放影研 RERF update
Radiation Effects Research Foundation News and Views
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Radiation Effects Research Foundation

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

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Editorial Policy

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

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From the Editors

Konnichiwa!

As the red Japanese maple leaves start falling and signal that the year 2008 is coming to an end, we welcome our readers to the second issue of *Update* Volume 19. It seems that time has passed quickly since the glowing sunflowers welcomed our many visitors to RERF's Open House back in August. A total of approximately 1,750 persons, including school children, foreign tourists, A-bomb survivors, and other interested Japanese citizens, participated in Open House activities in the two laboratories and learned about the important work going on here. That turnout was one of the largest totals in the last 14 years and was considered to be a big success.

Please find enclosed reports of this year's Scientific Council meeting and the Board of Directors meeting. In addition to staff news and information regarding visiting researchers, this issue includes reports on two symposia conducted at RERF, a science article, and a summary of a report by the RERF Committee on Biological Samples. Again, we hope that you enjoy this edition and that you will let us know how we might improve our reporting of RERF's many scientific activities.

Sincerely,

Evan B. Douple
Editor in Chief

Yuko Ikawa
Technical Editor

Report on the 35th Scientific Council Meeting

The 35th Scientific Council (SC) meeting, co-chaired by Dr. Teruhiko Yoshida (National Cancer Center Research Institute) and Dr. Theodore DeWeese (Johns Hopkins University) was convened on March 3–5, 2008 in Hiroshima to review the scientific program of RERF. The review of departmental research activities was restructured this year to concentrate primarily on the Departments of Clinical Studies, Epidemiology, and Statistics. Along with this transition to a focused review, RERF also invited three special scientific councilors with expertise in the areas selected for in-depth review to augment the review process. These included Dr. Sarah Darby of Oxford University, Dr. Fred Mettler, Jr. of the University of New Mexico, and Dr. Kazuo Tajima of Aichi Cancer Center Research Institute, who provided added strength to the in-depth reviews.

Dr. Toshiteru Okubo, Chairman of RERF, warmly greeted the scientific councilors and guests and noted that there had been several retirements and additions to the professional staff and leadership of RERF over the last year. He also mentioned that the Senior Review Panel had met several times, had received the report of the 34th SC and that the RERF leadership awaits the final report from the Panel. Finally, Dr. Okubo highlighted the fact that there is renewed focus toward thematic working groups at RERF that enhance collaboration among scientists of different departments and mentioned that monthly scientific colloquia also enhance inter-departmental interactions.

Dr. Roy Shore, Chief of Research at RERF, provided a review of the responses to the 34th SC recommendations, as well as a review of the status of research at RERF. Dr. Shore noted that the mandated reduction in force diminishes the needed flexibility to recruit young scientists. He highlighted how several of the unique research resources of RERF, such as the longitudinal biospecimen collection and data from the cohort studies, were increasing the external collaborative opportunities of RERF. He also mentioned the newly introduced performance review process of the scientific staff and department chiefs.

The Departments of Clinical Studies, Epidemiology, and Statistics then provided departmental

overviews including responses to the 34th SC's recommendations and multiple presentations on research programs, highlighting program achievements, ongoing research activities, and future plans. The Departments of Radiobiology/Molecular Epidemiology, Genetics, and Information Technology and the Public Relations program provided a limited summary of ongoing efforts.

The SC began their review by stating they believe that "RERF is one of the pre-eminent leaders in radiation risk research in the world and has the expertise, populations, and data sets to conduct investigations that cannot be carried out elsewhere. The support and assistance of the Japanese Ministry of Health, Labour and Welfare and the U.S. Department of Energy as well as guidance of the National Academy of Sciences continue to be critical to the mission of RERF. Without such support and the assistance of the survivors and their families, the ability of RERF to conduct substantive research that has great impact around the world would not be possible." Their principal assessments and general recommendations were:

- Continued important progress has been made in several areas over the last two years or so. The leadership should be highly commended for this improvement. In particular, there is clear evidence of increased collaboration among RERF scientists as noted in the programmatic reviews. This effort has improved several of the research projects and provides a good working model for developing young scientists.
- We would like to stress the movement toward greater use of biospecimens in RERF research efforts. The biospecimens collected by RERF represent a singularly unique resource from which appropriately designed projects can be created to yield new mechanistic information.
- We would encourage the leadership of RERF to engage in an internal strategic planning process aimed at clarifying the short, medium and long term goals of RERF, the research directions needed to reach those goals and the necessary projects that will be pursued.
- Strategic focus also allows teams to more effectively prioritize work by themselves and lessens the likelihood of inefficient use of resources. The SC notes that departments have a very large portfolio of projects, suggesting the need for more prioritization of research projects within RERF departments. The model for research project prioritization needs to include clear metrics, milestones, and timelines for progress.
- An efficient programmatic structure is necessary for any research organization to maintain high level activity, to bring the best people together on a given project, and to minimize duplication of effort. It may be helpful for the RERF leadership to consider an ad hoc, project-oriented team approach of cross- or inter-disciplinary experts that is conducted outside the conventional departmental structure. Such programmatic constructs, using core resources of the departments to support them, provides an effective mechanism of conducting collaborative research.
- A closer affiliation with Japanese universities and other institutions should be promoted. Such affiliations could facilitate access to facilities, students, and new scientific disciplines and ideas, as well as to other skilled investigators outside RERF.

