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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

Konnichi waii otenki desu ne!...

We do hope that you'll find the contents of this latest volume of the *RERF Update* both informative and enjoyable. Despite our best effort to catch on our reporting of RERF's activities, we're still a little behind. Please bear with us; for in getting this issue out, we believe that we will be able to start reporting on the most current of issues.

We thought that you'd appreciate seeing a picture of our new sign that has been recently installed in front of the main entrance to RERF. We find this addition, along with all the currently upgrading and renovations to the physical plant to be quite symbolic of RERF's current status.....full of new starts, new hopes, and plans for the future. The *RERF Update* is no exception, for we are intent on innovating and improving the quality and the timeliness of our reporting of RERF activities. For example, in terms of this volume of the *RERF Update*, we believe that you'll enjoy the science articles by Harry Cullings, summarizing the major findings of new DS02 report, and the report by Yuko Hirai on her new, rather surprising observations of the relatively high incidence of a genetic variant within the Life Span Study (LLS) cohort that has been previously linked to both radiosensitivity and susceptibility. Further, the human interest story by Akio Awa on RERF's involvement with a Chernobyl firefighter provides an insight into the global nature of RERF activities, specifically as they relate to the long term health effects of ionizing irradiation.

We are pleased to introduce below an e-mail let-

ter from Mr. Kenji Joji, who retired in 1984 as chief of the RERF Translation Office. He congratulates us on the revival of *RERF Update*.

So please enjoy this volume, and of course feel free to drop us a line and let us know your thoughts on our reporting of RERF's many activities.

Sincerely,



Thomas M Seed
Editor in Chief



Yuko Ikawa
Technical Editor



Letter to the Editor

Thank you very much for a copy of *RERF Update* Vol. 16, 2005, which I received in today's mail. I had been very concerned, for the last issue I received was Vol. 15, Spring 2004. I am looking forward to enjoying your latest issue, for *RERF Update* has been a historical documentation of RERF since its inauguration in 1989 with Dr. J.W. Thiessen being the first Editor-in-Chief and Ms. Beth Magura, the Managing Editor.

As I have the entire series in a number of binders, it would be greatly appreciated if you would kindly arrange to place me on your mailing list as in the past.

I am also grateful to your *RERF Newsletter** in bringing me up to date on the development and activities of RERF.

Sincerely yours,

Kenji Joji
September 30, 2006

* *RERF* intra-institutional publication distributed to former and present RERF employees

Recommendations of the 32nd RERF Scientific Council and Our Responses

The 32nd Scientific Council meeting was held on March 9–11, 2005 at the Hiroshima Laboratory, and co-chaired by Drs. Yasuhito Sasaki and Gloria M. Petersen, with the aim of reviewing RERF's research programs. The meeting opened with RERF Chairman Dr. Burton G. Bennett's remarks, followed by an address from Mr. John S. Shaw, Assistant Secretary of the U.S. Department of Energy. Subsequently, there was a Chief of Research report, including a summary of the tentative RERF future plans, and then the department chiefs made presentations summarizing the current status of departmental research programs. After that, departmental representatives reported on specific research projects; the departments of Epidemiology and Clinical Studies made presentations on the first day and the departments of Genetics, Radiobiology/Molecular Epidemiology, Statistics, and Information Technology on the second day. Upon completion of the departmental presentations, the Scientific Councilors held a one-hour closed meeting with the RERF administration in order to discuss other issues. Then there were informal department meetings attended by subgroups of the Scientific Councilors as well as the relevant research scientists, and over the course of the meetings, problems were reviewed and departmental in-depth reports made.

The 32nd Scientific Council made nine general recommendations. The following are our responses to the recommendations:

1. We very much appreciate the Scientific Council's consideration at what is a very crucial period for RERF, as in addition to three senior staff retirements, the Vice Chairman (Dr. Taira) and one Chief Scientist (Dr. Suzuki) left at the end of March, and the Chairman (Dr. Bennett) as well as the Chief of Research (Dr. Tahara) will step down at the end of June. As recommended by the Council, we will initiate strategic planning for the near-term future of RERF to ensure that scientific productivity will not be hampered.
2. We again appreciate the Scientific Council's strong recommendation that RERF's sponsors assemble an international Blue Ribbon Panel in consideration of the past two years of internal discussion on RERF's long-term future. We sincerely hope that this Panel evaluates all options, considering the world heritage scientific resources that have been stored, and facilitates planning of RERF's long-term future.
3. We agree whole-heartedly that RERF has an urgent need to recruit new scientists, particularly members of an international staff. We will make greater efforts to recruit such scientists through additional strategies proposed by the Council. Regarding a review of existing policies of reimbursement for overseas and domestic scientific meetings, we will consider changes in these policies to remove disincentives to attendance.
4. We very much appreciate the objective appraisal of the existing collaborations that have been established between RERF staff and outside scientists. We will further encourage RERF research scientists to develop even more collaborations.
5. RERF has already discussed collaborative partnerships to foster visiting scientists and training in the field of epidemiology and statistics between RERF and American or Japanese institutes. We will continue to discuss the possibility of establishing both Japanese and American institutional partnerships as indicated in the response by the Department of Epidemiology.
6. Regarding data/biospecimen sharing, explicit and transparent procedures for data/biospecimen sharing have already been made by the Data Sharing Committee, which was established in July of 2004. In order to promote collaborative studies, the committee thoroughly discussed internal procedures to assure that RERF abides by the law, to secure intellectual property rights, to give due consideration so that researchers involved do not feel that they are treated unfairly, and to maintain security of the databases. We are confident that a policy based on these procedures would encourage scientifically meritorious collaborations involving data/biospecimen sharing with joint internal-external authorship.
7. Regarding publication of the DS02 standards documentation, RERF has nearly completed the publication of the DS02 report on behalf of the U.S.-Japan Joint Working Group on the reassessment of the atomic-bomb dosimetry. Unfortunately, the Working Group has taken a long time to finish the documentation of their work, as many complex issues were involved. RERF has had no control of this, and we have had to await conclusion of these deliberations. All materials received by RERF from the Working Group have been immediately and systematically formatted, put into page set-up and passed on to the printer. The work at RERF is thus at an advanced stage. At present, almost all sections are completed, and we need only finish the galley checking and revision stage. The 1,000-page report should be published by the end of summer 2005.
8. We concur that the international visibility of RERF needs to be enhanced beyond the scope

of the radiation research community. We will make more efforts to publish in higher impact journals, to improve the RERF website, and to develop a public relations communications strategy.

9. We will make every effort to enhance communication, to stimulate more inter-departmental collaborations, and to foster intellectual exchanges by creating research protocols (RPs) writing manuscripts, obtaining external research fund, and holding informal inter-departmental seminars as well as international workshops. In addition, in order to maintain RERF's scientific edge, we will consider the development of policies to encourage the review of productivity and accountability of our scientific staff.

RERF Scientific Councilors

Dr. Yasuhito Sasaki, President, National Institute of Radiological Sciences

Dr. Ohtsura Niwa, Professor, Radiation Biology Center, Kyoto University

Dr. Toshitada Takahashi, Director, Aichi Cancer

Center Research Institute

Dr. Shinkan Tokudome, Professor, Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences

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

Dr. Gloria M. Petersen, Professor of Clinical Epidemiology, Mayo Medical School

Dr. Clarice Ring Weinberg, Chief, Biostatistics Branch, Environmental Diseases and Medicine Program, National Institute of Environmental Health Sciences

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

Dr. Roy E. Shore, Professor, Department of Environmental Medicine, New York University School of Medicine

Dr. Theodore L. DeWeese, Professor and Chair, Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine

The 40th Board of Directors Meeting in Washington, D.C.

The 40th meeting of the RERF Board of Directors was held for two days on June 22 and 23, 2005 at the National Academy of Sciences (NAS) in Washington, D.C. and attended by 28 individuals, including directors, supervisors, and observers. The Board approved the appointment of the new chairman and other new directors, and the submission of a request for establishment of a new Blue Ribbon Panel, a third party group, charged with deliberating RERF's future plans.

At the beginning of the meeting on day 1, RERF Chairman Burton G. Bennett introduced the attendees. Mr. John S. Shaw, Assistant Secretary for Environment, Safety and Health, the U.S. Department of Energy (DOE), then said that the Scientific Council in March had been a very productive meeting and that he was looking forward to working with RERF's new chairman Toshiteru Okubo in RERF's operations. Dr. Keiji Tanaka, Director-General, Health Service Bureau, Japanese Ministry of Health, Labour and Welfare, said that RERF is a unique research institute cosponsored by the Japanese and U.S. governments, and that the Japanese government has a high opinion of RERF's research and intends to support its research activities.

At the two-day meeting, all items for information and for deliberation and action were approved. Some of the major items are mentioned below.

Comments made concerning the present person-

nel status mentioned that RERF should probably review the possibility of increasing the retirement age to 65 to enable productive researchers to pursue research and that the age limit should be applied to NAS employees at RERF cautiously because there is no age limit system in the U.S. The Board decided that the RERF Executive Committee will further review these points together with a researcher performance evaluation system before these suggestions are deliberated on at next year's Board meeting.

The Board also deliberated on the report of the Analysis Subcommittee of the Scientific and Ethics Committees for the Health Effects Study of the Children of A-bomb Survivors, and agreed that the study of second-generation A-bomb survivors is important, that it is necessary to fully investigate if there are genetic effects, and that the study should be expanded by increasing as much as possible the number of second-generation A-bomb survivors with high parental doses.

NAS explained the status of its efforts to recruit employees to work at RERF. It has established a recruitment committee consisting of seven individuals and is presently conducting aggressive recruitment activities. It plans to recruit a total of six people: two statisticians, two epidemiologists, a head of the Statistics Department, and an Associate Chief of Research.

Then the Board endorsed the establishment of a

new Blue Ribbon Panel, as the RERF Scientific Council strongly recommended its establishment, and because it will be beneficial for RERF to receive administrative and scientific opinions and useful as justification for the continued support from the two governments. Details such as the timing of establishment and membership will be left up to the competent authorities.

In response, the Japanese government representatives commented that it will be useful for RERF's future to have its activities, including future plans, reevaluated by a third-party group. They also said that RERF should start dealing with the relocation issue by proposing an aggressive plan, including the type of facilities RERF needs to conduct its research in the future, if it wishes to relocate.

The DOE representatives commented in reply that, whereas the mission of the previous Blue Ribbon Panel had been limited to scientific aspects, the mission of the new panel seemed to be broader in scope as the panel would be required to deal with a wider range of issues, which would probably be a heavy load for the body.

RERF Supervisor Dr. Tomio Hirohata said, as part of the FY2004 research activities report and audit report, that the knowledge and wisdom of experts should be gathered from an international perspective to consider RERF's future because recently several researchers had resigned or moved to other institutions probably for reasons of insecurity about their future at RERF. He also recommended that RERF postpone the retirement of exceptional researchers till they reach the age of 65.

RERF Supervisor Mr. David Williams reported, as part of the FY2004 settlement of accounts and audit report, that although the RERF settlement of accounts had been reviewed by Pricewaterhouse Coopers (PWC), it was not an official audit because the financial documents did not include the unfunded portion of termination allowance liability or of the accrual item of seasonable allowance payable in June 2005.

The Board of Directors then proceeded to the election of officers. Deliberation was made concerning the appointment of successors to four Japanese directors (Drs. Toshiteru Okubo, Eiichi Tahara, Hiromichi Matsudaira, and Takefumi Kondo) and three U.S. directors (Burton G. Bennett, William J. Schull, and John E. Burris). As a result, it was approved unanimously that Dr. Okubo be appointed as chairman, Dr. Charles A. Waldren as vice chairman, Mr. Takanobu Teramoto as permanent director, Dr. Yasuhito Sasaki as director, and Dr. Senjun Taira as director, and that Dr. Schull be reappointed as permanent director and Dr. Burris as director. As successors to Scientific Councilors Drs. Yasuhito Sasaki, Gloria M. Petersen, and Tadatoshi Takahashi, Dr. Yoshiharu Yonekura (Director of Biomedical Imaging Research Center, University of Fukui), Dr.

Marianne Berwick (Professor and Chief of the Division of Epidemiology, Department of Internal Medicine, University of New Mexico), and Dr. Katsushi Tokunaga (Professor, Department of Human Genetics, Division of International Health, Graduate School of Medicine, University of Tokyo) were appointed, respectively.

It was decided that the next Board meeting would be held at Hiroshima RERF on June 21–23, 2006. At the end of the meeting, Dr. Paul L. Ziemer, on behalf of the Board, commended Dr. Bennett for excellent leadership at RERF, and wished him well in the future. With this, the Board completed discussion of all items on the agenda.

