),t(5;13)], four with other structural aberrations, and one with an aneuploid karyotype.

Subject 20. Twelve clones were obtained, of which ten clones had a normal karyotypes, one had a structural aberration, and one had an aneuploid karyotype.

Subject 21. Of the 18 clones obtained, 14 clones had a normal karyotype and four had an aneuploid karyotype.

Since most of the aneuploid clones obtained in this study involved the X chromosome, and X-chromosome aneuploidy is known to take place commonly in cultured lymphocytes from elderly women,[13] these clones were categorized as a "normal karyotype" in Table 2.

Additional chromosome aberrations detected by mFISH

The types and the numbers of additional chromosome aberrations detected in each subject are summarized in Table 2. The results were also shown by the pooled data of exposed and control subjects, as well as by the difference in karyotype such as normal, *in vivo* clone, and other independent aberrations. As shown in the table, we could detect various types of new additional chromosome aberrations (see Figure 3 for example).

In order to evaluate the effects of A-bomb radiation on the occurrence of chromosome instability, we performed statistical analyses concerning the frequency of newly-induced chromosome aberrations during long-term culture *in vitro*. It is well known that mFISH is the most reliable technique for the detection of exchange-type aberrations such as translocations (and derivative chromosomes in this study). Thus, the frequency of stable, exchange-type

Table 2. Frequency of additional chromosome aberrations detected in clonally proliferated T lymphocytes *in vitro*

Subject no.	Karyotypes	Total cells	Additional chromosome aberrations						
			t	der	dic	dup	del	f	Total
2	Normal	900	7	5	0	0	21	12	45
	in vivo clone [t(2;4)]	800	5	3	1	2	18	12	41
	Other aberrations	500	3	4	19	0	9	4	39
	Total	2,200	15(0.7%)	12(0.6%)	20(0.9%)	2(0.1%)	48(2.2%)	28(1.3%)	125(5.7%)
4	Normal	500	1	1	0	2	8	10	22
	in vivo clone [t(4;6),t(5;13)]	500	3	6	1	5	12	9	36
	Other aberrations	400	1	0	1	2	5	4	13
	Total	1,400	5(0.4%)	7(0.5%)	2(0.1%)	9(0.6%)	25(1.8%)	23(1.6%)	71(5.1%)
Exposed (subjects 2 + 4)		3,600	20(0.6%)	19(0.5%)	22(0.6%)	11(0.3%)	73(2.0%)	51(1.4%)	196(5.4%)
20	Normal	1,100	3	8	0	3	12	15	41
	Other aberrations	100	0	0	0	0	2	0	2
	Total	1,200	3(0.3%)	8(0.7%)	0(0.0%)	3(0.3%)	14(1.2%)	15(1.3%)	43(3.6%)
21	Normal	1,800	4(0.2%)	2(0.1%)	2(0.1%)	3(0.2%)	40(2.2%)	25(1.4%)	76(4.2%)
Control (subjects 20 + 21)		3,000	7(0.2%)	10(0.3%)	2(0.1%)	6(0.2%)	54(1.8%)	40(1.3%)	119(4.0%)

t = translocation, der = derivative chromosome, dic = dicentric chromosome, dup = duplication, del = deletion, f = fragment

aberration (translocation + derivative chromosome; t + der) was used for the statistical evaluation. The results indicated that the frequency obtained from the exposed cases (1.1%, 39/3,600) was greater than that of the control (0.6%, 17/3,000), the difference was not statistically significant, however ($P = 0.101$) (Table 3). Similarly, no statistical difference was found for the total structural aberrations ($P = 0.142$).

The frequency of additional chromosome aberrations in "*in vivo* clonal aberrations" that showed the highest frequency of additional aberrations among three different karyotypes in the exposed group, was also compared with that of "normal karyotype" populations in control subjects to examine the effects of the karyotype difference. As shown in Table 3, the frequency of new aberrations among the clonal cell populations was not much different from that in the control individuals ($P = 0.114$ for t + der and $P = 0.130$ for total structural aberrations).

As described above, there was no clear evidence suggesting the presence of chromosome instabilities among the clonally expanded lymphocytes *in vitro* from A-bomb survivors.