To highlight a few of the numerous recommendations to departments:

- The Department of Clinical Studies should be commended for its continued diligence in managing the Adult Health Study (AHS) and F_1 Clinical Study (FOCS) cohorts. These studies remain an essential backbone of RERF and directly inform ongoing clinical, epidemiologic, statistical, and radiobiological research. They also provide necessary biospecimens for basic and translational discovery efforts.
- The efforts to expand the AHS cohort by 2,300 subjects is endorsed as helpful, particularly collecting data from those subjects with low dose exposures and incorporating medical family history.
- The FOCS study should be continued as a longitudinal study since an increase in cancer and other outcomes is expected in the next two decades.
- The working group on medical exposures should continue its work to standardize the approach and methodology for this problem, though it is understood that individual dosimetry for diagnostic exposures will probably be limited to average dose for the type of examination and will have more uncertainty than the A-bomb doses.
- With the finding of cataracts occurring at relatively low doses, radiation exposure of eyes becomes a critically important issue. This finding is important for radiation protection of nuclear workers, for the many physicians using fluoroscopy for interventional purposes, and for the patients who receive millions of cranial CT scans each year that may have relatively high eye doses. Continued cataract investigations will provide greater predictive capability to assess the risk of radiation-induced cataract onset and the likelihood of resulting visual dysfunction.
- In the new Life Span Study (LSS) mail sur-

vey, important missing covariates will be obtained as well as important updated information on radiation effects and smoking history to inform future studies. Overall, significant effort should be expended to insure collection of information on as many members of this cohort as possible.

- The studies of dose-response curves for non-cancer diseases are a strength of the Epidemiology Department and appear to be yielding new and valuable information, particularly in the area of heart disease.
- Laboratory and clinical studies to investigate potential mechanisms of non-cancer effects will be especially important. Biological mechanisms by which low-dose radiation exposure may induce cardiovascular disease risks are currently unclear, and an extensive search is needed to explore alternative models. A workshop (including at least radiobiologists and cardiologists) may be helpful to discuss how best to elucidate mechanisms.
- The SC agrees with and fully supports the stated objectives for the Department of Statistics. Last year the SC recommended that the Statistics Department should expand its collaborative work with other departments. It was clear that considerable effort had been directed towards this end.
- One stated aim of the Statistics Department is to aid in the development of complete, accurate, and accessible research databases. This aim should become a priority for RERF as a whole. A detailed strategy should be developed to achieve this and to produce appropriate documentation for it.
- RERF should set up a biospecimen repository using the most contemporary processing, storage, annotation and backup systems. We suggest that RERF focus on best practices learned from institutions of repute with high volume biospecimen banks. RERF also should establish a vetting process that prioritizes specimen distribution and applications. We would suggest that substantial energy be spent in having a functioning and thorough system in place soon.
- The SC feels that the Genetics Department has made substantial contributions to the goals and mission of RERF, as well as to the larger scientific community. There is every hope and expectation that they will continue to do so.
- In the past 60 years, the central dogma of radiation carcinogenesis has been the straightforward hypothesis that radiation-induced DNA damage causes mutations responsible for development and progression of cancer. However, the working hypothesis of the immunology group challenges this dogma by offering an alternative mechanism of immune theory of radiation induction of cancer as well as non-cancer diseases. It is interesting to note that this neo-classic immune theory of carcinogenesis is now gaining recognition in the oncology fields.

The RERF leadership appreciates the tremendous effort that the research and support staff of RERF put into the development of materials and presentations for the Scientific Council. We believe the Council produced a very constructive report that will prove to be of much value to us.

RERF Scientific Councilors

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

Dr. Teruhiko Yoshida, Chief, Genetics Division, National Cancer Center Research Institute, *Co-chairperson*

Dr. Ohtsura Niwa, Deputy Director, Research Center for Charged Particle Therapy, National Institute of Radiological Sciences

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

Dr. Takashi Yanagawa, Professor, The Biostatistics Center, Kurume University

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

Dr. Marianne Berwick, Professor and Chief, Division of Epidemiology, Associate Director, Cancer Research and Treatment Center, University of New Mexico

Dr. John J. Mulvihill, Professor of Pediatrics, University of Oklahoma Health Sciences Center

Dr. David G. Hoel, Distinguished University Professor, Department of Biostatistics, Bioinformatics and Epidemiology, Medical University of South Carolina (Absent)

Dr. Michael N. Cornforth, Professor and Director of Biology Division, Department of Radiation Oncology, University of Texas Medical Branch, Galveston

Special Scientific Councilors

Dr. Sarah C. Darby, Professor of Medical Statistics, Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford

Dr. Fred A. Mettler, Jr., Professor, University of New Mexico, Chief, Radiology and Nuclear Medicine

Dr. Kazuo Tajima, Director, Aichi Cancer Center Research Institute

The 43rd Board of Directors Meeting in Washington, D.C.

The 43rd meeting of the RERF Board of Directors was held on June 18 and 19, 2008, at a meeting room of the National Academy of Sciences' Keck Center in Washington, D.C. On June 17, the day before the Board meeting, the report of the Senior Review Panel on Future Planning for RERF, a panel established by the Japanese and U.S. governments in 2006 for the purpose of reviewing future plans for RERF, was presented to the representatives of the two governments by the panel's Japanese and American co-chairs at the Japanese Embassy in Washington, D.C. The Board discussed with keen interest the actions that RERF would take in response to the report as well as important issues that could affect RERF's future direction, such as the organization's change of status to a public-interest foundation.

The FY2007 research activities report and audit report, the FY2007 settlement of accounts and audit report, the FY2008 research activities plans, and the FY2008 working budget, which is similar to that of the previous year, were approved as presented.

At its meeting in the previous year, the Board determined the policy of following up the cohort of children of A-bomb survivors. At this year's meeting, the Board approved, following the recommendations of the Senior Review Panel, RERF's proposal to begin preparations during this fiscal year with a view to resuming the follow-up in FY2009 or shortly thereafter.

As the Senior Review Panel submitted its report to the two governments the day before the Board meeting, as mentioned above, RERF invited the two co-chairs to attend the Board meeting and explain the panel's following recommendations: 1) continuation of RERF's cohort studies for the next 20 years; 2) necessity of negotiations between the two governments and RERF pertaining to the future of RERF after the completion of its cohort studies; 3) necessity of talks between the two governments toward their agreement concerning relocation of the Hiroshima facilities with a view to achieving its future vision; and 4) recruitment of young researchers and expansion of international research collaborations.

The Board welcomed these recommendations and agreed on the necessity of negotiations over the next two years on the specifics of each recommendation between the three parties (the two governments and RERF) and of formulating and implementing future strategies based on the negotiations.