List of Participants

Permanent Directors:

Dr. Burton G. Bennett, Chairman

Dr. Toshiteru Okubo, Vice Chairman

Dr. Eiichi Tahara, Permanent Director and Chief of Research

Visiting Directors:

Mr. Masaaki Kuniyasu, Former Ambassador Extraordinary and Plenipotentiary to the Republic of Portugal

Dr. Hiromichi Matsudaira, Consultant, Radiation Effects Association

Dr. Paul L. Ziemer, Professor Emeritus, Purdue University

Dr. James D. Cox, Professor and Head, Division of Radiation Oncology, University of Texas M.D. Anderson Cancer Center

Dr. John E. Burris, President, Beloit College

Supervisors:

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

Mr. David Williams, Senior Financial Advisor, National Academy of Sciences

Scientific Councilor:

Dr. Gloria M. Petersen, Professor of Clinical Epidemiology, Mayo Medical School

Representatives of Supporting Agencies:

Dr. Keiji Tanaka, Director-General, Health Service Bureau, Ministry of Health, Labour and Welfare (MHLW)

Dr. Kazunari Asanuma, Deputy Director, General Affairs Division, Health Service Bureau, MHLW

Mr. John S. Shaw, Assistant Secretary for Environment, Safety and Health, U.S. Department of Energy (DOE)

Mr. Steven Cary, Deputy Assistant Secretary for Health, Office of Environment, Safety and Health, DOE

Dr. Joseph F. Weiss, Japan Program Manager, Office of Health Studies, DOE

Mr. Kenji Kanasugi, Counselor, Embassy of Japan
Mr. Kazuhisa Takahashi, First Secretary, Embassy of Japan

Mr. Masahiro Mori, First Secretary, Embassy of Japan

Ms. Kristina Midha, Global Affairs Officer, Office of Japanese Affairs, Bureau of East Asian and Pacific Affairs, U.S. Department of State

Ms. Nicole Nelson-Jean, Energy Attaché, Director, U.S. Department of Energy Asia Office, Embassy of the United States of America in Japan

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, Board on Nuclear and Radiation Studies, Division on Earth and Life Studies, NRC, NAS

Dr. Evan B. Douple, Board on Nuclear and Radiation Studies, Division on Earth and Life Studies, NRC, NAS

Ms. Catherine S. Berkley, Administrative Associate, Board on Nuclear and Radiation Studies, Division on Earth and Life Studies, NRC, NAS

RERF Secretariat:

Mr. Eiji Akimoto, Chief of Secretariat

Mr. Douglas C. Solvie, Assistant Chief of Secretariat

Dr. Charles A. Waldren, Chief Scientist

Staff News

In terms of RERF's scientific staff, the "revolving door" continues to move. During the period from April 2005 to March 2006, there have been three new additions to the scientific staff, along with four departures. The most prominent of staff was the appointment of Dr. Elichi Tahara as a "Senior Consulting Scientist," and the invaluable role he has played in establishing the "Study Group on A-Bomb Diseases" and associated cancer pathology network for ongoing cancer studies here at RERF. [Note: Dr. Tahara's tenure as the Senior Consulting Scientist was unfortunately relatively short-lived, and has embarked on a course of full retirement.] Also on the management side of the organization, Dr. Thomas Seed joined the organization in December 2005 as the "Associate Chief of Research" for the purpose of providing additional support for the departing Vice Chairman and Chief of Research, Dr. Charles Waldren, and in turn, for the incoming new Vice Chairman, Dr. Roy Shore. Finally, the Department of Genetics was fortunate to have rehired (via the current "reemployment option" for retiring indi-

viduals) a very excellent cytogeneticist and research scientist, Dr. Mimako Nakano, who rejoined RERF under the title of Adjunct Specialist.

During this period, RERF lost some outstanding researchers who over the years made significant contributions to the RERF's science. They are: Dr. Catherine Sauvaget, a Research Scientist of Epidemiology Department, who worked on the epidemiology of "lifestyle issues" and who resigned on June 30, 2005; and Dr. Shoichiro Fujita, Research Scientist and former Assistant Chief of Statistics Department, who suddenly died in April 2005, leaving an emotional and scientific vacuum within the Statistics group. As Dr. John Cologne recently remarked on Dr. Fujita's scientific and statistical achievements in the *RERF Annual Report 2004* (page 21), "..... they were a large part of the success of RERF statistics program over the past several decades."

As mentioned above, RERF's very distinguished researcher and administrator, Dr. Charles Waldren, decided to vacate his post and to retire at the end of 2005.

Timofeef Award from the Russian Academy of Medical Sciences

On October 25, 2005, the Russian Academy of Medical Sciences (Chairman: Dr. Anatoly Tsyb) decided to present the Timofeef Award to the Radiation Effects Research Foundation for its significant contribution to research into radiation effects on human health, and on November 14, an awarding ceremony was held in the Chairman's Office at RERF's Hiroshima Laboratory. In the ceremony, Dr. Natalia Seleva, who was training at RERF as a research fellow from the Medical Radiological Research Center of the Russian Academy of Medical Sciences, presented a diploma and the commemorative medal on behalf of Chairman Tsyb to RERF's Chairman

Dr. Toshiteru Okubo.

The Timofeef Award was established in 1990 to commemorate the 100th anniversary of the birth of the late Russian scientist N.W. Timofeef and to recognize his professional achievements, including his advocating of the target theory of radiation damage and Neo-Darwinism. The award since that time has been presented to the researcher or researchers whose achievements in radiation research are truly remarkable. In 1994, Dr. Itsuzo Shigematsu, former RERF chairman, was the first Japanese recipient of the award.

Vice Chairman Dr. Charles A. Waldren Receives Failla Award

Dr. Charles A. Waldren was selected as the recipient of the 2005 Failla Award, which is given by the Radiation Research Society in the U.S. to an outstanding researcher in recognition of significant contributions to radiation research. An award ceremony and a commemorative lecture were held in Denver, Colorado, in the United States, on October 16, 2005. We at RERF are very proud of Dr. Waldren for his receipt of the award, and we would like to extend to him our sincerest congratulations. At the ceremony venue, nearly 1,000 researchers gathered as Dr. Robert Ullrich, president of the society, presented the award to Dr. Waldren. In his lecture after the ceremony, Dr. Waldren introduced with a bit of humor some of his past achievements and the untold

stories behind them. Since Dr. Waldren maintains close relationships with Japanese scientists including Dr. Akiko Ueno, a researcher with whom he has collaborated for many years, and Dr. Masami Watanabe, professor at Nagasaki University, he also mentioned his collaborative research with these scientists and concluded his lecture by introducing his research philosophy.

We sincerely congratulate Dr. Waldren on receiving the Failla Award. Although he retired from RERF in December 2005, we will always appreciate the contributions he made to RERF and wish him well in all his future personal and scientific activities.

(Kazuo Neriishi)

60th Anniversary of the A-bombings and 30th Anniversary of RERF's Founding

A number of commemorative events relating to the 60th anniversary of the atomic bombings were held during the year of 2005 in Hiroshima and Nagasaki. Although six decades have already passed since the first atomic bombings in human history, the A-bomb survivors still suffer from late effects of radiation, and humankind still remains under the threat of nuclear weapons. Amid continued aging of the A-bomb survivors, who survived the horror of the bombings after which it had been said that no plants or trees would grow for 70 years, serious discussion has taken place among related organizations about how to convey this A-bombing experience to future generations. For RERF, that anniversary has forced us to consider our future as a research organization in the face of the increasingly elderly population of A-bomb survivors, who continue to participate in our Life Span Study (LSS) and Adult Health Study (AHS), allowing us to obtain significant research results, and of projections of rapidly dwindling numbers in the near future of living A-bomb survivors.

In addition to the 60th anniversary of the atomic bombings, 2005 marked the 30th anniversary of RERF's founding. Thirty years had passed since the Atomic Bomb Casualty Commission (ABCC), founded in 1947 by the U.S. government, was reorganized in April 1975 into the Radiation Effects Research Foundation, an organization jointly funded by the governments of Japan and the U.S. As a commemoration of the anniversary, RERF held the 30th Anniversary of the Establishment of the Radiation Effects Research Foundation, and related lectures, at the Hiroshima Minami-Ward Community Cultural Center on November 8, 2005, and at Wel City

Nagasaki, a public Kosei-Nenkin meeting hall, on November 11. For the ceremonies, RERF invited the many A-bomb survivors who have cooperated over the years in RERF's health examinations. Many former staff members of RERF were also in attendance, and other guests, including representatives of the governments of the two nations, local individuals concerned, and A-bomb survivor representatives, offered their congratulations.

At the lecture meetings following the commemorative ceremonies, Dr. Ohtsura Niwa, professor at the Kyoto University Radiation Biology Center, gave a lecture titled "Contributions of RERF to Understanding Radiation Risk and Radiation Protection." Then, Dr. William J. Schull, RERF permanent director (Professor Emeritus and Ashbel Smith Professor of Academic Medicine, Human Genetics Center, School of Public Health, University of Texas, Houston), spoke on the topic "The Radiation Effects Research Foundation: After Thirty Years." Both lectures were thoughtful and highly informative.

As part of the commemorative events, a ceremony was held in Hiroshima involving the planting of a seedling from the offspring of the A-bombed *aogiri* (Chinese parasol tree), and an opening ceremony was conducted in Nagasaki for a permanent exhibition room introducing research activities to that facility's visitors. After the ceremonies, a collection of records of the ceremony atmospheres and lectures, words of encouragement from all sectors of society, and memories of RERF from participants in our studies in attendance at the ceremonies and from former employees of RERF was published as RERF's 30th Anniversary Special Issue of the RERF Newsletter.

RERF Meeting: Radiation and Cardiovascular Disease

Kazunori Kodama, Chief Scientist and Chief, Department of Epidemiology, Hiroshima

Recently, an increase in non-cancer disease (heart disease, stroke, liver and other diseases) mortality and incidence in RERF's Life Span Study (LSS) and Adult Health Study (AHS) cohorts was observed, but no conclusion has yet to be drawn over whether the increase is in effect attributable to A-bomb radiation. Under such circumstances, a workshop titled "RERF Meeting: Radiation and Cardiovascular Disease" was held on February 22–23, 2006, at the Auditorium in Hiroshima. The meeting's aim was the determination of the future direction of RERF's research activities through in-depth discussions by experts pertaining to such issues as "Is there sufficient epidemiological evidence proving the relationship between radiation exposure and cardiovascular disease?" and "If radiation causes cardiovascular disease, what is the relevant mechanism?"

Among participants from outside organizations were Dr. Kiyohiko Mabuchi (Expert, Radiation Epidemiology Branch, U.S. National Cancer Institute; and former chief of RERF Epidemiology Department, Hiroshima), Dr. Fiona Stewart (Group Leader, Experimental Therapy Division, Netherlands Cancer Institute), Dr. Steven E. Lipshultz (Professor and Chairman of Pediatrics, University of Miami School of Medicine), and Dr. Hirotsugu Ueshima (Professor, Department of Health Science, Shiga University of Medical Science), and all are internationally distinguished researchers in this field of research. In addition, three other specialists from Japan and the U.S., and two postgraduate students from Kurume University involved with the partnership program participated. Also, with participation of directors and research scientists from RERF, enthusiastic discussions were conducted over two days.

The meeting revealed that: 1) even though the

onset of cardiovascular disease due to high-dose radiation exposure is nearly unequivocally confirmed, we have insufficient epidemiological data showing association between the disease and mid- and low-dose radiation exposure, as was the case in the A-bomb radiation exposure, apart from the data in custody of RERF, and hence further accumulation and enlargement of such research data is required in order to confirm the effects of radiation; 2) there is no established theory for the mechanism of the relevant disease onset.

Among the future tasks for RERF pertaining to the relevant study are: 1) enhancement of collection of incidence data by way of enlargement of the AHS cohort; 2) utilization of autopsy specimens; 3) introduction of echocardiography and carotid artery echography to the AHS clinical examinations; 4) measurements of insulin and inflammatory cytokine levels as part of the clinical examinations; and 5) development of a new statistical analysis methodology. Needless to say, continuation of the ongoing follow-up studies is significant.

Even though more than 60 years have passed since the dropping of the atomic bombs, the entire picture of the health effects of A-bomb radiation has yet to be elucidated, including the theme of this meeting, which was association between "Radiation and Cardiovascular Disease." That means that there remain numerous tasks to be addressed by RERF. I also believe that everyone at RERF has the obligation and responsibility to work to elucidate all health effects of A-bomb radiation. I hope that all RERF staff will make the necessary efforts to fulfill their duties based on this common understanding.