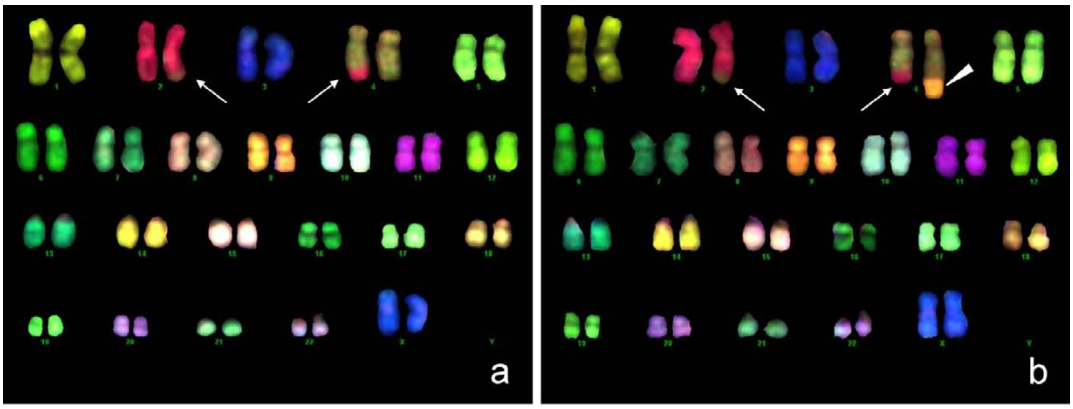

Figure 3. Detection of additional *de novo* chromosome aberrations with mFISH (Subject 2, *in vivo* clone in Table 2). Panel a: Translocation alone, 46,XX,t(2;4). Panel b: Translocation plus non-clonal aberration, 46,XX,t(2;4),der(4)t(4;9). Arrows indicate the translocation between chromosomes 2 and 4 and arrowhead shows the additional aberration (derivative chromosome) involving chromosomes 4 and 9. Two normal intact number 9 chromosomes are evident.

Table 3. Statistical analyses of the additional chromosome aberration frequencies

	t + der		Structural aberrations	
Exposed (subjects 2 + 4)	39/3,600 (1.1%)	*P = 0.101	196/3,600 (5.4%)	*P = 0.142
Control (subjects 20 + 21)	17/3,000 (0.6%)		119/3,000 (4.0%)	
In vivo clonal aberrations	17/1,300 (1.3%)	*P = 0.114	77/1,300 (5.9%)	*P = 0.130
Controls (only normal)	17/2,900 (0.6%)		117/2,900 (4.0%)	

* Wald test using quasi-likelihood method.

REASONS FOR A LACK OF CHROMOSOME INSTABILITY

As described above, we made an effort to find radiation-induced chromosome instability in the lymphocytes of A-bomb survivors, but no clear evidence was obtained in both *in vivo* and *in vitro* studies.

Although a number of studies have used human cells and focused on chromosome aberrations as an index for radiation-induced genomic instability, the results, both positive and negative, have not always been concordant.[14–26] Such inconsistencies might be due partly to different genetic backgrounds, or different radiation sensitivities, among individuals. Considering the polymorphism of individual genetic factors, the sample size of our present studies (1,300 cells from 19 people for the *in vivo* study, 6,600 cells from four persons for the *in vitro* study) might not be enough to evaluate the instability. Alternatively, the results are interpreted to indicate that the instability, if it exists, is not an event that is frequent enough to be easily detected in the experimental size that we used.

Additionally, it is possible that individuals among the A-bomb survivors who were genetically predisposed to the induction of radiation-associated instability were already eliminated from the population due to early death from cancer. However, this seems unlikely because cancer risk started to increase years after the radiation exposure and is still elevated today, in proportion to the increase in the background rate.

Since the numbers of studies searching for radiation-induced genomic instability with normal human cells are still insufficient, it is necessary to accumulate data by additional studies. Recently, an increase of relative risk of myelodysplastic syndrome (MDS) in A-bomb survivors has been reported.[27] That report suggests a possible involvement of genomic instability in radiation carcinogenesis in A-bomb survivors. In that context, further investigation of radiation-induced chromosome instability in hematopoietic stem cells of A-bomb survivors might be important. If any findings on genomic instability could be obtained at the blood stem cell level, they would serve as new data in terms of development of radiation-induced instability *in vivo*.