With regard to the change to a public-interest foundation, the Board requested that deliberation take place soon between the governments regarding such basic issues as organizational composition (including establishment of a Council), and then determined that the Board would proceed with detailed procedures based on the deliberation results.

The Board discussed the appointment of directors, scientific councilors and others, and approved the proposed one-year extension of Mr. David Williams' appointment as an American supervisor because efforts to nominate his successor before the meeting had failed, and the appointment of Mr. Takashi Kono, a certified public accountant and tax accountant at the Hiroshima General Law/Accounting Office, as the successor to Dr. Tomio Hirohata, the Japanese supervisor. The Board also approved the appointment of Dr. Kiyoshi Miyagawa (Professor, Laboratory of Molecular Radiology, Center for Disease Biology and Medicine, Graduate School of Medicine, The University of Tokyo) as the successor to Dr. Teruhiko Yoshida, a scientific councilor. The Board reappointed Dr. John J. Mulvihill for another term as a scientific councilor, and decided to conduct a mail ballot to appoint a successor to Dr. Theodore L. DeWeese, a scientific councilor who had expressed his intention to resign from his post, as soon as a successor is nominated.

The Board agreed to hold its next meeting over the three-day period from June 24 through 26, 2009, in Hiroshima.

List of Participants

Directors:

Dr. Toshiteru Okubo, Chairman
Dr. Roy E. Shore, Vice Chairman and Chief of Research
Mr. Takanobu Teramoto, Permanent Director
Mr. Masaaki Kuniyasu, Former Ambassador Extraordinary and Plenipotentiary to the Republic of Portugal
Dr. Yasuhito Sasaki, Director General, Radiology Center, International University of Health and Welfare
Dr. Senjun Taira, Permanent Director, Japanese Association of Quarantine Inspection Hygiene
Mr. James W. Ziglar, President and Chief Executive Officer, Cross Match Technologies, Inc.
Dr. James D. Cox, Professor and Head, Division of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center
Dr. John E. Burris, President, Beloit College

Supervisors:

Dr. Tomio Hirohata, Professor Emeritus, Department of Public Health, Faculty of Medicine, Kyushu University
Mr. David Williams, Senior Financial Advisor,

National Academy of Sciences

Co-chairmen Senior Review Panel on Future Planning for RERF:

Dr. Sadayoshi Kitagawa, Director General, Japan Public Health Association

Dr. Paul Gilman, Senior Vice President and Chief Sustainability Officer, Covanta Energy Corporation

Co-chairman Scientific Council:

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

Representatives of Supporting Agencies:

Mr. Osamu Okabe, Director, General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare (MHLW)

Mr. Takahiro Maeda, Chief, Relief Budget Unit, General Affairs Division, Health Service Bureau, MHLW

Dr. Masaharu Tantou, Group Leader, General Affairs Division, Health Service Bureau, MHLW

Mr. Masahiro Mori, First Secretary, Embassy of Japan

Mr. Glenn S. Podonsky, Chief Health, Safety and Security Officer, Office of the Secretary of Energy, U.S. Department of Energy (DOE)

Mr. Michael A. Kilpatrick, Deputy Chief for Operations, Office of Health, Safety and Security, DOE

Dr. Michael J. Ardaiz, Department of Energy Chief Medical Officer, Office of Health, Safety and Security, DOE

Dr. Joseph F. Weiss, Japan Program Manager, Office of International Health Studies, Office of Health, Safety and Security, DOE

Ms. Julie Liu, U.S. Department of State

Dr. Warren R. Muir, Executive Director, Division on Earth and Life Studies, National Research Council (NRC), National Academy of Sciences (NAS)

Dr. Kevin D. Crowley, Director, Nuclear and Radiation Studies Board, Division on Earth and Life Studies, NRC, NAS

Ms. Laura Llanos, Financial and Administrative Associate, Nuclear and Radiation Studies Board/ RERF Program, Division on Earth and Life Studies, NRC, NAS

RERF:

Mr. Eiji Akimoto, Chief of Secretariat

Dr. Evan B. Douple, Associate Chief of Research

Dr. Nori Nakamura, Chief Scientist

Dr. Kazunori Kodama, Chief Scientist

Mr. Douglas C. Solvie, Associate Chief of Secretariat

Staff News

Since April 2008, two scientists have been recruited to RERF and have recently moved to Hiroshima. We have asked them to tell you a little about themselves and their interest in the work of RERF.

Munechika Misumi

I received my B.S. Degree in Environmental Studies from Nagasaki University and an M.S. in Statistics from North Carolina State University in Raleigh, North Carolina, with a biomedical concentration. While at the North Carolina State University I was encouraged to study the mathematical modeling of radiation health effects by the director of the Biomathematics Program, Dr. Charles Smith, who had spent some time working at RERF as a Gilbert W. Beebe Fellow. I accepted the position of RERF Research Scientist and began my work in the Department of Statistics in June, 2008. Prior to my arrival in Hiroshima I was an Assistant Professor of Biostatistics in the Graduate School of Medicine of Kyushu University. I have had an interest in multistage models of carcinogenesis and am especially pleased to be at RERF and joining my new colleagues in analyzing the very special resource of data and contributing to the mission of RERF. Currently I am working on the application of measurement error models to RERF data, and I am looking at the molecular-level effects of radiation in carcinogenic processes with the scientists in the Radiobiology/ Molecular Epidemiology Department.

Kotaro Ozasa

I recently joined RERF as the Chief of the Epidemiology Department in November of this year. Prior to arriving in Hiroshima, I was an Associate Professor in the Department of Epidemiology for Community Health and Medicine in Kyoto Prefectural University of Medicine's Graduate School of Medical Science. I had received my M.D. and Ph.D. also from the Kyoto Prefectural University of Medicine. My major research interests have focused on epidemio-

logical studies such as large-scale cohort studies to elucidate cancer pathogenesis, studies on Japanese cedar pollinosis, and evaluation of the effectiveness of influenza vaccinations. Other projects and activities in which I have been involved include the Kyoto Prefectural Cancer Registry projects, health-education efforts, and anti-smoking countermeasures. During my career I participated in the 1991 Summer Program of the New England Epidemiology Institute in Boston, Massachusetts in the U.S. and I served for five months in 1997 as an Honorary Lecturer in the Department of Public Health Medicine in the United Medical and Dental School of Guy's and St. Thomas' Hospitals in London, U.K.