— Program —

February 22, 2006

"Opening Remarks"

Toshiteru Okubo (RERF)

Session 1: "Introduction"

Chairperson: Kazunori Kodama (RERF)

"Evolution of studies on radiation and cardiovascular disease at ABCC-RERF"

Kazunori Kodama (RERF)

"Goals of the workshop: Future research directions"

Roy E. Shore (RERF)



Participants of the meeting on radiation and cardiovascular disease held at the RERF Hiroshima Laboratory

Session 2: "Epidemiology on radiation and cardiovascular disease"

Chairperson: Kiyohiko Mabuchi (NCI)
 "Radiation and non-cancer disease mortality in the Life Span Study"

Yukiko Shimizu (RERF)

"Radiation effects on the incidence of cardiovascular disease and its risk factors (Adult Health Study)"

Michiko Yamada (RERF)

"Radiation exposure and coronary atherosclerosis (Adult Health Study)"

Masazumi Akahoshi (RERF)

Session 3: "Epidemiology on radiation and cardiovascular disease (continued)"

Chairperson: Kiyohiko Mabuchi (NCI)
 "Late cardiovascular abnormalities following mediastinal irradiation in long-term survivors of childhood cancer"

Steven E. Lipshultz (University of Miami)

"Review of epidemiological studies on radiation and cardiovascular disease"

Kiyohiko Mabuchi (NCI)

February 23, 2006

Session 4: "Possible mechanisms of radiation-induced atherosclerosis"

Chairperson: Gen Suzuki (NIPH)
 "Immune function, inflammatory markers and atomic bomb radiation"

Yoichiro Kusunoki (RERF)

"Radiation-induced atherosclerosis in cancer survivors: Possible mechanisms and preventative intervention strategies"

Fiona Stewart (Netherlands Cancer Institute)

"Metabolic syndrome as a risk factor of cardiovascular disease: Results of Tanno-Sobetsu Study"

Shigeyuki Saitoh (Sapporo Medical University)

"Elevated risk of non-cancer disease can be a result of adaptive response"

Nori Nakamura (RERF)

Session 5: "Discussion"

Chairperson: Roy E. Shore (RERF)
 "Closing remarks"

Roy E. Shore (RERF)

List of Participants

Dr. Fiona Stewart, Group Leader, Experimental Therapy Division, Netherlands Cancer Institute, the Netherlands

Dr. Steven Edward Lipshultz, Professor and Chairman of Pediatrics, University of Miami School of Medicine, USA

Dr. Kiyohiko Mabuchi, Expert, Radiation Epidemiology Branch, National Cancer Institute (NCI), USA

Dr. Dale L. Preston, Principal Scientist, Hirosoft International, USA

Dr. Hirotsugu Ueshima, Professor, Department of Health Science, Shiga University of Medical Science

Dr. Gen Suzuki, Director, Department of Environmental Health, National Institute of Public Health (NIPH)

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Dr. Kei Nakachi, Chief, Department of Radiobiology/Molecular Epidemiology

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Japan-U.S. Cooperative Cancer Research Seminar on Molecular Epidemiological Characteristics of Lung and Colon Cancer Development among Atomic-bomb Survivors

Kei Nakachi, Chief, Department of Radiobiology/Molecular Epidemiology

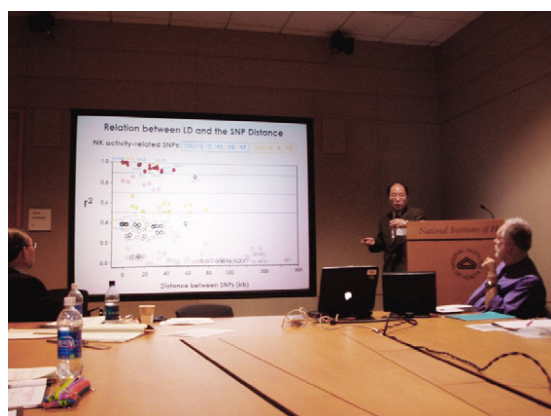
This seminar was held on February 23–24, 2006, in Bethesda, Maryland, as an activity of the Japan-U.S. Cooperative Cancer Research Program for a research project titled Molecular Epidemiological Characteristics of Lung and Colon Cancer Development among Atomic-bomb Survivors (Japanese Principal Investigator, Kei Nakachi and U.S. Principal Investigator, Curtis C. Harris; duration, April 1, 2004 – March 31, 2006), supported by both the Japan Society for Promotion of Science and the U.S. National Cancer Institute (NCI). Mechanistic understanding of radiation-associated carcinogenesis is indispensable for the establishment of cancer prevention for those exposed to excess radiation, including atomic-bomb survivors. This Japan-U.S. Cooperative Cancer Research Seminar was held to investigate future directions of molecular epidemiology studies on radiation-associated cancer, on the basis of the data obtained thus far from studies in progress. In the opening address, Dr. Curtis Harris (NCI, U.S.) welcomed and thanked all the participants on behalf of the Japan-U.S. Cooperative Cancer Research Seminar. Dr. Eiichi Tahara (RERF, Japan) also thanked the participants and extended his gratitude to Dr. Harris and the staff of his laboratory for organizing and hosting the seminar.

Overview of molecular epidemiology studies among atomic-bomb survivors

Dr. Kazue Imai (RERF, Japan) gave an overview on the occurrence of cancer and other diseases among atomic-bomb survivors in relation to their past

exposure to atomic radiation. Using data collected by the RERF Epidemiology Department, Dr. Imai indicated that increased risk of cancer is to date the most important late effect of radiation exposure. Following excess leukemia seen in the early years after atomic-bomb exposure, significant excess risk of selected solid cancers also has been observed. Importantly, there is still excess risk for many solid cancers among radiation-exposed survivors even 60 years after the atomic bombings. However, the mechanisms underlying these epidemiological findings remain unclear.

Based on these cancer data of atomic-bomb survivors, Dr. Kei Nakachi (RERF, Japan) overviewed the molecular epidemiology studies currently being carried out at RERF, emphasizing the need for a mechanistic understanding of health effects of radiation exposure, not only for disease prevention among atomic-bomb survivors but also for establishing prevention strategies for radiation-associated cancers and other diseases in general. The prevention of radiation-associated diseases, cancers in particular, is an important issue for many people, such as patients undergoing radiation therapy, those occupationally or accidentally exposed to excess radiation, and even to people in the general population exposed to diagnostic X rays. In order to better understand more about the mechanisms and prevention of radiation-related diseases, RERF Radiobiology/Molecular Epidemiology Department is currently using the three approaches of immunology, immunogenome, and molecular oncology-based studies. Evidence has recently accumulated supporting the idea that many lifestyle-associated diseases such as coronary heart disease, diabetes mellitus, and even cancer are associated with immunological alterations (e.g., chronic inflammatory responses and disturbances of immunosurveillance systems) of the host. This association has been investigated on the basis of the altered immunity found among atomic-bomb survivors, which can be observed even now, 60 years after the bombings. Immunology and immunogenome studies include (i) T-cell repertoire and clonal expansions, (ii) T-cell functions and inflammatory response, and (iii) association between cancer development and immune-related gene polymorphisms. Molecular oncology studies using thyroid, lung, and colorectal cancer tissue of atomic-bomb survivors have recently begun at RERF with



Dr. Kei Nakachi making a presentation (center) and Dr. Curtis Harris (right)

the intent of discovering critical molecular events within these cancers, but perhaps not in non-radiation-associated (sporadic) cancers. This study may therefore underpin the molecular characteristics of radiation-associated carcinogenesis.

Lung cancer – radiation-associated and sporadic

Dr. Michael Alavanja (NCI, U.S.) explained that tobacco smoke and ionizing radiation might share a common genotoxic mechanism, inducing oxidative stress by transmitting or generating reactive oxygen species (ROS). Dr. Alavanja hypothesized that glutathione-S-transferase M1 (*GSTM1*) null homozygotes would have decreased ability to neutralize ROS, which might increase susceptibility to lung cancer. A case-only design was used with archival tissue samples and radon concentration and second-hand smoke (SHS) exposure data among never-smokers from lung cancer cases pooled from three previously completed case-control studies. Radon concentrations $>120.62 \text{ Bq m}^{-3}$ were associated with a >3 -fold risk of lung adenocarcinoma for *GSTM1* null homozygotes compared with *GSTM1* carriers. SHS exposure among never-smokers revealed a 2-fold risk. Dr. Alavanja emphasized that genetic predisposition factors are probably more important in low-dose carcinogenesis such as with SHS and radon exposures in home settings. Additionally, these findings supported the hypothesis that radon and SHS promoted neoplasia through shared elements of a common pathway.

To investigate the mechanisms of radiation-associated lung cancer, we need to understand the mechanisms of sporadic (non-radiation-associated) lung cancer among the general population. Dr. Leah Mechanic (NCI, U.S.) examined association between sporadic lung cancer and 14 *TP53* polymorphisms, including haplotype tagging and coding single nucleotide polymorphisms (SNPs), in an ongoing NCI-Maryland Lung Cancer Case Control study, and subjects in a case-only study from the greater Baltimore area were genotyped. Of these polymorphisms, *TP53_01* (Arg72Pro) and *TP53_11* (T>G, IVS7+92) were associated with increased risk of lung cancer in African Americans. Individuals with combined *TP53_01* (Arg/Pro or Pro/Pro) and *TP53_11* (T/G or G/G) genotypes had elevated risk of lung cancer. Moreover, individuals with Pro-T-A-G haplotypes of the combined *TP53* polymorphisms *TP53_01*, *TP53_65*, *TP53_66* and *TP53_16* had increased risk of lung cancer, compared to those with Arg-T-A-G haplotypes. The *TP53* Arg72Pro polymorphism was shown to modulate p53 transcription-independent apoptosis, through more effective mitochondrial localization. In this case-only study, *TP53* haplotypes were associated with increased *TP53* somatic mutation frequency in lung cancer in Caucasians. The

association between *TP53* haplotypes and lung cancer will be further studied in radiation-associated lung cancer.

RERF epidemiology studies have indicated that excess relative risk of lung cancer among atomic-bomb survivors remained high even 60 years after the atomic bombings. Dr. Masataka Taga (research associate, NCI, U.S. and RERF, Japan) reported on the current progress of a molecular oncology study on lung cancer among atomic-bomb survivors, which has been carried out in collaboration between the Department of Radiobiology/Molecular Epidemiology, RERF and the Laboratory of Human Carcinogenesis, NCI, since 2004. *P53* (exons 5–8), *EGFR* (exons 18, 19 and 21), and *K-ras* (codons 12, 13 and 61) gene mutations were examined in archival cancer and adjacent non-cancer tissue samples from 44 non-exposed patients and 28 exposed patients among atomic-bomb survivors. The mutations were further analyzed in relation to clinicopathological factors including atomic-bomb radiation dose. Radiation-exposed patients showed higher frequency of *p53* mutation than that among non-exposed patients, although the difference was not statistically significant. Median radiation dose among lung cancer patients with *p53* mutation of either G:C>T:A transversion or deletion was significantly higher than that among patients with other types of *p53* mutations or that among patients without *p53* mutations. Of 15 exposed patients with lung adenocarcinoma or squamous cell carcinoma, two patients were found to have *p53* double mutations. On the other hand, *EGFR* (or *K-ras*) mutations did not show association with radiation exposure. The results from this preliminary analysis support the necessity of extended study with an increased number of patients, specifically those exposed to high doses of radiation, along with analysis of other molecular events.

Dr. Naoko Sueoka (Saga Univ., Japan) reported on *EGFR* mutations within sporadic lung cancer of Japanese patients. *EGFR* mutations in lung cancer. *EGFR* mutations were observed in 34 of 97 patients (35%); *EGFR* mutations were comprised of 1, 18, and 15 mutations in exons 18, 19, and 21, respectively. Thirteen of the fifteen patients with exon 21 mutations were female non-smokers whose pathological type was adenocarcinoma with bronchioloalveolar carcinoma (BAC). The 18 patients with exon 19 mutations included eight male current or former smokers. BAC was observed in eleven of these patients, which was less frequent than the case of exon 21 mutations. These results of *EGFR* mutations in exon 21 and exon 19 suggest different mutagenesis and carcinogenesis pathways involving *EGFR*. Next, genetic host factors involved in occurrence of *EGFR* mutations were reported with specific reference to relationships between *EGFR* mutations and the length of a CA-repeat in intron 1.

Allelic distribution of *EGFR* CA-repeat in lung cancer patients showed that 16 and 20 CA-repeat were frequently observed. *EGFR* mutations were more frequently observed in female non-smokers with fewer CA-repeat. In addition, dividing study patients into three groups by number of CA-repeat (i.e., 16 or fewer, 17–19, 20 and more), *EGFR* mRNA levels in normal adjacent tissue with 16 or fewer CA-repeat were found to be higher than those of the other groups.

Dr. Yun-Ling Zheng (Georgetown Univ., U.S.) reported on relationships of γ -radiation-induced G2/M arrest and DNA repair capability as assessed in an ongoing case-control study on lung cancer, measured by quantifying bleomycin-induced chromosome breaks in cultured peripheral lymphocytes of study subjects. The mean percentage of γ -radiation (1 Gy)-induced G2/M arrest was significantly lower in cases than in both the general population group and the hospital control group, and that, when dichotomized at the 50th percentile value in combined control groups, a lower level of γ -radiation-induced G2/M arrest was associated with increased risk of lung cancer among African-Americans. In addition, mean number of bleomycin-induced breaks per cell was significantly higher in cases compared with that in the control groups. These results imply that both bleomycin-induced chromosome breaks and less-efficient G2/M arrest induced by γ -radiation (1 Gy) are associated with increased risk of lung cancer among African-Americans, although the association was weaker in Caucasians.