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Participating in the Health Examination/Consultation Project for A-bomb Survivors Living in South Korea

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[Summary]

A health examination/consultation project for A-bomb survivors residing in North and South America has been conducted for some time under the leadership of the Hiroshima prefectural government, but no comparable project targeted A-bomb survivors living in South Korea. A contract for an assistance program for A-bomb survivors residing in South Korea was signed in August 2003 between the Nagasaki prefectural government, entrusted by the Japanese government, and the Republic of Korea National Red Cross, entrusted by the South Korean government. The aim of the program was to promote issuance of A-bomb survivor health handbooks for those residing in South Korea and to help the survivors visit Japan to undergo medical treatment. As part of the program, the health examination/consultation project was begun in fiscal year (FY) 2004. The project's objectives include "working on early detection and treatment of disease via health examinations, addressing concerns about aftereffects of A-bomb radiation exposure in cooperation with Japanese A-bomb disease experts, and endeavoring to enhance the health of A-bomb survivors."

For the purpose of detecting potential problems ahead of the FY2005 introduction of the full-scale project targeting about 2,400 A-bomb survivors living in South Korea, a pilot consultation project was performed twice in 2004, once in the rural area of Hapcheon and once in the cities of Dejong and Pyeongtaek. On the basis of the results of the trial runs, it was decided with regard to the procedures for the full-scale health examination/consultation project that health examinations would be performed in advance at regional Red Cross hospitals and that Japanese physicians would make final diagnoses and provide health consultation with use of the relevant laboratory data and clinical findings, in addition to information from the questionnaire survey conducted on the day of the consultation project.

Ultimately, the first full-fledged round of the project was conducted in Seoul in June 2005 in cooperation with the Seoul Red Cross Hospital. Since A-bomb survivors reside throughout the country, the project was subsequently performed biannually in Tegu, Hapcheon, Busan, Masan, Gwangju, Pyeongtaek, and Dejong, where a relatively large number of survivors live, with support from the respective regional Red Cross hospitals, for a total of nine times through September 2009. The second cycle of the project is currently under way. Every round of the relevant project garners particularly high interest among A-bomb survivors residing in South Korea: about 72% of the target population has undergone health examinations at regional Red Cross hospitals, and about 83% of that number have participated in the final diagnoses and health consultation conducted by Japanese physicians.

Members of the health examination/consultation team for A-bomb survivors living in South Korea including Korean collaborators. Dr. Masazumi Akahoshi is the fourth person from the right in the front row.

[Details of the health examination/consultation project for A-bomb survivors]

The health examinations conducted in advance at regional Red Cross hospitals are classified into two types: comprehensive health examinations (exclusively for those with A-bomb survivor health handbook and/or certificate acknowledging A-bomb exposure) and basic health examinations (for those without the relevant handbook/certificate). The contents of the comprehensive examination are considered equal to those of the regular health examinations conducted

under the Adult Health Study (AHS). Based on the results of laboratory tests, physicians at the regional Red Cross hospitals indicate a preliminary, comprehensive diagnosis and describe overall findings (in notes to participants) in medical charts, which are translated into Japanese by the translation staff from the Republic of Korea National Red Cross. With regard to the tests—electrocardiogram, chest X ray, computerized tomography, gastric endoscopy, abdominal ultrasonography, and mammography—actual images are borrowed from the respective hospitals and are used as needed during final diagnoses/health consultations. In this regard, I have the utmost respect for the efforts made by the staff in charge of such operations. In collaboration with the Takashi Nagai Memorial International Hibakusha Medical Center, Nagasaki University Hospital, and the Republic of Korea National Red Cross, a database for laboratory data and names of diagnosed diseases obtained under the health examination/consultation project was established one year ago. We are allowed access to this useful database and permitted to utilize the data in making our final diagnoses and conducting the health-consultation activities. As if this work provided a good opportunity to forge international relationships, a Japanese physician from the medical center apparently married a Korean staff member from the Red Cross sometime this year.

On the day of the final diagnosis/health consultation, volunteer nurses performed body temperature and blood pressure measurements, as well as conducted a questionnaire survey. On the basis of the health examination results, which were translated into Japanese, and information from the relevant questionnaire survey, we Japanese physicians took about one hour to talk to each of the participants, explain about the relevant health issues, and make final diagnoses. We also gave advice to Korean physicians regarding detailed examinations and/or provided guidance on courses of treatment. Different from the health examination program targeting A-bomb survivors in North and South America, very few Korean participants were able to understand Japanese, and even though some participants could pick up on the meaning of Japanese conversation, they were unable to speak. Consequently, interpreters, whose dedication has always impressed me, were assigned to each physician for support.

I had the impression that a large number of Korean people suffer from back/knee pain, presumably due to the South Korean lifestyle on the *ondol*, or heated Korean floors. This was the reason for including in the project team an orthopedic surgeon, a physical therapist, and a nurse that instructed the participants in calisthenics. In South Korea, rehabilitation following orthopedic surgery is lacking, and hence guidance for rehabilitation by the physical therapist and calisthenics instruction by the nurse were apparently well received among those concerned.