I am pleased to join the research scientists of RERF and look forward to assisting my fellow epidemiologists continue their important work. I am especially indebted to the contributions of my predecessor, former Acting Chief, Dr. Fumiyoshi Kasagi, as well as the other Epidemiology department chiefs who have established a long legacy of research based on the important RERF cohorts. I thank all of RERF staff who have accepted me warmly!

Visiting Scientists

Sung Ho Moon

I am a radiation oncologist from the Proton Therapy Center in the Research Institute and Hospital of the National Cancer Center in South Korea. I received my M.D. from Seoul National University College of Medicine and my Master of Medical Science from the Seoul National University Graduate School. I arrived at RERF in Hiroshima for research training on the biological effects of radiation with special emphasis on the interaction between radiation and histone deacetylase inhibitors on breast cancer cell lines. During my two-month stay I have benefited from the RERF's International Exchange Program and appreciate very much the research facilities and collegial staff of RERF's Department of Radiobiology/Molecular Epidemiology.

David Richardson

After several months of preparation, I arrived in Hiroshima in late May. The visit was an opportunity to engage in some specific analytical projects, but also an opportunity to meet the staff at RERF, learn about the organization, and to develop a better understanding of the consequences of the atomic bombings of Hiroshima and Nagasaki and the experiences of the survivors who have participated in this important research program.

I was stationed for the summer in the offices of the Department of Epidemiology at RERF, where I had proposed to work on analyses of associations between ionizing radiation dose and mortality due to lymphatic and hematopoietic cancers. In recent years, I have had a particular interest in leukemia and lymphoma and the temporal patterns of these diseases following exposure to ionizing radiation. While there has been a lot of epidemiological research on leukemia mortality among A-bomb survivors, the focus has been on leukemia of all types, considered in aggregate. Over the summer I drafted a report on mortality by type of leukemia among the A-bomb survivors in the Life Span Study. During this period, I also finalized a report on lymphoma mortality among male A-bomb survivors. Both reports are now in the form of manuscripts under review.

As an academic (Assistant Professor in the Department of Epidemiology, School of Public Health, University of North Carolina), it is unusual for me to have a period of months to focus on a single project with no distractions; and, it is extremely unusual to be surrounded by others with a shared interest in radiation epidemiology. We are a rare breed. Being located at RERF meant that I had an opportunity to participate in weekly meetings and informal discussions. The experience was tremendously productive. I learned a great deal from those meetings, and the experience sparked new ideas and suggested new research questions. Furthermore, I had the pleasure of getting to know some of the RERF staff personally. I want to thank everyone at RERF for this generous opportunity and, in particular, for the hospitality shown by the RERF staff.

Jacob Adams

I (Jacob Adams, M.D., M.P.H., an Assistant Professor of Epidemiology in the Department of Community and Preventive Medicine at the University of Rochester School of Medicine and Dentistry) spent the summer and early fall at RERF in the Department of Epidemiology investigating the potential association between radiation dose and chronic kidney disease mortality. This investigation was inspired by prior investigations in the Life Span Study (LSS) by Drs. Yukiko Shimizu, Kazunori Kodama, Kiyohiko Mabuchi, and others that repeatedly showed an association between cardiovascular disease mortality and radiation dose. While at the

RERF between June 11th and September 30th, I worked very closely with Eric Grant to clean and recode the data he used from the LSS database and to learn how to use Epicure. In addition to evaluating a possible association between radiation dose and chronic kidney disease, I also evaluated the validity of self-reporting of hypertension in the 1965, 1978, and 1991 LSS surveys compared to measured blood pressure and medication data in those survivors who participated in the concurrent AHS visits.

I am especially interested in the late effects of cancer therapy, particularly radiation therapy on the cardiovascular system. I found my experience at RERF to be invaluable to my career development as it provided me the opportunity to learn how to model excess relative risk using the Epicure progam while modeling real data that I hope will contribute to two publications with my collaborators at RERF. The skills I learned will also allow me to further my analyses of the Rochester, NY area Thymus Irradiation Cohort (a cohort originally started by Dr. Louis Hempelmann) which I restarted in 2004 after 17 years of dormancy as part of an NIH (National Institute of Health) career development award. Dr. Roy Shore, RERF's Vice Chairman and Chief of Research, served as an advisor for my study. I want to thank Dr. Shore and the NCI (National Cancer Institude) Radiation Epidemiology Branch for support of my career and for encouraging me to apply for a visiting research fellowship at RERF. I want to also thank the RERF staff and scientists, especially in the Department of Epidemiology, for their support and wonderful hospitality. I look forward to maintaining contact with RERF while working on the above-mentioned manuscripts and exploring potential collaborations, including one already suggested by Dr. Yoichiro Kusunoki and Dr. Kei Nakachi in the Department of Radiobiology/Molecular Epidemiology.

Yoshisuke Nonaka

I arrived in RERF in April, 2008 as a visiting scientist and to continue my postdoctoral fellowship in the Department of Epidemiology as part of a Partnership Program between RERF and Kurume University. Prior to my arrival I had been a postdoctoral fellow in the Biostatistics Center of Kurume University where I was studying statistical modeling based on the regularized local likelihood methods as applied to clinical data. I was also developing and applying the mixed-effect model to repeat-measurement data. I received my Ph.D. in Mathematics from Kyushu University in 2004. At RERF, I have been working on selection of relative-risk models using information criteria related to the RERF Life Span Study.