Dr. Peter Shields (Georgetown Univ., U.S.) overviewed several studies on cigarette smoking and genetics, focusing on polymorphisms in the human dopamine transporter (*DAT1*) gene and the dopamine receptor (*DRD2*) gene. A case (smokers)-control (nonsmokers) study revealed that smoking status was greatly dependent on *DRD2* genotype; a cohort of high school students also showed that the risk of progressing from “puffing” to habitual smoking involved this genotype. A clinical trial using bupropion to promote smoking cessation also showed greater odds ratios (ORs) for the combined genotype of *DAT1* and *DRD2* than that for use of bupropion vs. a placebo. These findings suggest that future anti-smoking intervention will need to consider genetic factors of individual smokers.

Colorectal, thyroid, and stomach cancers found in atomic-bomb survivors

Epidemiological findings from the RERF cohort study in atomic-bomb survivors have revealed that colon cancer showed significant risk elevation, while rectum cancer did not. Microsatellite instability (MSI) reflects major genomic instability; MSI is associated with proximal sites of the sporadic colon carcinogenesis. Dr. Hidetaka Eguchi (RERF, Japan)

reported on the current progress being made in a molecular oncology study on colorectal cancer among atomic-bomb survivors, focusing on MSI in relation to atomic-radiation exposure. This study uses archival cancer and adjacent non-cancer tissue samples collected from 10 non-exposed and 27 exposed patients. MSI-positive colorectal cancer was frequently observed at proximal sites in females, and this was also the case in sporadic colorectal cancer. Median radiation dose in MSI-positive colorectal cancer patients was significantly higher than that in MSI-negative patients; median age at the time of atomic bombing or diagnosis in MSI-positive patients was significantly lower than that in MSI-negative patients. The latter finding seems to be in accordance with the previous finding that colorectal cancer among atomic-bomb survivors showed higher excess relative risk among those exposed to atomic-bomb radiation at younger ages. The results from this preliminary study suggest possible association between radiation exposure and MSI status in colorectal cancer occurring among atomic-bomb survivors. Further analyses with an increased number of patients will be needed, however.

Dr. Kiyohiro Hamatani (RERF, Japan) reported on current progress in a study of thyroid papillary cancer (PTC) among atomic-bomb survivors, in view of epidemiological data that this cancer was strongly associated with radiation exposure. Archival cancer and adjacent non-cancer tissue samples from 56 radiation-exposed (≥ 5 mGy) survivor patients and 29 non-exposed patients with PTC were analyzed, in terms of the initial events in thyroid papillary carcinogenesis: *RET* rearrangements (*RET/PTC*) and *BRAF*^{V600E} mutation. Median radiation dose among PTC patients with *RET/PTC* was significantly higher than that among patients without *RET/PTC*. On the other hand, median radiation dose among the patients with *BRAF*^{V600E} mutation was significantly lower than that among patients without this mutation. Furthermore, median latency period (time period elapsed from atomic bombing to diagnosis) and age at diagnosis in exposed patients with *BRAF*^{V600E} mutation were significantly longer and higher, respectively, than those without the mutation; no association was found between age at the time of atomic bombing and *BRAF*^{V600E} mutation. *RET/PTC* rearrangements and *BRAF*^{V600E} mutation were mutually exclusive. These results suggest that initial choice of either *RET/PTC* rearrangements or *BRAF* mutation may be influenced by atomic-radiation exposure, although each of them activates the RET/RAS/BRAF MAPK signaling pathway.

Dr. Tomonori Hayashi (RERF, Japan) described recent findings on stomach cancer development among atomic-bomb survivors, in terms of interaction between immunological host factors and radiation exposure. Immunological host protection is

considered to play an important role not only in the development of virus-related cancer, but also in carcinogenesis in general. On the other hand, exposure to radiation affects the immune system of the host in a dose-dependent manner. Case-control studies within a sub-cohort of the RERF Adult Health Study were conducted on the basis of immune-related gene polymorphisms. One recent finding is an association between inflammation-related gene polymorphisms and stomach cancer development. Although overall risk of stomach cancer significantly increased with increased radiation dose, this risk was greatly modulated in both non-exposed and radiation-exposed survivors by *IL-10* haplotypes, making possible the identification of people at high risk of radiation-associated stomach cancer. This study also demonstrated that plasma levels of IL-10 among individuals, which increased with past radiation dose and varied by *IL-10* haplotype, indicated stomach cancer risk of individual survivors as a promising surrogate marker of this cancer.

Mechanisms of radiation effects – *in vitro* studies

Dr. Simon Powell (Washington Univ., U.S.) focused on the role of p53 as a central regulator of homologous recombination (HR) and replication, independent of its transactivation activity. By employing a plasmid-based HR assay in p53-null H1299 lung carcinoma cells, the HR-suppressing properties of a panel of p53 mutants, which varied in ability to interact with human replication protein A (RPA), were studied. Both wild-type p53 and a transactivation-deficient p53 mutant suppressed HR and prevented RPA from binding to ssDNA both *in vitro* and *in vivo*. Conversely, p53 mutations that specifically disrupt the RPA binding domain without compromising the p53 transactivation function did not affect HR or RPA binding to ssDNA. Suppression of HR was also lost with missense mutations in the p53 core domain, which retained the ability to interact with RPA, suggesting that additional binding interactions of p53 can also impact HR. After substituting endogenous RPA2 either with an intact myc-tagged analog (RPA2Wt), or with a phosphomimetic or a phosphorylation-deficient (RPA2D or RPA2A) myc-tagged mutant, UV treatment led to dissociation of the p53-RPA complex and an increase of p53 transcriptional activity in the cells expressing RPA2Wt or RPA2D. RPA2A expression, on the contrary, stabilized the p53-RPA complex and attenuated transcriptional activation of wild-type p53, although RPA2A failed to abolish transcriptional activation of p53 mutated within RPA binding domain. These findings confirmed that the p53-RPA interac-

tion was critical for this regulation, and that the interaction was regulated by RPA phosphorylation; RPA phosphorylation regulated p53 transcriptional activity only in S-phase. Finally, the magnitude of suppression of HR by p53 was greater for replication-associated HR, relative to DSB-induced HR. These data suggest that p53 sequestering by RPA regulates p53 transcriptional activity during S-phase, and that p53 binding to RPA regulates HR in S-phase. The role of p53 in maintaining genome stability might be significantly mediated by the p53-RPA interaction in S-phase.

Dr. Tom Hei (Columbia Univ., U.S.) reported on recent *in vitro* studies on low-dose radiation and the bystander response. Observation of a bystander effect—i.e., induction of biological effects in cells not directly traversed by a charged particle but in close proximity to cells that are—represents a paradigm shift in understanding of radiation biology and target theory. This “bystander” effect was demonstrated by chromatid damage within primary human bronchial epithelial cells not directly hit by traversing α -particles generated by a microbeam irradiation, but that simply neighbor these cells that are directly hit. Multiple pathways were involved in the bystander phenomenon, and different cell types responded differently to bystander signaling. In confluent monolayers, gap junctional communication played a crucial role in mediating the bystander effect. Cells without connexin gap junction protein showed no bystander response, and p53 thus may not be essential. On the other hand, reactive oxygen and reactive nitrogen species have been implicated as mediating molecules in subconfluent cultures. A recent study suggests that the cyclooxygenase-2 signaling cascade plays an essential role in the bystander process. Treatment of bystander cells with NS-398, a COX-2 inhibitor, significantly reduced the bystander effect including HPRT mutation. Furthermore, upregulation of the extracellular signal-related kinases (ligands: TNF- α , TGF- β , IGF, IL-1, and IL-8) and mitogen activated protein kinases, specifically Erk and p38, appear to represent important intercellular signaling events of the bystander phenomenon. The implication of bystander observations is that the relevant target for various radiobiological endpoints is far larger than the individual cell. This suggests a need to reconsider the validity of linear extrapolation in calculating risk estimates for low-dose radiation exposure.

All participants at this seminar agreed with the necessity of promoting further collaboration between Japan and U.S. researchers, to understand the effects of radiation and the mechanisms of cancer induction for the benefit of all mankind.

The Frequency of XPA Heterozygotes Bearing a Founder Mutation among Individuals Who Resided in Hiroshima and Nagasaki

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Introduction

Many cancer-prone autosomal recessive hereditary disorders are known to be caused by congenital defects in DNA repair genes, but the frequency of such disorders is quite low (on the order of several cases per 100,000 individuals). However, the frequency of the heterozygotic condition is not at all rare (in the order of one percent). Nevertheless it is not well documented if the heterozygous carriers of these mutations are predisposed to cancer as well. To address this issue, we sought to examine the frequency of heterozygotes bearing a specific mutation in the *xeroderma pigmentosum group A (XPA)* gene in a small Japanese cohort.

XP is a rare autosomal recessive disorder in which there is extremely high incidence of UV-related skin cancers associated with an impaired ability to repair UV-induced DNA damage.¹ Eight genes, denoted as XPA through XPG, plus a *variant* are known to be responsible for the development of the XP disorder. XPA to XPG proteins work in a coordinate manner during the process of nucleotide excision repair (NER) of UV-induced DNA damage. In contrast, patients with the *XP variant* are nearly normal in NER but defective in post-replication repair due to a mutation in the DNA polymerase η , a translesional DNA polymerase.²

In Japan, the overall frequency of XP patients is estimated as 1 per 40,000–100,000 newborns,³ which appears to be more than 10 times higher than that in Western countries.⁴ Interestingly, more than 50% of Japanese XP patients belong to group A (XPA, gene location: 9q22.3, OMIM 278700), clinically the most severe form of both skin and neurological symptoms (Table 1) and this proportion is nearly twice that seen in other countries.^{4,5} Further, about 80% of them have an identical G to C base-change mutation (a founder mutation).⁴ This founder mutation, at the 3' splice acceptor site of intron 3, results in no detectable protein production and creates a sensitive site within

Table 1. Percentage of registered cases in the eight XP complementation groups*

Complementation groups	Japanese cases	Non-Japanese cases
A	55.3	28.6
B	0	1.6
C	3.4	26.6
D	5.5	14.6
E	3.4	1.0
F	6.9	2.1
G	0.7	2.1
Variant	24.8	23.4

*From ref. 4.

the restriction enzyme *A1wNI* recognition sequence (denoted as the A1wNI mutation).^{6–8} Accordingly, it is only necessary to examine one specific position in the XPA gene in order to identify approximately 80% of XPA heterozygotes in Japanese people.

As a first step toward a molecular epidemiologic assessment of cancer risks in XP heterozygotes, we developed a simple PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) method to identify XPA heterozygotes bearing the founder mutation. We screened about 1,000 individuals who resided in Hiroshima or Nagasaki and collected direct information on the frequency of the XPA heterozygotes, which should provide key information for determining the sample size of skin cancer case in the subsequent study.⁹

Materials and Methods

Study subjects

We examined 1,884 Japanese donors, 904 from Hiroshima and 980 from Nagasaki (only one sibling in each family was included in the present study). These donors were the offspring of randomly selected control subjects in a cytogenetic study aimed at clarifying the genetic effects of radiation in the progeny of atomic-bomb survivors. Control subjects were

born to parents who were exposed to <10 mGy of atomic-bomb radiation or born to those who were not present in the city of Hiroshima or Nagasaki at the time of the bombings.¹⁰

Materials

Archived Giemsa-stained blood lymphocytes, collected about 20 to 30 years ago, were the source of the DNA for analysis. All the samples were coded so that no links to the identity of the donors could be determined. Followed by removing mounting resin from the slide by xylene, the Giemsa-stained lymphocytes were scraped off the slides by scalpels. The cells were treated with proteinase K and the DNA was concentrated by ethanol precipitation. The DNA was suspended in H₂O, and subjected to PCR-RFLP analysis.

PCR and RFLP analysis

The DNA region that includes the founder mutation was amplified by PCR method. Our method made use of two PCR primers (5'-TGGACTTA-ATCTGTTTTCA-3' and 5'-CCTCTGTTTG-GTTATAAG-3') to amplify sequences that include intron 3 and exon 4 of the *XPA* gene. Aliquots of the amplified fragments (61 bp) were then digested with *Alw*NI or *Hind* III enzyme and subjected to polyacrylamide electrophoresis (12%) for separation. If the founder mutation was present, the amplified 61-bp DNA was further cleaved into two shorter fragments (25 bp and 36 bp long) with *Alw*NI. *Hind* III treatment also cleaved the DNA into two shorter (but differently sized) fragments (23 bp and 38 bp), regardless of whether the mutation was present, and served to confirm that the PCR-amplified fragments were in fact derived from the relevant region of the *XPA* gene (Figure). When a sample was suspected to carry the mutation, PCR-RFLP was repeated using the same DNA for confirmation. Subsequently, DNA was extracted from a second slide and the same tests

were repeated to confirm the character of the sample. Finally, the amplified fragments analyzed the sequence to confirm the presence of the founder mutation.