Observed among many A-bomb survivors living in South Korea are such lifestyle diseases as obesity, fatty liver, hypertension, diabetes, and cancer, not very different from the diseases in Japan. In Hapcheon, however, in a first for the Japanese physicians, several participants suffered from clonorchiasis, presumably due to their custom of eating raw river fish.

Many of South Korea's A-bomb survivors already have either A-bomb survivor health handbooks or A-bomb exposure certificates and thereby receive medical allowances. For those who do not possess those two documents, however, staff members from the Nagasaki prefectural and municipal governments and South Korea's Red Cross provide consultation services concerning acquisition of such materials. Furthermore, the staff members provide consultation services concerning administrative procedures relating to applications for health management allowance, A-bomb disease recognition, the assistance project for medical treatment in Japan, and other issues.

With regard to the full-scale project, each team is typically composed of four internal medicine specialists, one orthopedic surgeon, one physical therapist, one nurse, and four employees of the Nagasaki prefectural and municipal governments from Japan; and one physician, nine employees from South Korea's Red Cross, eight interpreters, six volunteer staff members from the Red Cross, and four volunteer nurses from South Korea. With regard to successful completion of the total of nine rounds of the health examination/consultation project for A-bomb survivors residing in South Korea carried out thus far, I would like to express my great appreciation for the cooperation and mutual understanding of those concerned, with the hope that any future projects yield fruitful results.

Work at the Nursing Sections in Hiroshima and Nagasaki

When ABCC started its research in 1947, there were only two nurses. As the research project developed, however, additional nurses were recruited, and by the time of initiation of the Adult Health Study (AHS) 50 years ago, the nurses numbered 40 and 16 in Hiroshima and Nagasaki, respectively. The nurses were required to work under circumstances quite different from those of other medical organizations, and with by paying special attention to the study participants' feelings, they contributed significantly to the development of nursing at ABCC-RERF and to the success of the institution. The observations below are excerpted from the writings of current chief nurses **Michiko Kuwamoto** (Hiroshima) and **Yumiko Yamashita** (Nagasaki) reflecting back on the 50th anniversary of AHS and the 25 cycles of biennial examinations.

In the early stage of AHS there was a long series of struggles and adjustments. The first director of the ABCC nursing staff was Ms. Louise Cavagnaro from the U.S. The second director, the late Ms. Chiyoko Watanabe from Japan, wrote in her memoir about the early days of ABCC: "Post-war Japanese medicine, nursing in particular, developed with an American influence. ABCC was a place where such an influence could be felt firsthand. We could learn many things through our daily work, as if we were studying aboard. We were surprised at everything we saw or heard just like we were still nursing students. To persons who know only modern-day prosperity, this may be a laughing matter, but back then, for example, we saw paper towels for the first time and were shocked to know that these towels were disposable. We could not help folding and keeping used paper towels on the edge of a shelf out of thrift—a habit that would evoke Ms. Cavagnaro's chiding 'No good!' to our embarrassment."

ABCC received patients and the nurses periodically rotated themselves between the sickroom and the outpatient department. The sickroom was equipped with about 10 beds, and the majority of patients had blood-related disorders. There were many U.S. physicians at ABCC then, and the hospitalized study participants may have had an uneasy feeling stemming from communication difficulties with these American doctors so it is not hard to imagine that the nurses at that time had many challenges. Of the outpatient department, a former chief of nurses remembers: "Flow of medical consultation at that time was different from that of today. Examinations and consultation by Japanese doctors would be followed by checks by American doctors. During the waiting time in between, some study participants would start telling stories involving the atomic bombings. The stories were often painful for us to listen to; however, we found that such stories were very important to enable us to really understand the survivors' concerns and feelings, and to fully comprehend the disastrous events that occurred in Hiroshima and Nagasaki."

Nursing Section staff in 1953, Hiroshima Laboratory

In 1972, there were changes in the work of the nurses. The sickroom, where treatment took place, was closed, and in addition to the clinical examinations, ABCC staff visited the homes and hospitals of study participants who were unable to visit ABCC. Staff were each assigned to visit 2–3 persons in a half-day time period. Due to busy schedules, the staff often had just enough time for only examinations and little time for conversation with the participants. In the limited time, however, staff tried to talk with the participants and provide as much advice as possible. The ABCC staff initially wore a white robe to visit

the participants, but were told that the participants did not like to receive persons in white, because such clothes would catch the attention of their curious neighbors. So the staff began conducting the visits wearing street clothes and a name tag. They also reevaluated the gown and slippers, into which the participants changed at the clinical department, and made necessary changes for the participants' convenience and comfort.