Student Researcher

Javad Mohammadi-Asl

I arrived at RERF in Hiroshima in August 2008, with my wife and three sons from Iran where I am a Ph.D. student in the Medical Genetics Department of the Tehran University of Medical Sciences. I am also currently a faculty member in the Biochemistry Department of the Ahwaz Joundi-Shapor University of Medical Sciences in Ahwaz, Iran, where I had received my B.Sc. in Genetics. I had also received an M.Sc. in Human Genetics from Tehran University of Medical Sciences. I am especially pleased to be able to work with RERF scientists in the Radiobiology/Molecular Epidemiology Department where I am studying promoter methylation of RASSF1A, P16, MGMT, and TSHR genes, BRAF gene mutations, RET mRNA expression, and PTC1 and PTC3 rearrangement on malignant thyroid nodules. RERF's excellent facilities and collegial research staff have been of great value to me as I continue my research and pursuit of the Ph.D. I would like to thank RERF for accepting me and my family and I really appreciate the assistance of Drs. Kiyohiro Hamatani, Kei Nakachi, Roy Shore, and Evan Douple, as well as other RERF staff who have helped me during my stay in Hiroshima.

2008 Distinguished Lecture Series

The third lecturer of this year's Distinguished Lecture Series was Dr. Albrecht Wieser from the Helmholtz Zentrum and German Research Center for Environmental Health in Munich. Dr. Wieser's lecture on April 23, 2008, was entitled "Comparison of EPR (electron paramagnetic resonance), FISH (fluorescence *in situ* hybridization), and film badge reconstructed doses for Mayak workers."

Award Received by an RERF Scientist

Receiving "Presentation of the Year" award at 15th annual meeting of the Japanese Society of Immunotoxicology

Tomonori Hayashi, Chief, Immunology Laboratory
Department of Radiobiology/Molecular Epidemiology

The 15th annual meeting of the Japanese Society of Immunotoxicology was held in Tokyo on September 11 and 12, 2008, and my presentation titled "Elevation of aging-associated inflammatory markers among atomic-bomb survivors" received the "Presentation of the Year" award, which is granted to one from among all presentations each year. This year's meeting was held jointly with the 52nd meeting of the Japan Society for Occupational Health Research Group on Allergy and Immunotoxicology, at which research results regarding natural immunity and mucosal immunity and those targeting a wide variety of substances including drugs and medicines, dietary components, environmental chemicals, and nano-particles were comprehensively reported, and hence this scientific meeting was precisely suited for its theme "New developments in immunotoxicology."

In the presentation I reported on the presence of significant positive correlations between radiation dose and inflammation-related substances on the basis of results from analysis on impairment of immune function with increased radiation dose, conducted through use of such inflammation-related markers as peripheral inflammatory cytokines (IL-6, TNF-α, and others) and reactive oxygen species (ROS). A majority of the previous reports on association between radiation dose and inflammatory response came from *in vitro* studies, with any reported findings involving only the acute phase after radiation exposure. There are thus no previous reports targeting a cohort as many years after radiation exposure as that in my report. The relevant study was the first to have reported on the possibility that increased cancer/non-cancer risk with increased radiation dose might be caused by radiation-enhanced immunological aging, and that was presumably the reason for the recognition the annual meeting bestowed upon our study. Needless to say, the report resulted from research activities based on the understanding and cooperation of RERF's Adult Health Study participants. I received the award on behalf of the staff of the Department of Clinical Studies; Dr. Yoichiro Kusunoki, who has long studied effects of radiation exposure on immunity, the technicians at the Immunology Laboratory, Dr. Kei Nakachi, Department Chief, who has brought new perspective to immunology research and contributed to that field's further development, and many other people contributed. I would like to express my heartfelt appreciation to all of them for their cooperation and support.

I will continue to make efforts to promote immunology research, and everyone's continued guidance would be greatly appreciated.

Symposium on Health Effects of Radiation and Smoking

10 March 2008, Hiroshima Laboratory

Ritsu Sakata, Research Scientist
Department of Epidemiology, Hiroshima

Tobacco smoke contains many carcinogens, and smoking's association with development of many cancers, such as of the lung and stomach, has been confirmed. Based on studies of effects of smoking on mortality in various regions around the world, it also has become clear that smoking is the most important cause of early death in many populations over the past several decades. Because of just such serious health effects, smoking is considered to be a factor that must be considered in estimating health effects of radiation. Studies on the effects of smoking in Japanese populations have shown, after adjustment for amount of smoking, less significant health effects from smoking than in populations of Europe and the United States. It is still unclear whether this difference is due to the fact that smoking became prevalent somewhat later in Japan than in other countries or because of the presence of other factors that modify smoking effects.

In the mail surveys and interviews that RERF has conducted thus far, questions on smoking have been asked repeatedly. Although several studies have been conducted using the results of those surveys, most of the studies only used responses from a single survey; no study has been conducted using multiple responses from the same subjects. Thus, clearly there is potential for making better use of the results.

To discuss methods for more effective use of RERF data on smoking status, the "Symposium on Health Effects of Radiation and Smoking" was held at the Hiroshima Laboratory on March 10, 2008. Invitees from outside research organizations to the symposium included Drs. Sarah Darby and Paul McGale of the Clinical Trial Service/Epidemiological Research Unit at Oxford University, who were involved in a study on British physicians, one of the most important studies in the world concerning effects of long-term smoking on mortality, and Dr. Tomotaka Sobue of the Center for Cancer Control and Information Services, National Cancer Center, who has been involved in many cohort studies on health effects of smoking in Japan.

First, Dr. Darby showed the latest results of analysis in the 50-year follow-up study of British physicians. She reported that smoking increased age-specific mortality from all diseases and that, when mortality was examined by disease, smoking also increased age-specific mortality from many of the diseases. She also reported that there were differences by birth cohort in mortality risks of smokers and non-smokers: the difference in mortality between smokers and non-smokers is larger in the population born in the first half of the 20th century than in the population born in the latter half of the 19th century. It was also reported that quitting smoking even between the ages of 50–64 was effective in reducing subsequent mortality risks.