Statistical analysis

Confidence intervals for the prevalence of the *XPA* founder mutation in the general population were calculated for the binomial distribution using Stata/SE for Windows 9.1 (StataCorp LP, College Station, Texas), which gives confidence intervals of the Clopper-Pearson type.¹¹

Results

Among the 1,884 lymphocyte samples that were examined, the 61-bp-long DNA sequence was successfully amplified in 1,020 samples; 512 from Hiroshima and 508 from Nagasaki. The overall success rate for PCR amplification was 54%. Among the 1,020 amplified samples, we found nine candidate mutation carriers where approximately half of the amplified 61-bp fragments were cut into two smaller fragments (25 bp and 36 bp) following *Alw*NI digestion (Figure). Among these, four were from Hiroshima and five from Nagasaki. All the *Alw*NI digestion results were reproduced in a second assay using the same DNA samples. In subsequent tests using DNA from a second slide containing cells from the possible nine mutation carriers, seven DNA samples were successfully amplified, and all of the seven samples produced the same results as those which were obtained from the first slides. Furthermore, PCR products of two of these seven samples were sequenced and confirmed as they carry the *Alw*NI mutation in heterozygous conditions (results not shown). However, two DNA samples out of the nine failed to yield PCR products using DNA from second slides. It seems likely that these two cases are also heterozygotes for the mutant allele since all of the other seven successful PCR samples gave rise

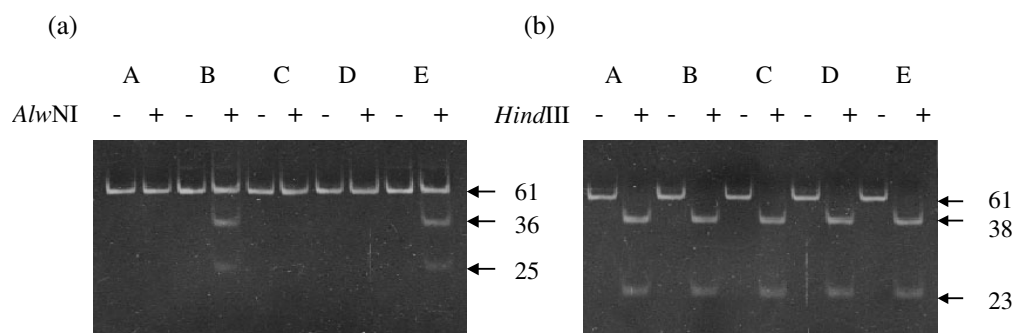


Figure. Representative electrophoresis patterns of PCR-RFLP with *Alw*NI (a) or *Hind*III (b) digestion. Lane A = normal control, B = positive control of XPA heterozygote carrying the founder mutation, C–E = test samples of which C and D are normal, and E is a heterozygous carrier which is indicated by the two shorter fragments (25 and 36 bp long) after *Alw*NI digestion (a).

to consistent results in the two independent sets of PCR-RFLP tests.

The results indicate that the overall frequency of XPA heterozygotes bearing the founder mutation in the samples tested was 9/1,020 (0.88%, or 1 in 113) with 95% confidence interval (CI) from 0.40% to 1.67%. There was no indication of differences between Hiroshima and Nagasaki in the frequency of the heterozygous individuals.

Discussion

This is the first molecular genetic, population-based study focusing on XP heterozygotes. The present study showed that the frequency of XPA heterozygotes bearing the founder mutation was 0.88% (1 in 113) among more than 1,000 donors from Hiroshima and Nagasaki population. If this estimate were representative of the general population, there would be approximately 1 million carriers of the XPA founder mutation in the 120 million people in Japan. And this value is somewhat higher than the frequencies of XPA heterozygotes (0.47–0.74%) and XPA heterozygotes bearing the founder mutation (0.41–0.65%) previously estimated by theoretical extrapolation from the summarized findings of small-scale clinical investigations of XP patients.³ We believe that our value, which was obtained by examining the DNA from 1,020 individuals, is likely to be the most realistic available to date.

Overall frequency of XP patients and heterozygotes in Japan

The results reported here can be used to estimate the overall frequency of XP patients and heterozygotes bearing a mutation in any one of the eight XP genes as follows. If we assume that the population frequency of normal allele as p and mutant allele frequency as q ($= 1 - p$), the ratios of A = normal individuals : B = XPA heterozygotes : C = XPA homozygotes (patients) are expressed as $p^2 : 2pq : q^2$ (the Hardy-Weinberg equation). From the present data, the frequency of heterozygotes is $2pq = 0.0088$

± 0.0030 , so the frequency of XPA patients with the AlwNI mutant allele is $q^2 = 1.96 \pm 1.31 \times 10^{-5}$ assuming random marriages (panmixia). Next, it was previously shown that 72 out of 92 XPA patients (78%) were homozygous for the founder mutation, and almost all of the remaining cases were compound heterozygotes; i.e., one allele contains the founder mutation and the other allele contains a different mutation in the same gene.⁴ Thus, the frequency (1.96×10^{-5}) was divided by 0.78 to estimate the frequency of all XPA patients, which gave $2.51 \pm 1.68 \times 10^{-5}$ (Table 2, second line, column C). Using this value and relative frequency of XP patients in each complementation group obtained from nearly 300 Japanese XP patients (Table 2, column B), the frequency of homozygous patients was calculated for each group from XPB to XP variant (Table 2, column C), which gave the overall frequency of XP patients of $4.54 \pm 3.04 \times 10^{-5}$ (1 in 22,000) (Table 2, last line, column C).

The frequency of heterozygous carriers of a mutation in each XP gene was estimated as $2pq$ (Table 2, column D). The sum of $2pq$ of all the XP groups gave $2.95 \pm 1.04 \times 10^{-2}$ (1 in 34 individuals, Table 2, last line, column D). The frequency of heterozygotes for all of the XP disease genes comprising 1 out of 34 Japanese is impressively high.

In the past, several attempts were made to estimate the frequency of XP or XPA patients and heterozygotes in the Japanese population by indirect methods. These are summarized in Table 3 along with the present estimates. The past estimates used the Weinberg-Dahlberg equation, $q = c(1 - k)/(16k - 15c - ck)$ where c represents the proportion of first-cousin marriages in a general population and k represents the proportion in the parents of patients. It is clear that the present estimate of the frequency of XPA heterozygotes (1 in 113) or XP heterozygotes (1 in 34), lies close to the highest value among the past estimates.

It should be noted, however, that the present estimate of the frequency of heterozygotes of the XPA

Table 2. Estimated frequencies of heterozygotes bearing mutant XP genes

XP group	No. of XP patients [A]	Fraction to the total XP patients (%) [B]	Frequency of patients (per 10 ⁵) [C]	Frequency of heterozygotes (per 10 ²) [D]
A	161	55.3	2.51 ± 1.68	1.00 ± 0.34
B	0	0	0	0
C	10	3.4	0.16 ± 0.12	0.25 ± 0.09
D	16	5.5	0.25 ± 0.18	0.32 ± 0.11
E	10	3.4	0.16 ± 0.12	0.25 ± 0.09
F	20	6.9	0.32 ± 0.22	0.35 ± 0.13
G	2	0.7	0.03 ± 0.03	0.11 ± 0.05
Variant	72	24.8	1.12 ± 0.77	0.67 ± 0.23
Total	291	100	4.54 ± 3.04 (1 in 22,000)	2.95 ± 1.04 (1 in 34)

Table 3. Summary of previous estimations on the frequency of XP (XPA) patients and heterozygotes in Japanese

Genes	Frequency of patients (q^2)	Frequency of heterozygotes ($2pq$)	References
XPA	1/42,000	1/100	Present study
XPA	1/570,000	1/376	Maeda (ref. 13)
XP	1/23,000	1/34	Present study
XP	1/18,000 to 31,000	1/67 to 88	Neel (ref. 14)
XP	1/100,000	1/170	Takebe (ref. 3)

founder mutation, 0.88% (9/1,020), includes a rather wide 95% CI from 0.40% to 1.67%. If we assume a true frequency equal to the lower bound, 0.4%, the frequency of XPA patients is calculated as 0.51×10^{-5} (1 in 195,000), nearly 5 times lower than the estimates using the mean value. Under these conditions, the overall frequency of XP patients would be estimated to be 0.93×10^{-5} . Consequently, the frequency of heterozygotes at any XP gene is estimated as 1.32×10^{-2} (or 1 in 76 individuals), which is nearly one half of the estimate using the mean value. This value closely related to past values.

We think there is no discrepancy between present and past values from the view point that the registration of XP patients is unlikely to be complete (for example, the symptom is mild and skin cancer is developed over age of 40 in some complementation groups). However, it is quite conceivable that the mean frequency of heterozygotes observed in this study could happen to be higher than the actual frequency in the general population and/or the Hiroshima and Nagasaki population might not provide a good representation of the Japanese general population.

Cancer risk in XP heterozygotes

The cancer risk of heterozygotes has only been estimated in one large epidemiologic study of the members of 31 XP families. Swift and Chase reported 30 out of 1,046 clinically normal adult blood relatives had skin cancer versus 11 out of 855 spousal controls.¹² This represents an odds ratio of 2.27 with a 95% CI of 1.13 to 4.55. This result indicated that the frequency of skin cancer among blood relatives was significantly higher than that in spouse controls. Further, the skin cancers in blood relatives were concentrated in four families, and at least one of the families contained a mutation in the XPA gene, and the risk in the blood relatives in these four families was nearly 15 times higher than among the spousal controls, while the risk in the relatives of the remaining 27 families did not show a statistically significant increase when compared to risks in the spousal controls. The underlying cause for the skewed distribution of excess risks in the four XP families is not known, but could be partly due to a difference, either in the defective genes (severe vs. mildly af-

ected phenotypes) and/or in the extent of the UV exposure (i.e., the result of residing in the southern vs. the northern states in the U.S.). This study was published 25 years ago before any XP genes were cloned, so there was no laboratory test capable of identifying which of the blood relatives were heterozygotes.

Thus, skin cancer risk of XP heterozygotes seems to be higher than that of normal individuals, although how much higher is unclear.

In most other populations the frequency of XP is much lower than in the Japanese population, each of the genes has many different disease causing mutations, and not all of these mutations have been identified. Any attempt to determine the frequency of XP heterozygotes of any XP group in other populations would require examination of a large number of possible sites in the relevant XP gene and as a result would be virtually impossible. In this regard, the Japanese population is unusual because nearly one half of the XP patients have mutations in the XPA gene, and the vast majority of XPA patients bear the identical founder mutation. Thus, a population-based study on the influence of the XPA AlwNI mutation and cancer risks in XPA heterozygotes in the Japanese population is a feasible future study.

The frequency of XPA heterozygotes observed in this study suggested the possibility that the risk of skin cancer in XPA heterozygotes can be elucidated, if we examine several hundreds of skin cancers. We are preparing a research plan to evaluate the risk of skin cancer in XPA heterozygotes.

Conclusion

We screened approximately 1,000 individuals who resided in Hiroshima or Nagasaki to estimate the frequency of heterozygotes bearing the founder mutation at *xeroderma pigmentosum group A* (XPA) gene with PCR-RFLP method, as a preliminary study for evaluation of excess risk of skin cancer among the XPA heterozygotes. We identified nine such heterozygotes among 1,020 individuals screened (0.88%). This rate, if representative, implies that there are about 1 million carriers of the XPA founder mutation in the Japanese population. Thus, investigation of their cancer risk may be warranted.

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The Introduction of Dosimetry System DS02 and Its Impact on Survivor Doses and Related Risk Estimates

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In 2003, RERF implemented a new dosimetry system, DS02. DS02 was developed primarily to address questions about the reliability of the neutron dose calculations of its predecessor, DS86: questions that arose from environmental measurements related to neutrons from the atomic bombs. The related issues were discussed in an earlier issue of the *RERF Update*.¹ In addition to complete new calculations of the fundamental quantities on which the estimates of survivor doses are based (radiation output of the bombs and transport of the radiation to locations on the ground), the developers of DS02 provided a number of shielding modifications to address issues that arose in the years after the introduction of DS86. The new calculations of bomb output and radiation transport resulted in minor (order of 10%) but uniform (same proportional change for all individual survivors at a given distance) changes in the unshielded (“free-in-air”) doses that the dosimetry system calculates at ground level at all distances where survivors were located.^{1,2} In contrast, the shielding modifications produced some fairly large changes in estimated dose in some individuals, but these average out to minimal when averages for the full Life Span Study (LSS) cohort are taken over reasonable-sized categories of DS86 dose or distance, except for low-dose survivors in Nagasaki. In this communication, we summarize briefly the effects of DS02 on the doses calculated for survivors, and we discuss initial evaluations of the resulting impact on risk estimates.