It was important for the nurses to understand a participant's individual feelings and circumstances. For example, some unwillingly visited ABCC for examination because they could not refuse the repeated requests from ABCC staff, or visited ABCC unwillingly because the staff came over to pick them up. Paying close attention to the participants' feelings, making their visits as comfortable as possible, and sending them home without any problems were all part of the mission of the nurses and something they always kept in their minds as an attitude that has been maintained since the earliest ABCC years.

ABCC sometimes received thank-you letters from the participants after examinations, and often these letters said, "You listened to my stories well," or "You gave me appropriate advice." Unlike the visitors to other hospitals, a majority of those visiting ABCC-RERF were relatively healthy persons who were asked to take time to visit Hijiyama, who sometimes took our well-intentioned health tips as something uninvited, and who often were required to stay at RERF for a prolonged time to fill out lengthy questionnaires. Since our participants who provide support to the AHS are aging, nurses are required to change their approaches and always seek better approaches.

The Nursing Section has made a continued effort to develop trust with the study participants by properly treating individual participants, in the hope that all participants will visit the organization again for examinations every two years. There have been participants, who complained about the foundation, were upset about the content of questions requiring lengthy answers, or who indignantly questioned the nurses why their diseases had not been detected earlier despite their continued participation in examinations for years. Some said that they would never come for the examinations again. If we had such participants as described above, we made contact with the Clinical Contacting Section and tried to accurately tell them why the participants were unsatisfied or unhappy, so that the contactors could utilize our report when they contacted the participants in the future.

In the early years, the survivors were often in poor hygienic and nutritional conditions, and some visitors to ABCC were suffering from infectious diseases. On such occasion, extra care was paid to prevent infection at ABCC, and after the examinations, the examination room including its walls was wiped with antiseptic solution, and used linen was all disinfected. Iron was prescribed for participants with anemia until their conditions returned to normalcy. Also, there were some participants with persistent general dermatitis, which was cured by ABCC's ointment that gave the survivors great comfort. Special examinations in the Nursing Section included a gastrocamera and a bone marrow puncture. Participants suspected of leukemia underwent bone marrow puncture and were introduced to hospitals with their examination records from ABCC. Although the Nagasaki Laboratory did not receive patients for treatment, medicine was prepared there also and, according to the doctors' instructions, limited provision of medicine was available for those with the above-mentioned anemia and skin disease.

Ms. Cavagnaro also visited Nagasaki to instruct the staff there. Based on a translated version of Manual of Nursing Procedures, she prepared nursing procedures for the staff, which have been modified for use. In 1967, a revised version was prepared by Chief Watanabe of the Nursing Section in Hiroshima and others, and later, a third revision was published. The late Ms. Teiko Ohki, who served as a chief of the Nursing Section in the early years of AHS, wrote about the directions for nurses as follows: "Nurses are persons who can understand the basic matters required for human health and best respond to the persons in need of such matters. To achieve their goals, nurses must acquire knowledge in nursing in line with scientific progress of the society, fully utilize the knowledge as required by individuals or society, and have an ability to collaborate/cooperate with other specialists including physicians and pharmacists. At ABCC in particular, nurses are also required to try their best to create an environment, in which the study participants can feel a sense of trust and safety."

Since ABCC was an organization conducting epidemiological research, standardizing protocol procedures was most important. That required maintaining close contact between the Hiroshima and Nagasaki Laboratories. The success of the AHS examinations owes much to the Hiroshima and Nagasaki nurses for their consistent performance of multiple tasks, their required skills, and for their patience and understanding in being the primary contact with the AHS participants. As Ms. Yamashita summarized: "To this day, there are many participants who nostalgically mention the names of some former nurses, and I feel that a trust has long been established between the participants and the Foundation."