Chief Scientist Kazunori Kodama then made an introductory presentation concerning RERF cohorts, results from several past studies of health effects of smoking, and research on interaction between smoking and radiation. At the end of the morning session, Dr. Sobue presented information on changes over time in terms of cancer mortality in Japan; whereas lung cancer mortality has started to decrease in England and the United States, a similar reduction in lung cancer mortality in Japan has been delayed compared with other developed countries. He also showed yearly changes in amount of tobacco consumption in Japan and the United States. Comparison of results of studies on lung cancer risks related to smoking in European countries, the United States, and Japan showed that the risks observed in Japanese populations were lower. Reasons for the lower risks were explained as possibly due to a smaller amount of smoking, high lung cancer risk among non-smokers, effect modification from other lifestyle factors, or low genetic susceptibility.

Participants of the Symposium on Health Effects of Radiation and Smoking

In the afternoon session, details of data obtained by RERF and Oxford Univer-

sity were presented. First, information on smoking maintained at RERF was explained. Research Scientist Eric Grant of the Department of Epidemiology reported the number of respondents in past mail and interview surveys, the number of subjects who responded on multiple occasions, age distribution of respondents, and information regarding lifestyle factors other than smoking that has been obtained from such mail surveys. Then, the author of this article, also of the Department of Epidemiology, introduced distribution of smoking status and number of cigarettes smoked by survey, and explained that, because questions in some cases varied by survey, analysis required special care. This was followed by a presentation by Dr. McGale, who stated that almost perfect follow-up had been achieved in the study of British physicians, and that the response rate of all five past mail surveys conducted for the study exceeded 90%.

Lastly, all the symposium participants engaged in discussion on future plans for collaborative research. It was agreed that, in order to make full use of smoking information maintained at RERF, a collaborative study should be conducted utilizing Oxford University's extensive experience. Based on such a collaborative study, it will become possible not only to incorporate smoking information in risk estimation of radiation exposure but also to apply to Japanese populations the same analytical methods used in the study on British physicians. This will enhance the possibility of further comparison and may provide valuable additional information on the effects of smoking on public health in Japanese populations. It also will likely be necessary to fully utilize mail and interview survey data, obtained thanks to the cooperation of many subjects and RERF staff.

I would like to express my appreciation for the opportunity to hear presentations on the use of smoking data by leading scientists and to be involved in collaborative studies.

RERF Symposium on Bioinformatics

24–25 March 2008, Hiroshima Laboratory

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High-throughput technologies that can yield massive amounts of data are often referred to as " 'omics" technologies, such as genomics, proteomics, and metabolomics. Those technologies are widely used in current medical research. They can provide information to build better predictive models of diagnosis and prognosis and to identify and characterize key signaling networks in cell culture or *in vivo*. But the technologies present researchers with a great challenge: the task of extracting meaningful statistical and biological information from huge numbers of variables measured simultaneously, along with considerable noise. Using the technologies, a single sample can have hundreds or even thousands of measurements, usually obtained by running a single microarray. There are great opportunities here at RERF to use such technologies to explore radiation effects as well as other biological questions. The RERF is uniquely poised to benefit from these 'omics technologies because of its biospecimens resources, virtually unparalleled in the world, provided generously by the atomic-bomb survivors in Hiroshima and Nagasaki. Multiple biosamples collected on thousands of subjects provide many potential opportunities for research in this area.

The complex new research technologies involving high-dimensional data require tools to effectively manage and analyze large amounts of data. In that context, the area of bioinformatics provides many such tools for handling those issues, and the research in computational and systems biology provides new ways of analyzing data and looking for meaningful patterns and associations.

The goal of this symposium was to bring together experts to provide a forum for the discussion of bioinformatics here at RERF and in general. The symposium was considered a first step to exploring potential applications and methods that could be applied to the RERF atomic-bomb survivor cohort data, which could also generate benefits for bioinformatics research in general. Another goal of this symposium was to provide an opportunity for experts in bioinformatics to meet with RERF researchers, where the invited speakers could obtain a better understanding of the resources and the research conducted here and we could all explore potential collaborations for the future.

The first day of the symposium consisted of two sessions: one on bioinformatics with talks given by the invited bioinformatics scientists, and one by RERF directors and department chiefs regarding the activities of the various research departments at

RERF and the research areas of interest that may benefit from bioinformatics initiatives and 'omics (e.g., genomics, proteomics, metabolomics) research. The invited speakers were leaders in bioinformatics from the United States and Japan, and included: Dr. John Quackenbush from Harvard University, Dr. Peter Li from Mayo Clinic, Dr. Hiroshi Mizushima from Tokyo Medical and Dental University, Dr. Tatsuya Akutsu from Kyoto University, and Dr. Toshio Kojima from RIKEN Genomic Sciences Center. Each speaker gave interesting and thought-provoking presentations on varying areas of bioinformatics. After hearing about the research ideas and interests of the invited speakers, the RERF directors and department chiefs presented different aspects of the research and resources here at RERF; this naturally led to discussion of the potential for the applications of the research and ideas presented earlier. On the second day of the symposium, we had a roundtable discussion with the invited speakers, the RERF directors, and many research scientists from RERF representing all research departments. The discussion focused on research interests as well as the necessary resources. Specific challenges and tasks were also identified in order for RERF to more effectively utilize bioinformatics research.

The result of the bioinformatics symposium was an increased knowledge among research scientists at RERF regarding bioinformatics and its intersection with the high dimensional data technologies such as genomics and proteomics. In meeting with the invited bioinformatics speakers, the RERF research leadership was able to identify steps that would need to be taken as well as challenges in incorporating this science into RERF's research initiatives. I believe that the invited speakers also benefited from hearing about the interesting research done here and were impressed by the virtually unparalleled biological resources at RERF and the opportunities they provide. In the end, we felt that this symposium was an important first step toward exploring the potential to fully implement the research initiatives of bioinformatics and computational biology here at RERF.