The dose (D) calculated for any organ of any survivor can be factored into a free-in-air kerma (K) times a transmission factor (T), so that the organ dose D changes in proportion to the changes in K and T.

That is, $\frac{D_{DS02,n}}{D_{DS86,n}} = \frac{K_{DS02,n}}{K_{DS86,n}} \times \frac{T_{DS02,n}}{T_{DS86,n}}$ for neutrons

and $\frac{D_{DS02,g}}{D_{DS86,g}} = \frac{K_{DS02,g}}{K_{DS86,g}} \times \frac{T_{DS02,g}}{T_{DS86,g}}$ for gammas, and

we can conveniently summarize changes in D as changes in K and T. The T can be further factored into two parts: one for the external (to the survivor’s body) shielding provided by buildings and hills, and the other for the shielding provided by the body itself, i.e., the shielding of deeper organs by overlying tissues, e.g., for neutrons, $T_n = T_{external,n} \times T_{body,n}$.

Although the same relationships apply to both neutrons and gamma rays, the quantities D, K and T and their ratios are generally different, and the relationships for neutrons will be discussed separately and distinctly from those for gamma rays.

Changes in K are described and explained in ref. 1: they are dominated by a change in the gamma component, which is an increase of approximately 7% to 10%, for both Hiroshima and Nagasaki, at all distances relevant to survivors. Changes in T, on the other hand, are a combined effect of changes in the energy spectrum of the radiation reaching a survivor’s location in the absence of shielding, and changes in the way that shielding is calculated. Changes in the energy spectrum can be summarized quite succinctly: there was very little change in the gamma-ray spectrum in either city, and a minor reduction in overall neutron energy in both cities.^{2,3} However, a few explanatory notes are in order, especially in regard to the resulting changes in $T_{external}$ and T_{body} .

In regard to gamma rays, it should be noted that there was a change in the spectrum of prompt primary gamma rays in the calculated output of both bombs,² i.e., those that were produced in the fission chain reaction and “leaked” out of the bomb casing prior to the termination of fission, as well as an increase in their total numbers. However, prompt primary gammas are a relatively minor part of the total contributing to survivor dose, which is dominated by prompt secondary and delayed gammas. Therefore, there is virtually no change in $T_{external,g}$ that is due to the gamma-ray energy spectrum—the only changes in $T_{external,g}$ are due to the shielding modifications of DS02. And, because DS02 calculates the body’s self-shielding by the same methods as DS86, there is no substantial change in $T_{body,g}$ for any of the organs.

As to neutrons, the decrease in overall energy results in a small decrease in $T_{external,n}$ before the specific shielding modifications of DS02 are considered. That is, for example, for house shielding that is not affected by the shielding modifications of DS02, the change in neutron energy causes $T_{external,n}$ to be a bit (~5%) less than that of DS86. This effect is attenuated in population averages by the fact that it does not apply to persons who were outdoors. A slightly

larger effect, which applies uniformly to all survivors, is the effect of the change in neutron energy on $T_{\text{body,n}}$ for deeper organs. For colon, for example, $T_{\text{body,n}}$ in DS02 is about 6% to 9% less than in DS86.

The effect of DS02 shielding modifications on T_{external} for both neutrons and gamma rays can best be understood by considering the nature of each modification and the characteristics of the survivors affected by it. The changes noted below are for $T_{\text{external,g}}$ because gamma dose predominates; changes in $T_{\text{external,n}}$ are generally similar.

- For persons in typical Japanese wooden houses, the “frontal” shielding provided by adjacent buildings in the direction of the bomb was not considered in DS86 if the adjacent structure was more distant from the survivor than twice its own height, on the assumption that such more distant structures were at too low an angle to block out a significant fraction of the radiations coming from the bomb. However, it was determined later that the effect of such more distant frontal shielding is not negligible, particularly at longer distances from the hypocenter where the bomb is at a low angle of elevation above the horizon. DS02 calculates this additional shielding by using certain rules to divide the Monte Carlo results from the DS86 house and tenement model clusters into three categories based on the extent of such more distant frontal shielding. During implementation of DS02, the frontal shielding parameter for all affected survivors, 5,383 in Hiroshima and 2,166 in Nagasaki, was re-coded by using geometric templates to apply the same classification rules to their shielding history diagrams. Those in the new category with least amount of “distant frontal shielding” had an average increase of about 10% to 12% in their $T_{\text{external,g}}$, those in the middle category had a change of only 1% to 2%, and those in the new category with most such shielding had decreases of about 12% to 17%. These changes average out to almost zero in the full group of affected survivors, which is consistent with the fact that they essentially represent a rearrangement of the same Monte Carlo results from the model house and tenement clusters that were used in DS86.
- A new “school” building model was developed for persons in wooden schools and other similar large wooden buildings, to replace the use in DS86 of the model house and tenement clusters. In essence, buildings such as wooden schools were not being properly represented by the model house and tenement clusters because they have larger rooms than houses and tenements; therefore the radiation passing through a school type building encounters fewer wall and roof surfaces per unit distance, on average, than in a wooden house or tenement. The

new model resulted in an increase averaging 31% for the T_{external} of 639 persons in such buildings in Hiroshima and 67 in Nagasaki.

- In 1989, the developers of DS86 provided RERF with a method for calculating the shielding of survivors in two generic types of factory buildings in Nagasaki, but these calculations modeled only the walls and roof of the building and not any of its interior features. For DS02, a large, three-dimensional forward-adjoint Monte Carlo calculation was performed with a detailed model that included some model workbenches with tools and metal parts situated on top of them, and two sets of calculations were performed for each of 40 modeled worker positions, for a standing person and a person lying on the ground. In the implementation of DS02, workers were considered to be standing until the arrival of the blast wave, then lying down. Under these assumptions, doses were reduced only for positions within about 2 m behind a bench that was >30 m from the wall of the factory in the direction of the bomb, and this reduction, which affects only 97 of the 650 workers with position data in factories to which the models apply, was only about –8% on average.
- In DS86, persons who were outside but near to buildings had their shielding calculated by a so-called “globe” method. This was based on a similar T65D method, for which a specially created variable had been evaluated for each survivor by using a spherical coordinate projector (a light bulb inside a clear sphere with markings) with a scale model of the survivor’s surroundings, to determine the fraction of solid angle in specific directions, relative to the direction to the bomb, that was blocked by buildings. In DS86, a weighted sum of these increments of solid angle was calculated for each person and used to determine the *single* best Monte Carlo result to use from among a number of such outdoor locations that were calculated in the model house and tenement clusters. DS02 uses an average of the *six* outdoor Monte Carlo results from the model house and tenement clusters that have the nearest weighted solid angle to the survivor whose shielding is being calculated. This results in rather large changes for some of the affected individuals, with a standard deviation of about 15% in Hiroshima and 19% in Nagasaki for the % change in the $T_{\text{external,g}}$. However, as with the change in frontal shielding for those inside of houses, this essentially represents a rearrangement of Monte Carlo results that were already being used in DS86, and the change averages to almost zero for the affected 2,294 survivors in Hiroshima and 593 in Nagasaki.

- In DS86, a method was devised to adapt T65D globe calculations for small hills, but it was never implemented. In 1989, one of the developers of DS86 provided RERF with a new, Monte Carlo based method for calculating terrain shielding based on angles of elevation measured in five horizontal directions relative to the direction to the hypocenter of the bomb: $0, \pm 45^\circ, \pm 90^\circ$. This module was used for small hills in Nagasaki, which is much more hilly than Hiroshima. It was not clear if this method could be used for the large hills Hijiyama in Hiroshima and Konpirasan in Nagasaki, but in developing DS02 it was established that this could be done. The implementation in conjunction with DS02 resulted in an average reduction of the $T_{\text{external,g}}$ of about -6% for 2,675 survivors in Hiroshima who were coded as being affected by such “distal terrain” shielding, and -38% for 4,899 survivors in Nagasaki.

Thus, of all the shielding modifications, only the last one listed, distal terrain shielding, produced a substantial effect on relevant averages of doses calculated for the major RERF cohorts, predominantly in Nagasaki because of the much larger size of Konpirasan and the lower epicenter height of the Nagasaki bomb, and only at longer distances beyond that of Konpirasan. The frontal shielding and globe modifications average out to very small differences if taken over reasonably large subsets of survivors classified in categories of distance or DS86 dose, the school model affects too few survivors to have much impact on averages based on the full cohort, and the new Nagasaki factory model produced little change in calculated shielding.

It should also be noted at this point that DS02 results regarding the Hiroshima hypocenter have no effect on survivor distances or resulting doses. The

use of a geographical information system (GIS) in developing DS02 resulted in a new alignment of the war-era U.S. Army maps with more modern and detailed Japanese maps produced in 1979 for Hiroshima and 1981 for Nagasaki. These newer maps are more accurate as well as more detailed, have coordinates that are verifiably correct in modern geographical coordinate systems, and generally conform to the street plans of present-day Hiroshima and Nagasaki. The new map alignment allowed new estimates of the locations on the newer maps that correspond to hypocenter estimates that had been produced completely in the context of the U.S. Army maps. Based on the new map alignment, the location of the Hiroshima hypocenter on the 1979 map was about 15 m west of two locations determined circa 1985 during the development of DS86, whereas the location of the Nagasaki hypocenter on the 1981 map was less than 3 m from the location estimated circa 1985. Because the survivor distances currently used at RERF are still based on the coordinates of the U.S. Army maps, and the estimated locations of the hypocenters on the U.S. Army maps are not changed by the work done for DS02, there has been no change in estimated survivor distances.

To sum up the effect of DS02 on survivor doses, including the effect of changes in $T_{\text{body,n}}$ on the doses to important deeper organs and tissues, the figure addresses changes in colon dose. The curves in the figure are plots of $\frac{D_{DS02,n}}{D_{DS86,n}}$ and $\frac{D_{DS02,g}}{D_{DS86,g}}$ for each city, produced by grouping survivors on 50-m intervals of distance and smoothing the results. The curves for gamma rays look very much like the changes in K_g , which are shown in a similar plot in the previous discussion in the *RERF Update*,¹ because there are no substantial changes to T_g . The exception is that the effect of Konpirasan is seen in the downward

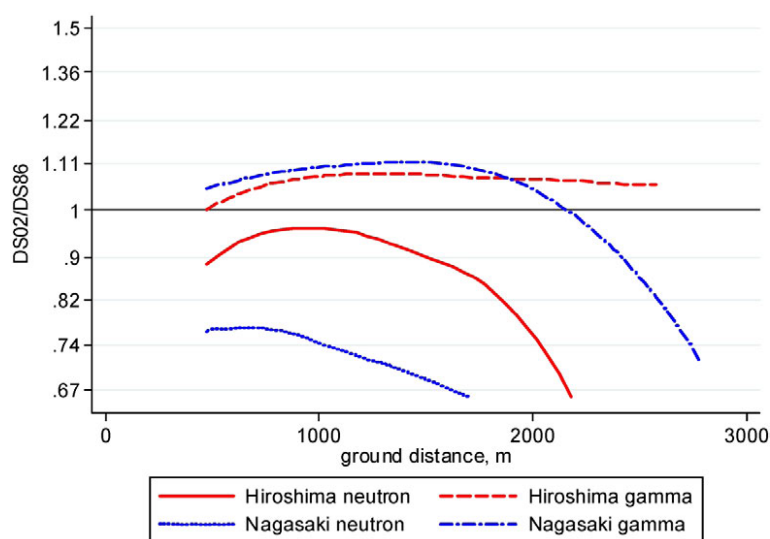


Figure. Ratio of DS02 colon dose to DS86 colon dose vs. distance.

trend for Nagasaki at distances beyond about 2 km. The curves for neutrons, however, are shifted downward by the effect of the lower neutron energy spectrum of DS02 on $T_{\text{external},n}$ and $T_{\text{body},n}$. For similar reasons, at all distances in both cities, for all organs and tissues, the ratio of neutron dose to gamma dose is less in DS02 than in DS86: $\frac{D_{DS02,n}}{D_{DS02,g}} < \frac{D_{DS86,n}}{D_{DS86,g}}$. In Nagasaki this difference is quite pronounced, but of negligible consequence because $\frac{D_{DS86,n}}{D_{DS86,g}}$ was already very small in Nagasaki.

Shortly after the implementation of DS02, its effect on risk estimates was initially evaluated for solid cancer and leukemia mortality in the LSS.⁴ The estimates of excess relative risk (ERR) per gray, modeled as linear for solid cancer and linear-quadratic for leukemia, both decreased by about 8% due to the increases in estimated gamma dose. There were no other changes attributable to the DS02 vs. DS86 dosimetry, including no substantial changes in age-time patterns and sex differences. This does not establish, of course, that changes would necessarily be negligible for other RERF cohorts or subcohorts, particularly in studies utilizing smaller groups of

survivors in which individual dose changes due to the DS02 shielding modifications may not be subject to as much averaging as in the full LSS.