In Memoriam

The RERF family was saddened to learn that Victoria Margaret Schull, the wife of William J. Schull, died on October 13, 2009 after a prolonged illness. Born March 11, 1922, Mrs. Schull was 87 years old. She and Dr. Jack Schull had recently celebrated their 63rd wedding anniversary. "Vicki" as she was affectionately known, joined her husband in Hiroshima in 1949 during the early days of ABCC, shortly after Jack was hired by the National Research Council to join ABCC, and as soon as housing became available in Hiroshima. Vicki embraced Japanese culture, became proficient in speaking Japanese, and her companionship helped serve as an inspiration to Jack for his frequent service to ABCC and RERF over a period of almost 50 years, including holding the position of Vice Chairman and Chief of Research as late as 22 January 1997.

William Jack (left) and Victoria (center) Schull with former RERF chairman Itsuzo Shigematsu (right) at a farewell party in 1987

RERF Staff's Strengths Demonstrated at Open House Events

Takanobu Teramoto, Permanent Director

RERF held Open House events on August 5 and 6, 2009, in Hiroshima and on August 8 and 9 in Nagasaki, with this year marking the 15th and 13th of the annual summer events, respectively. Some visitors attend the Open House every year, such as A-bomb survivors, local citizens, and employee family members, while some individuals from all over Japan and the world for that matter visit RERF for the first time on the dates commemorating the atomic bombings of Hiroshima and Nagasaki. Taking the opportunity presented by the Open House to publicize RERF's activities, we start preparations for the events around the beginning of each year by deciding on the year's event theme and specific plans. Then in the spring of the year we establish Open House working committees. This year's theme was "Radiation and health sciences founded on the basis of international cooperation," a future-oriented theme that reflects RERF's commitment to expand its research collaborations and become a global center of excellence, as stated in its future plans. In the special exhibition on this theme, RERF's worldwide collaborations with research institutes and international agencies, researchers visiting RERF from various parts of the world for training, and RERF researchers' global activities were introduced using a world map. We felt very encouraged when several visiting Japanese Diet members, who were astounded to know that RERF's international collaboration extends to five continents throughout the world, promised their firm support for RERF.

Of special note about this year's events is that employee participation was further strengthened and employee ingenuity was utilized in numerous ways. In addition, as part of employee training, some of our staff members studied how to greet and welcome visitors and put such instructions into practice at the time of the Open House. Cooperation and coordination between Hiroshima and Nagasaki Laboratories were also enhanced through preparations and displays of posters and leaflets.

Visitors totaled 617 and 566 in Hiroshima and Nagasaki, respectively. The turnout in Hiroshima was down considerably from last year's 1,355, due to activities related to the Lower House elections. However, there was also a positive side to the lower numbers, because we were able to spend more time with each visitor and explain our operations in more detail. The turnout in Nagasaki was higher by as much as 46%, compared with last year's 388. Although the Nagasaki event also was held during the election campaign, the efforts of the Nagasaki Laboratory staff to publicize the event proved particularly effective. They allowed day-care programs for school children during the summer vacation to incorporate the RERF visit into their education programs. On the days of the events, children took turns looking at their own bodies' cells with a microscope and watched flowers being frozen solid by –196°C liquid nitrogen. It probably was their first science experiment.

The Open House in Nagasaki this year was held on Saturday and Sunday. For that reason, the event must have been a burden on the staff and their

After a swab of their mouths, children were able to look through a microscope at their own buccal cells at Open House 2009, Nagasaki Laboratory

Number of Visitors to RERF Open House

Year	2004	2005	2006	2007	2008	2009
Hiroshima	850	1,062	1,382	967	1,355	617
Nagasaki	230	306	528	484	388	566
Total	1,080	1,368	1,910	1,451	1,743	1,183

families. The staff in Hiroshima had the same experience a few years ago. However, considering the meaning of the A-bombings for the mission and research activities of RERF, we have maintained the policy of holding the Open House events on the anniversary of the atomic bombings, and the previous day in each city.

Meanwhile, the Green Club at Hiroshima RERF grew beautiful sunflowers in time for the Open House. The typical impression of a research institute—indifferent and unfriendly— seems to have vanished from RERF over the years. I would like to express my sincere appreciation to all directors and staff at RERF and the RERF Labor Union for their cooperation and support during the Open House events.

DS02 Errata

It is not unexpected that in the course of publishing a two-volume treatise such as the revised dosimetry for the A-bombs (DS02), that subsequent review would yield some typographical or technical errors. The following errata have been called to RERF's attention:

Chapter 4, Table 5A, page 240: In the title of the table, change the first coordinate of the DS02 hypocenter from "27.721" to "26.721."