Lastly and most importantly, we would like to express our sincere appreciation and gratitude to all who helped to make this symposium possible, the RERF leadership and researchers who made informed and interesting presentations and participated in and contributed so much to the discussions. Special thanks also are given to the staff members of the Statistics Department, the Secretariat, and the Information Technology Department who were an integral part in helping to organize this symposium.

RERF Symposium on Bioinformatics held at the Hiroshima Laboratory

Preferential Gene Alterations in Adult-onset Papillary Thyroid Cancer among Atomic-bomb Survivors: Chromosomal Rearrangements vs. Point Mutations

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Introduction

Thyroid cancer is one of the malignancies most associated with ionizing radiation in humans. The excess relative risk of papillary thyroid cancer in atomic-bomb (A-bomb) survivors was 1.2 per Gy, and it increased with increased radiation dose.[1] A histopathological study has revealed that the thyroid cancers found in A-bomb survivors were largely conventional papillary in nature, and this is also the case of spontaneous thyroid cancer in the Japanese population at large. Solid variant papillary thyroid cancer was not found in A-bomb survivors, although this cancer has been frequently found among post-Chernobyl children.[2,3] However, it still remains to clarify molecular mechanisms of how radiation exposure affects the development of thyroid cancer.

Gene alterations that lead to constitutive activation of the MAP kinase-signaling pathway are frequently found in papillary thyroid cancer. Those alterations are mutually exclusive, non-overlapping events that involve rearrangements of the *RET* and *NTRK-1* (neurotrophic tyrosine kinase receptor 1) genes and point mutations in the *RAS* and *BRAF* genes.[4–6]

In papillary thyroid cancer, the *RET* proto-oncogene is known to be activated by fusion of the *RET* TK domain with the 5′ terminal sequence of one of different heterologous genes via rearrangements that generate a series of chimeric-transforming oncogenes collectively described as *RET*/*PTCs*. To date, at least 12 rearranged forms of the *RET* gene have been isolated, of which *RET*/*PTC1* and *RET*/*PTC3* are by far the most common.[7] *RET*/*PTC* rearrangements were commonly found in childhood papillary thyroid cancer regardless of radiation history.[8,9] *RET*/*PTC* rearrangements, especially *RET*/*PTC3*, were frequently encountered in papillary thyroid cancers with relatively short latency among children from contaminated areas at the Chernobyl nuclear accident in 1986. Amongst those early-onset carcinomas, solid variants and follicular variants of papillary thyroid carcinomas were found at an unusually high frequency. Among children in Chernobyl contaminated areas, *RET*/*PTC3* appeared to be strongly associated with solid variant-type carcinomas and with a short latency period after exposure.[9,10]

On the other hand, in the Japanese general adult population, typical frequency of *RET*/*PTC* seems to be of the magnitude of 10 to 40%, though a wide variation, ranging from 2.6 to 70%, has been observed in different geographic areas.[11–13] *RET*/*PTC* rearrangements, especially *RET*/*PTC1*, were reported as being detected at higher frequency in papillary thyroid cancer from adult patients with a history of radiotherapy than in those without radiation history,[14] but another report disputed such findings.[15] Interestingly, we also found that *RET*/*PTC1* rearrangement could be induced in human thyroid cells by X-irradiation *in vitro* and *in vivo* as tissue transplants in scid mice, and that the rearranged *RET* oncogene was constitutively expressed for two months after X-irradiation *in vivo* (50 Gy).[16] Those findings may provide supporting evidence that activation of the *RET* oncogene via rearrangements plays a crucial role in radiation-associated papillary thyroid carcinogenesis.

BRAF^{V600E} mutation has thus far been described as occurring with a frequency ranging from 29% to 83% in papillary thyroid cancer among an adult general population.[17] The alteration is detected in a part of micropapillary thyroid carcinoma, suggesting that *BRAF* point mutation is an important event involved in the early step of adult-onset papillary thyroid carcinogenesis. Regarding the relationship with radiation exposure, the *BRAF*^{V600E} gene mutation was studied in post-Chernobyl childhood papillary thy-

roid cancer. A very low frequency of *BRAF*^{V600E} mutations in this papillary thyroid cancer has been reported (range: 0–12%).[18–22] However, prevalence of *BRAF*^{V600E} mutation was originally low (range: 0–6%) in papillary thyroid cancer among children, unrelated to their history of radiation exposure.[18,19,22]

In order to clarify mechanistic relationships between radiation exposure and the development of papillary thyroid cancer, we have conducted experiments to identify which types of gene alterations, e.g., chromosomal rearrangements or point mutations, preferentially occurred in adult-onset papillary thyroid cancer among A-bomb survivors. Toward this end, we analyzed *RET*/*PTC* rearrangements and *BRAF*^{V600E} point mutations in 71 adult-onset papillary thyroid cancer cases among A-bomb survivors, since the major initial event of this cancer is either *RET*/*PTC* rearrangements or *BRAF* mutations, which appear to occur mutually exclusive.

Material and Methods

Study subjects and tissue specimens

Study subjects comprised 71 adult-onset papillary thyroid cancer cases consisting of 50 exposed and 21 non-exposed subjects found among A-bomb survivors in Hiroshima and Nagasaki.

All study materials were formalin-fixed and paraffin-embedded papillary thyroid cancer tissue specimens surgically resected during 1956–1993. This study has been conducted under approval of the Human Investigation Committee and the Ethics Committee for Genome Research at the Radiation Effects Research Foundation (RERF).

DNA and cDNA preparation

RNA and DNA were extracted from microdissected non-cancerous or cancerous regions using the High Pure RNA Paraffin Kit (Roche Diagnostics GmbH; Manheim, Germany) and QIAamp DNA Micro Kit (QIAGEN; Hilden, Germany), respectively, as described previously.[23,24] Reverse transcription (RT) was performed with random primers (9 mer) using 100 ng total RNA as template, as described previously.[23]

Detection of RET/PTC rearrangements and BRAF^{V600E} mutation

RET/*PTC1* and *RET*/*PTC3* were analyzed by *BamH* I digestion of obtained fragments after RT-PCR amplification with primers sandwiched the fusion point, as described previously.[25] *RET* rearrangements other than *RET*/*PTC1* or *RET*/*PTC3* were examined by improved 5′ RACE method. *BRAF* gene mutation causing amino acid substitution of glutamic acid for valine at codon 600 (*BRAF*^{V600E}) was determined by restriction fragment length polymorphism (RFLP) using *TspR* I (New England Biolabs; Beverly, MA) and direct sequencing, as described previously.[24]

Statistical analyses

Mann-Whitney's U test was used for non-parametric two-sample comparisons of continuous variables. Fisher's exact test was used for categorical variables. The Cochran-Armitage test was used for non-parametric trend analysis. All statistical analyses were performed with SPSS software (version 12.0).