Contemporaneously with the implementation of DS02, the roster of survivors with calculated doses was considerably expanded, as detailed in ref. 3. As noted in that summary, research and related work will continue on a number of areas of implementation, including the methods used to deal with dose error, the use of the GIS with maps, aerial photographs and survivor shielding history drawings to improve estimates of survivor location and possibly some aspects of shielding, and particular attention to the case of the Nagasaki factory workers. Much greater detail on all of the matters related to DS86 and DS02 is given in the related reports, which are available online at RERF's website under "Publications." For example, Chapter 11A of the DS02 report² explains why the anticipated changes in dose estimates for the Nagasaki factory workers were not realized, and suggests areas for further research. In addition, the U.S. National Cancer Institute has graciously made the extensive review of dosimetry in ref. 3 available to the public free of charge on their website at <http://dceg.cancer.gov/radia/res35.html>.

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Ties Strengthen Between Scientists at RERF and REAC/TS: An Update

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The 2nd International Conference on Biodosimetry and the 7th International Symposium on EPR Dosimetry and Applications were held on July 10–13, 2006, at the Uniformed Services University of the Health Sciences in Bethesda, Maryland. This meeting provided an ideal venue for scientists affiliated with RERF and REAC/TS to present a joint paper entitled, “An Automated Method to Quantify Radiation Damage in Human Blood Cells” authored by Drs. Gordon Livingston and Mark Jenkins of REAC/TS and Dr. Akio Awa, cytogenetic consultant to RERF. A fruitful collaboration between Drs. Awa, Nori Nakamura, and myself had already developed via e-mail over the previous two years but it was not until the biodosimetry conference that the investigators finally had an opportunity to meet each other in person (see the photo below).



(From left) Dr. Akio Awa from RERF, Drs. Gordon Livingston and Patrick Lowry from REAC/TS, and Dr. Yoshiaki Kodama from RERF. (Not pictured from REAC/TS are Drs. Al Wiley and Mark Jenkins—photographer)

As described in the previous issue of the *RERF Update*, a fruitful collaboration developed as a result of two publications, one authored by Dr. Mimako Nakano and co-workers in the Cytogenetics Laboratory at the RERF that compared cytogenetic data based on solid Giemsa staining with FISH-based staining for 230 A-bomb survivors and the second by Dr. Awa, entitled “Biodosimetry of Human Exposure to Radiation: A Manual for Detecting Stable Chromosome Aberrations by the Conventional Giemsa Staining Method” published on the RERF website. These two RERF publications combined to provide the stimulus for me to further evaluate

chromosome preparations obtained from former U.S. plutonium workers on whom FISH-based studies had already been completed. Surplus slides were available for further evaluation for 15 controls and 15 exposed individuals using conventional Giemsa staining and automated karyotype analysis. The use of the 7–8 year old unstained slides presented a unique opportunity to validate and confirm the earlier RERF studies and to compare data from the A-bomb survivors whose exposures were acute external doses with former plutonium workers whose exposures were chronic and mainly the result of internal deposition of plutonium. Furthermore, it was worthwhile to compare the data from the FISH and conventional Giemsa staining methods to see whether the frequency of total translocations was similar using different methods of analysis. Results showed good agreement for both the control and exposed groups. The data obtained from the former plutonium workers confirmed the earlier work published by scientists at the RERF on atomic bomb survivors who had demonstrated the value of solid Giemsa staining in detecting stable chromosome aberrations (see the Figure).

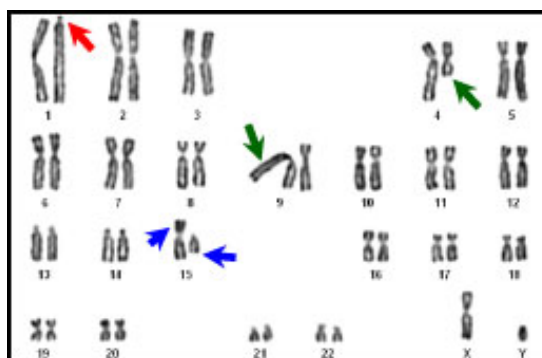


Figure. Karyotype showing chromosome aberrations: Inversion in chromosome (1)/Translocations in chromosomes (4, 9) and (15, 15).

The follow-up cytogenetic study of the plutonium workers was ultimately funded by the Department of Energy (DOE) through the National Institute for Occupational Safety and Health (NIOSH), and the DOE-EH (Office of Environment and Health) continues to support the REAC/TS Cytogenetic Biodosimetry Laboratory (CBL) in Oak Ridge, Tennessee.

In addition to the attendance and collaboration on the presentation at the Biodosimetry Conference in Bethesda, Drs. Kodama and Awa traveled to Oak Ridge to serve on the REAC/TS CBL Scientific Advisory Board (SAB). The SAB will provide technical advice and guidance on the re-establishment of a cytogenetics laboratory at the Oak Ridge Institute for Science and Education (ORISE)/REAC/TS. The SAB will help to ensure that the REAC/TS Cytogenetic Biodosimetry Laboratory will be re-established in a timely manner and will produce the highest quality analyses.

While in Oak Ridge for the day, the international members of the SAB and some of the REAC/TS staff took an opportunity to visit the International Friendship Bell that is the first monument between a U.S. Manhattan Project city and Japan and serves as an expression of hope for everlasting peace.



(From left) Drs. Daniela Stricklin (FOI-Sweden), Joe Weiss (U.S. DOE-EH), David Lloyd (HPA-England), Patrick Lowry, Gordon Livingston (REAC/TS-USA), Akio Awa, and Yoshiaki Kodama (RERF-Japan) visited the International Friendship Bell in Oak Ridge. (Not pictured is Dr. Mark Jenkins [REAC/TS]—photographer.)

Memory of a Firefighter of Chernobyl Accident

Akio Awa, former Associate Chief of Research

For me, the year of 1989 was a busy one, and one to be remembered. Early in 1989, I received an invitation letter as a speaker of the plenary session from the organizing committee of the International Conference on “Chromosome Aberrations—Basic and Applied,” to be held in Essen, West Germany, 5–7 October 1989. That was a month before two Germany countries were reunited. Soon after I accepted this invitation, I was asked by Professor Kenjiro Yokoro to give a talk on the genetic effect of atomic radiation of the offspring of A-bomb survivors at the symposium of the International Physicians for the Prevention of Nuclear War (IPPNW) to be held in Hiroshima and Nagasaki on October 5–12, 1989. Dr. Yokoro then was a professor in the Pathology Department of the Research Institute of Radiation Biology and Medicine at Hiroshima University, and concurrently the secretary-general of the Japan IPPNW branch office. To my surprise and perplexity, dates of two international meetings overlapped perfectly, and about as far separated on the globe as one could get, i.e., the one meeting in Europe and the other in Japan. Nevertheless, I found a way to attend both the meetings, provided a neat and tight schedule was followed. I ended up giving a one-hour talk at Essen in the evening of October 5, and immediately left the next day for Narita, Japan, via stopovers in Düsseldorf and Frankfurt. Although the travel schedule was tight and rather difficult, it was the only way to get back to Hiroshima to make IPPNW meeting and to give my talk on schedule.

Somehow I managed it, but it felt as though I was walking on a tight-rope.

The IPPNW Colloquium opened in the morning of October 8 at the International Conference Center Hiroshima in Peace Memorial Park. The majority of the speakers at the colloquium were RERF scientists, and all of the papers were well received by those in attendance. After my session, Dr. Itsuzo Shigematsu, a former RERF chairman, told me that one of the Chernobyl firefighters was attending the meeting and would be visiting RERF on October 10 and would be receiving various clinical and laboratory examinations. The firefighter’s name was Major Leonid Petrovich Telyatnikov, the commander of the Chernobyl Fire Department at the time of the accident, April 26, 1986. He was invited by the conference organizers to come to Hiroshima and to give a talk about his own experience in fighting the fires associated with the Chernobyl reactor accident. Due to my getting to conference a bit late, I didn’t have a chance to listen to his lecture, but I was told that his talk was highly informative and deeply moving.

Mr. Telyatnikov visited RERF in the morning of October 10. He was quiet and kept smiling all the time. He was 38 years old at the time of examination, being 3 and-a-half years after the Chernobyl accident. When we met he looked apparently healthy. When I saw his dark hair, it was hard to imagine his hairless head at the time he was out of the hospital after emergency treatment in 1986. In those days, I had a chance to read many books regarding the

Chernobyl disaster in which many photographs of his with loss of hair were documented.

His blood was drawn by Dr. Kazuo Neriishi at the RERF clinical facilities (for detail, see *RERF Update*, Volume 1, Issue 4, Winter 1989–90, pages 1–2). The blood was brought to Cytogenetics Laboratory where tissue culture and preparations of microscopic slides for chromosome aberration analysis would have been conducted. We employed all available cytogenetic techniques, such as conventional stain, trypsin-Giemsa banding stain (GTG), Fluorescence plus Giemsa (FPG) stain with BrdU. In those days, however, FISH (Fluorescence *in situ* hybridization) stain technique was not available at RERF.

The purpose of chromosomes aberration study was to estimate radiation dose received by him by means of cytogenetic biodosimetry analysis. The



Portrait of Mr. Leonid Petrovich Telyatnikov (date of photography unknown), by courtesy of Mrs. Larisa Ivanovna Telyatnikova.

chromosome analysis was performed successfully. In accordance with our anticipation, we could detect a large number of complicated structural rearrangements of chromosomes in his peripheral blood lymphocytes. This indicated that he must have received as high as fatal radiation dose during his fire-fighting ac-

tivity. We could confirm that our suspicion proved to be true. After analysis and calibration of data, his radiation dose was estimated to be in the range of 4–5 Gy that corresponds to the LD50 dose in man. Subsequently, a summary form of the results was submitted to the Chairman's office.

In December of 2004, I learned through the news media that Mr. Leonid Telyatnikov passed away at the age of 53 due to cancer of the jaw. The year 2006 is the 20 years anniversary of the Chernobyl nuclear power plant accident. This reminded me two important things which I completely ignored for years. One was that I did not report of our findings to our client, Mr. Telyatnikov, and the other was that the data had been left unpublished. For the former, thanks to the strong support of the staff of Kyodo Press in Japan and in Moscow, the report of our data was delivered to his bereaved family members in Kiev, Ukraine, together with my apology for not sending any report to them. The apology was accepted by the family.

I started to re-visit the cytogenetic data, which have been kept as an official document of the Department of Genetics. The data seemed to include some important findings. I personally consulted this matter with my old friend who is known as an expert in this research area. He gave me advice that the data be published promptly, and that it is not yet too late to do so. A manuscript is being in progress and ready for receiving criticisms and comments from the RERF Scientific Report Review Committee for approval of publication.

Before closing this personal account of recollection, I wish to thank all of the research and technical staff of the Cytogenetics Laboratory, as shown in the following. Professional staff: Dr. Yoshiaki Kodama, Dr. Kazuo Ohtaki, and Dr. Mimako Nakano. Technical staff: Ms. Sumie Murata, Mr. Masashi Hiramoto, Ms. Kaori Muramoto, Ms. Miwa Miura, and Mr. Junso Takayama (photographer).

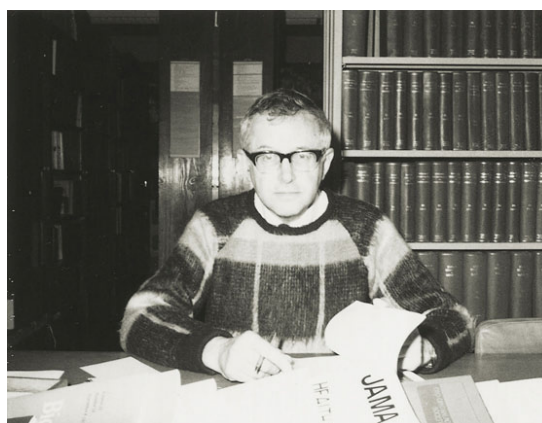
Mourning the Death of Dr. Robert W. Miller

Kiyohiko Mabuchi
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Dr. Robert W. Miller, who greatly contributed to the epidemiological research of A-bomb survivors at ABCC and RERF, passed away at the end of February in 2006. As a pediatrician, Dr. Miller was interested in radiation biology and genetics, and made important and unique contributions to the study of association between congenital deformities and cancer and to many other fields of study. Dr. Miller came

to Hiroshima in 1953 and was assigned to the position of chief of ABCC's pediatrics department. He produced important study results in terms of microcephaly and mental retardation among children exposed *in utero* and childhood leukemia, although his achievements failed to attract any attention at that time. In those days, the framework of epidemiological research of A-bomb survivors, with the Life Span

Study playing a key role, was established under the Francis Committee. During this most important transitional period in ABCC-RERF's history, Dr. Miller made notable contributions as a pioneer in epidemiological research at RERF. After returning to the United States, he was appointed the first chief of the epidemiology department at the U.S. National Cancer Institute (NCI). Stressing the importance of epidemiological research on A-bomb survivors, Dr. Miller consistently supported RERF's study program through the National Academy of Sciences (NAS) and the RERF Scientific Council. Dr. Miller also initiated the tissue registries in Hiroshima and Nagasaki through NCI. Furthermore, under the U.S.-Japan joint study group he organized, Dr. Miller promoted cooperation with many Japanese researchers outside RERF. Based on his own experience, Dr. Miller emphasized that keen observation at a patient's bedside would lead to the identification of the cause of his/her disease. He did not like to follow the crowd, and had unique viewpoints in every respect. On one of its cover pages, the *New Yorker* once carried a photograph of several birds on an electric wire looking in one direction, with only one bird looking the



Dr. Robert W. Miller in 1979

other way. Dr. Miller considered himself to be like that single bird. Dr. Miller's memoirs of ABCC-RERF consisting of four parts were published in the *RERF Update* from 1993 through 1998. The memoirs show his intellectual energy, keen powers of observation, and sense of humor. Mrs. Holly Miller is Japanese and used to be a nurse at RERF.