Chapter 12, Table 7, page 844: In the section of the table for Neutrons, replace the energy group upper bounds as follows:

Group Number	Upper energy bound (MeV)	
Neutrons	(previously published value)	correct value
3	(1.45E+1)	1.49E+1
4	(1.40E+1)	1.42E+1
19	(2.05E+0)	2.31E+0
20	(1.61E+0)	1.83E+0
21	(1.26E+0)	1.42E+0
22	(1.03E+0)	1.11E+0
43	(5.71E-5)	1.07E-5

Research Protocols Approved in April–September 2009

RP 1-09 A Nested Case-Control Study of Factors Contributing to Acceleration of the Development of Hepatocellular Carcinoma Using Stored Sera (Addendum to RP 1-04)
Ohishi W, Fujiwara S, Cologne JB, Akahoshi M, Nishi N, Suzuki G, Tsuge M, Chayama K

This research protocol is an addendum to RP 1-04. The objective of RP 1-04 is to study the effects of radiation exposure, hepatitis virus infection, and lifestyle-related factors on the risk for development of hepatocellular carcinoma (HCC). In this study, we indicated that hepatitis B virus and hepatitis C virus infection, obesity, and alcohol consumption are independent risk factors for HCC. Furthermore, the ongoing analyses suggest that radiation exposure may contribute to increased HCC risk, irrespective of hepatitis virus infection. With this addendum protocol, we will measure biomarkers related to chronic inflammation and/or insulin resistance that are considered important factors contributing to acceleration of the development of HCC using stored sera among subjects of this nested case-control study (RP 1-04), as well as examine their contribution to HCC risk.

RP 2-09 Study on Secondary Cancer Risks after Radiotherapy among A-bomb Survivors
Yoshinaga S, Nishi N, Soda M, Akahane K, Doi K, Moriwaki H, Hsu WL, Hida A, Yamada M, Katayama H, Shimada Y, Fujiwara S, Akahoshi M, Suyama A, Kasagi F, Ozasa K

The studies of cancer risks among A-bomb survivors have mainly focused on the relationship with A-bomb radiation, and less attention has been paid to other sources of radiation. The primary goal of this study is to evaluate the combined effects of the A-bomb radiation and therapeutic radiation delivered at two different times. The study population is a subgroup of members of the Life Span Study who were confirmed to undergo radiotherapy in the preceding study. Outcomes of primary interest are cancer incidence and mortality after radiotherapy. In addition to analyzing risk of second cancers in relation to therapeutic radiation dose, we will also analyze the modification effects of A-bomb radiation on the second cancer risk associated with radiotherapy. This study will provide new insight into the possible effects of two different types of radiation delivered at different times on cancer risk.

RP 3-09 Development of an Integrated Scoring System for Human Immune Competence as It Relates to Age and Ionizing Radiation
Hayashi T, Kusunoki Y, Imai K, Yoshida K, Ito R, Ohishi W, Fujiwara S, Ozasa K, Furukawa K, Geyer SM, Weng NP, Sempowski GD, Yasutomo K, Koyasu S, Murasko D, van den Brink MRM, Manley NR, Nikolich-Zugich J, Hirabayashi Y, Iwama A, Inoue T, Inaba K, Seed TM, Douple EB, Nakachi K

RERF's epidemiology and clinical studies have long indicated that there are significant increased risks of age-related and immune system/inflammation-related diseases among A-bomb survivors. Further, the noted radiation effects on the immune system are similar to those associated with simple aging. The objective of this study is to develop an integrated scoring system for evaluating immunological and inflammatory status of individuals as a function of age and radiation dose, and predicting the effects of radiation on the immune system and somatic mutation in exposed subjects. A cross-sectional analysis is proposed that will include about 2,300 Hiroshima Adult Health Study (AHS) subjects as well as an additional 1,300 subjects in an extended AHS cohort of Hiroshima survivors. A longitudinal analysis is proposed that will include a subset of 300 AHS subjects randomly selected from the 2,300 AHS subjects who had samples collected between 2000–2002 and will use stratified random sampling based on radiation dose group, age group, and gender. Biomarkers will be measured on 600 plasma samples collected from the 300 AHS subjects using antibody chip arrays. Two samples will be used for each of the randomly selected subjects; those collected between 2000–2002 and those collected between 2010–2012, resulting in sets of samples about 10 years apart. Telomere length assays will also be conducted on DNA from the same 600 samples. Effects of radiation exposure on aging markers in the thymus will be evaluated based on pathological review and molecular analysis. The results will be utilized to construct integrated scoring systems that effectively reflect overall immune-related health, and how that immune status differs across varying age and radiation groups.

RP 4-09 Effects of Ionizing Radiation Exposure and Aging on Vaccination Responses
Hayashi T, Kusunoki Y, Imai K, Yoshida K, Misumi M, Ohishi W, Fujiwara S, Ozasa K, Geyer SM, Yasutomo K, Koyasu S, Sempowski GD, Murasko D, van den Brink MRM, Weng NP, Manley NR, Nikolich-Zugich J, Hirabayashi Y, Iwama A, Inoue T, Inaba K, Seed TM, Douple EB, Nakachi K

Our past studies have revealed that radiation exposure was associated with reductions in the relative numbers of naïve T cells and IL-2-producing cells, both of which are closely involved in determining an individual's protection in response to vaccination. In addition to an impaired immune system, the tendency of a persistent inflammatory response is still observed in some of the atomic-bomb

(A-bomb) survivors, even more than 60 years after the A-bombings. Therefore, it is important to examine whether the impaired immune system results in a modified vaccine response among A-bomb survivors. This study is designed to evaluate the effects of prior A-bomb radiation exposure on the immunological capacity of aging individuals to respond to influenza vaccination. We will recruit 50 subjects for a pilot study and 300 subjects for the full-scale study by stratified random sampling of dose group, age group, and gender. Adult Health Study subjects will be recruited to this study over a period of three years. Collection and storage of blood plasma and lymphocyte samples will be conducted before and three weeks after the vaccination. The primary endpoint will be the change in anti-influenza virus antibody titer levels from before to three weeks after vaccination. Secondary endpoints to be analyzed include levels of cytokines and inflammation-related proteins, lymphocyte subsets, intracellular activation markers (mRNA and protein), and *HLA* genotype. Those parameters will be analyzed in relation to age and dose of prior radiation exposure.

RP 5-09 Effects of Radiation Exposure and Aging on Hematopoietic Stem Cells (HSCs) and Dendritic Cells (DCs)—Analyses of Numerical and Functional Changes

Kusunoki Y, Yoshida K, Hayashi T, Geyer SM, Misumi M, Ohishi W, Fujiwara S, Ozasa K, Hirabayashi Y, Iwama A, Koyasu S, Yasutomo K, Inoue T, Inaba K, Manley NR, van den Brink MRM, Sempowski GD, Nikolich-Zugich J, Weng NP, Murasko D, Seed TM, Douple EB, Nakachi K

Sufficient ionizing irradiation can diminish homeostatic control of blood cell production, including the primary cells comprising the immune system. Recent mouse studies suggest that advancing age is associated with a deficiency in the maintenance of hematopoietic function as well as an effect on adaptive immunity. Dendritic cells (DCs) are thought to be crucial, not only in triggering primary immune responses against pathogens, but also in the control of adaptive immunity. To delineate the long-term consequences of prior A-bomb irradiation and advancing age on homeostatic control of hematopoietic stem cells (HSCs) and DCs, we will analyze numerical and functional changes within the circulating HSC and DC pools among several hundred individuals who are currently participating in the Adult Health Study (AHS) at RERF in Hiroshima. Although blood samples to be provided by the AHS participants will primarily be analyzed at RERF, some of the assays will be done outside RERF by collaborating investigators, i.e., DC functional molecules will be assessed at a laboratory in the United States (Duke University) using total RNA/culture supernatant from DC cell fractions; and self-renewal and differentiation potentials of HSCs will also be analyzed at another laboratory in the United States (Memorial Sloan-Kettering Cancer Center) if methods for these HSC functional assays cannot fully be introduced at RERF. Finding significant alterations in the numbers and functions of circulating HSCs in relation to age and radiation dose would support our working hypothesis that A-bomb irradiation accelerated aging of the lymphohematopoietic system. Further, if significant alterations in the numbers and functions of circulating DCs are observed as well (i.e., in relation to age and radiation dose), this would support our hypothesis that A-bomb irradiation affected primary and adaptive immunity, possibly by altering DC populations toward T-cell inhibitory types. In order to support these A-bomb survivor studies, we will develop a series of *in vitro* and *in vivo* assay systems for the purpose of a) determining the functional and differentiation status of HSC and DC populations following *in vitro* or *in vivo* irradiation, and b) uncovering radiobiological mechanisms of immunosenescence relative to HSC and DC populations.

Recent Publications

(Japanese): the original article is in Japanese.

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Publications Using RERF Data

The following publications represent research done by non-RERF scientists based on the data publicly available from RERF.

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