In Memory of Dr. Shoichiro Fujita

**Fumiyoshi Kasagi, Assistant Chief
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It was April 3, 2005, when I received the sad news of the sudden passing of Dr. Fujita. When I hurried to his home and saw him lying in peace on his bedding, I could not stop crying. His personality appealed to many people. He had his own clear standards of right and wrong, and he always dealt with people based on those standards, uninfluenced by self-interest. When he pleaded with someone about something, he did it in all seriousness, often turning red in the face. Even in his earnest remonstrance, though, his compassion for others was always evident. When he talked with people in his office, his voice echoed throughout the corridor, at times encouraging or chiding, at other times erupting in big-hearted laughter. One year and eight months have passed since Dr. Fujita's voice was last heard at RERF.

In March 1968, Dr. Fujita was hired as a research scientist of the Department of Statistics at ABCC (now RERF). He was the first person to assume the position of senior research scientist at RERF. After serving as Assistant Chief of the Department of Statistics, he retired from RERF in December 2002, upon reaching mandatory retirement age. Subse-

quently, he was reemployed as a research scientist at the Department of Statistics. He devoted his efforts over 37 years to the research of ABCC and RERF. His expertise in dosimetry was eagerly sought after by various organizations. He served as a committee member for the Nuclear Safety Research Association's "Evaluation of Health Effects of Radiation Exposure," as a researcher for the National Institute of Radiological Sciences' "Study of Dose Effect in Low-dose Region," and as an expert member for the Japan Atomic Energy Research Institute's "Low-dose Radiation Safety Evaluation Database," among others. In 1995, he appeared on TV as a lecturer for a Hiroshima University extension lecture series to talk about atomic bomb radiation dose. Beforehand, he practiced his lecture over and over again in his office, tripping over a word, and saying to himself, "It may be better to explain it this way for viewers to readily understand." In front of the camera on the day of shooting, Dr. Fujita calmly interacted with the announcer. When I said to him, "It went quite smoothly," he responded with smile, "I thrive under pressure."

The foundation of RERF's health risk assessment

is estimation of radiation dose (exposure variable). It is undisputable that Dr. Fujita's contributions included his putting a great deal of effort toward the development and introduction of the different dosimetry systems used at RERF. He played a role in the U.S.-Japan joint reassessment of atomic bomb radiation dosimetry, which started in 1981, as one of the Japanese members, and greatly contributed to the establishment of the Dosimetry System 1986 (DS86). Even after the promulgation of DS86, he was involved in efforts to collect exposed materials (tile, brick, concrete, iron, copper, etc.) in Hiroshima and Nagasaki for analysis of the uncertainties in the estimate system, traveling to the collection sites as a collection supervisor. It is with a feeling of nostalgia for us now to look at the photographs taken in



Dr. Shoichiro Fujita collecting samples on the top of Mt. Kompira in 1997

November 1997 at the time of collection of concrete cores from the buried anti-aircraft bunker on the top of Mt. Kompira in Nagasaki. In creating the Japanese version of the recently published Dosimetry System 2002 (DS02) report, Dr. Fujita cloistered himself in his home for two months to edit the Japanese translation despite his illness. This clearly shows what he was like. He devoted himself singleheartedly to fulfill his responsibilities, leaving nothing unfinished.

There are simply too many stories to tell about Dr. Fujita, who was loved by everybody. We had a small party on the occasion of Dr. Fujita's retirement in 2002. This photograph taken on that occasion reminds me of several unforgettable scenes: Dr. Fujita listening to messages from people at the party,



Dr. Fujita at his farewell party in 2002

and Dr. Fujita breaking out in a large grin after receiving a bouquet of flowers. At that time, nobody knew that two years later the time would come to bid Dr. Fujita a sorrowful farewell. Dr. Fujita passed away on April 3, 2005 (Sunday). He was 63 years old. We mourn Dr. Fujita's untimely death. May his soul rest in peace.

Facts and Figures

In the previous issue (volume 16 of the *Update*) we had likened RERF's vast *Biosample Archive* to "crown jewels." Well, RERF's "treasures" extend beyond the stored biosamples: RERF has a sizable collection of historical documents, publications, and references as well.

This component of the RERF's archive has been recently reviewed and summarized by the Office of the Permanent Director, Mr. Takanobu Teramoto. The salient features of this report are listed below and include the following archival elements: ABCC-RERF Publications, RERF's Database System, and the RERF Library Archives.

ABCC-RERF Publications

There are seven distinct categories of publications currently available for review by RERF researchers, and with the exception of the *RERF Newsletter* and *RERF Annual Report*, all are accessible by the outside scientific community via RERF's website.

The seven publication categories include: RERF's Research Protocols, *ABCC-RERF Technical Report* and *RERF Report* series, *Commentary and Review* series, the joint U.S.-Japan reports on the dosimetry reassessments of atomic bomb irradiation of Hiroshima/Nagasaki Life Span Study (LSS) cohort members, *RERF Annual Reports*, *Newsletters*, and its own journal, the *Update*.

1. Research Protocols (abstracts only) are available for inspection on the web page. This number includes 66. All protocols, past and present (approximately 550 in total since 1959) are available upon request by study participants and research collaborators.
2. *ABCC-RERF Technical Reports* and *RERF Reports* are available on various studies that have been conducted from 1947 to present. There are some 3,679 items in this category, with approximately a third (1,146 out of the 3,679) processed under RERF's current review system. A series of LSS reports (21 issues of a periodic update on analyses of the LSS cohort) along with a comparable series of reports (9 issues) on the Adult Health Study (AHS) cohort have been published and are available as well.
3. *Commentary and Review* series have been published on an intermittent basis in order to disseminate ideas, stimulate discussion on given topics, and to solicit comments from the research community at large on RERF's ongoing research.
4. U.S.-Japan reports on the reassessment of the atomic bomb radiation dosimetry for Hiroshima and Nagasaki are available and include the DS86 report (2 volumes) and the DS02 report (2 volumes). It should be noted that the earlier T65D reports were published as *ABCC Technical Reports*.
5. *Annual Report* series includes 69 issues and covers the period from 1952 to present.

6. *Update* journal focuses on current RERF's research activities and seeks to target both RERF researchers and outside investigators alike. The series has 40 issues, covering the period from 1989 to present.
7. *Newsletter* is an informational publication for both former and present RERF employees. There are 823 issues in the series and it covers the period from 1963 to present.

RERF Database System

The database includes the following seven partitioned databases: a core resource database, research and document databases, research information management system, library and historical document databases, and a website-accessible database for the outside scientific community and interested laypersons.

1. Core Resource Database consists of a variety of research data, plus the inclusion of personal and confidential information. Due to the latter, access to this database is strictly limited to fully authorized RERF staff members on a need-to-know basis.
2. Research Database serves as an essential, basic research tool for RERF researchers in carrying out a variety of analytical procedures on given datasets. In contrast to the above listed "Resource Database" datasets contained within this database have been thoroughly scrubbed and are free of any/all personal and confidential information.
3. Document Resource System serves as an analytic operations documentation resource.
4. Research Management Information System is dedicated to providing details on RERF's publication procedure, from the initial submission to the Scientific Reports Review Committee, through internal review and authorization, to final journal submission.
5. Library Database contains electronic listing of current library holdings, including all scientific journals, textbooks, and references. In addition, Library Database contains a general listing of procedures for library patrons.
6. Historical Materials Database contains records pertaining to early ABCC-RERF research activities, including microscopic-image slides, photographs, and newspaper articles.
7. RERF website contains an assortment of research data from specific clinical and experimental studies that are accessible and available for free downloading; e.g., mortality data, chromosome aberration data, etc.

RERF Library Archives

RERF Library maintains approximately 39,000 reference items (specialized textbooks, references, and journals) related to radiation effects research.

Research Protocols Approved in 2005

RP 1-05 Glaucoma Study in Atomic Bomb Survivors

Minamoto A, Tsukamoto H, Yokoyama T, Tsuiki E, Uematsu M, Ogawa T, Mishima HK, Kitaoka T, Nakashima E, Neriishi K, Hida A, Fujiwara S, Akahoshi M

It is well known clinically that radiation exposure induces glaucoma. The relationship between glaucoma and radiation in the Adult Health Study (AHS), however, is not consistent: The AHS Report 8 indicates a significant negative association between incidence of glaucoma and radiation dose, while a cataract study indicates no association between radiation dose and glaucoma-associated findings, i.e., papilla atrophy and intraocular pressure. Both studies, however, are too incomplete to draw any conclusions about the relationship. This study was therefore planned.

All AHS subjects will be screened during the period from 2007 to 2009 with a visual field screener and fundus photos, and those diagnosed by ophthalmologists as having abnormalities will be referred to the ophthalmology departments of the Hiroshima and Nagasaki university hospitals, where detailed ophthalmologic examinations will be conducted. Copies of the data from the examination findings will be collected and analyzed at RERF.

RP 2-05 Could Genetic Factors Cause Population Bias among Proximal A-bomb Survivors?—A Test of Whether the Same Genetic Factors Are Risk Factors for High Inflammatory Status and Myocardial Infarction among A-bomb Survivors 40–50 Years Later

Fujiwara S, Suzuki G, Ohishi W, Yamada M, Akahoshi M, Cologne JB

This study will test whether genetic factors relating to inflammatory responsiveness altered the fate of survivors upon radiation injury, burn, and infection after atomic bombing and caused a population bias among highly exposed A-bomb survivors. Subjects are all the 1,100 individuals who participated in the first cycle of clinical Adult Health Study examinations and who were exposed when young (<30 years of age at the time of bombings) to at least 1 Gy of radiation, and 1,100 of their sex-, age-, and city-matched <5 mGy exposed controls. The *LTA* and *TLR2* gene-polymorphism will be typed using genomic DNA extracted from cover-slipped peripheral blood smear samples.

RP 3-05 Inflammation and Cancer Incidence in Atomic Bomb Survivors

Neriishi K, Hsu W-L, Nakashima E, Little MP, Tatsukawa Y, Nishi N, Soda M, Yamada M, Fujiwara

S, Cologne JB, Akahoshi M

Experimental and epidemiological studies report a close relationship between inflammation and cancer. Because A-bomb survivors have radiation dose-dependent increases of inflammatory biomarkers, we will investigate the relationship between the biomarkers and cancer incidence among 12,870 Adult Health Study participants followed from 1965 to 1999.

We will examine white blood cell counts (measured since 1958), erythrocyte sedimentation rate (since 1958), alpha 1 and alpha 2 globulins (since 1985), and sialic acid (1988–1992) as parameters. We will obtain cancer incident data for 1965–1999 from the Hiroshima and Nagasaki tumor registries. We will perform multivariate analysis including inflammatory diseases, smoking, alcohol consumption, and body mass index as risk factors. To assess inflammation effects on cancer development we will apply first principal component analysis, growth curve models, the Cox regression model, and a quasi-mechanistic bystander effect model (indirect effect model) to the data.

Recent Publications

(Japanese): the original article is in Japanese.

(Bilingual): the original article is in both English and Japanese.

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Asia Pacific Cohort Studies Collaboration (RERF: Nakachi K). Joint effects of systolic blood pressure and serum cholesterol on cardiovascular disease in the Asia Pacific region. *Circulation* 2005 (November 29); 112(22):3384-90.

Asia Pacific Cohort Studies Collaboration (RERF: Nakachi K). Smoking and elevated blood pressure are the most important risk factors for subarachnoid hemorrhage in the Asia-Pacific region: an overview of 26 cohorts involving 306 620 participants. *Stroke* 2005 (July); 36(7):1360-5.

Asia Pacific Cohort Studies Collaboration (RERF: Nakachi K). A comparison of lipid variables as predictors of cardiovascular disease in the Asia Pacific region. *Annals of Epidemiology* 2005 (May); 15(5):405-13.

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Publication Using RERF Data

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

Zhang W, Muirhead CR, Hunter N. Age-at-exposure effects on risk estimates for non-cancer mortality in the Japanese atomic bomb survivors. *Journal of Radiological Protection* 2005 (December); 25(4):393-404.