Results

There was no statistical significant difference in pathological and epidemiological characteristics between exposed and non-exposed subjects (Table 1). In addition to eight papillary thyroid cancer

Table 1. Pathological and epidemiological characteristics of study subjects by radiation exposure status

		Life Span Study (LSS) cohort†		
		Exposed (Dose > 0 mGy) (n=50)	Non-exposed (n=21)	P
Gender	Male (n) Female (n)	6 44	2 19	1
Histological subtype	Conventional PTC (n) Follicular variant (n)	47 3	21 0	0.6
Median age ATB*	(yr) (range)	22 1–47	22 0–52	0.3
Median age at diagnosis	(yr) (range)	50 18–89	48 24–84	0.9
Median time after exposure	(yr) (range)	24 11–46	–	–
Median radiation dose	(mGy) (range)	203 0.4–2758	–	–

*ATB: at the time of the bombings.
†LSS cohort: 120,000 atomic–bomb survivors (including non–exposed subjects) in Hiroshima and Nagasaki at baseline.

patients with only *RET/PTC1* and one with both *RET/PTC1* and *RET/PTC3* who were detected among 50 exposed patients, we identified a novel type of *RET/PTC* rearrangement as well as rare *RET/PTC8* in A-bomb survivors exposed to high radiation dose (1.5 Gy and 2 Gy, respectively), expression of which was confirmed by RT-PCR (Figure 1). Although the exposed patients showed a higher frequency of *RET/PTC* rearrangements than did non-exposed ones, this difference was not statistically significant (Table 2). On the other hand, frequency of *BRAF*^{V600E} mutation was marginally lower in exposed patients than that in non-exposed ones (P = 0.06, Table 2).

In 50 exposed papillary thyroid cancer cases, there was no case having both *RET/PTC* rearrangement and *BRAF* point mutation, suggesting that these alterations are mutually exclusive. To examine the relationship between *RET/PTC* rearrangements and *BRAF*^{V600E} mutation and radiation dose, exposed papillary thyroid cancer patients were divided into three groups harboring *RET/PTC* rearrangements (11 cases), *BRAF* point mutation (28 cases), and other unknown gene alterations (11 cases) by dose tertiles. *RET/PTC* rearrangements were more frequently found in patients with increased radiation dose (P_{trend} = 0.002, Figure 2). On the other hand, prevalence of *BRAF*^{V600E} mutation significantly decreased with radiation dose (P_{trend} = 0.00006). In addition, papillary thyroid cancer patients having wild-type *RET* and *BRAF* showed a marginally significant increasing trend with radiation dose (P = 0.08, Figure 2).

RET/PTC rearrangements and *BRAF*^{V600E} mutation were further studied in relation to time since radiation exposure (Figure 3). *BRAF*^{V600E} mutation significantly increased with increased time since exposure, while unidentified alterations in papillary thyroid cancer having wild-type *RET* and *BRAF* drastically decreased with increased time since exposure. In contrast, *RET/PTC* rearrangements showed a peak at time since exposure around 22 years. These findings revealed that the cases with *RER/PTC* rearrangements developed cancer sooner following exposure than did the cases with *BRAF* mutation.

Age at diagnosis and age at the time of the bombings (ATB) were compared between 11 papillary thyroid cancer patients having *RET/PTC* rearrangements and 28 patients having *BRAF*^{V600E} mutation. As shown in Figure 4, age at diagnosis in the cases with *RET/PTC* rearrangements was significantly younger than in the cases with *BRAF* mutation (P = 0.005, Figure 4A). Furthermore, the papillary thyroid cancer cases with *RET/PTC* rearrangements tended to show younger age ATB than did those with *BRAF* mutation (P = 0.06, Figure 4B).

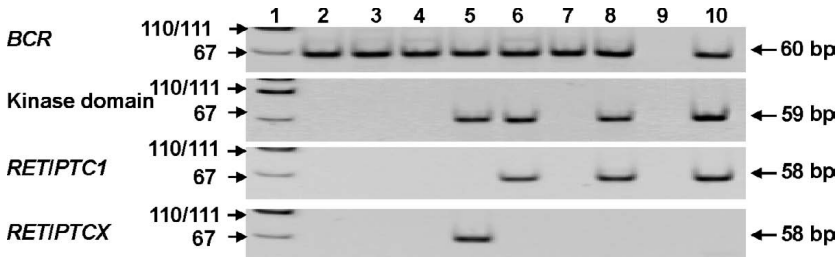

Figure 1. Expression of *RET/PTC* rearrangements in papillary thyroid cancer (PTC) from A-bomb survivors. Lanes 2–8 indicate RT-PCR products from RNA in PTC cancer specimens of A-bomb survivors. Lanes 2, 3, 4, and 7 showed no detectable expression of *RET* TK domain; lane 5, novel *RET/PTC* (*RET/PTCX*) rearrangement; lanes 6 and 8, *RET/PTC1*; lane 9, H_2O (negative control); lane 10, cell line TPC1 harboring *RET/PTC1*. Lane 1 indicates pUC19-*Msp*I digest for DNA size marker.

Table 2. Frequency of *RET/PTC* rearrangements and *BRAF*^{V600E} mutation by radiation exposure status

		LSS cohort		
		Exposed (Dose > 0 mGy) (n=50)	Non-exposed (n=21)	P
RET/PTC rearrangements	Absence (n)	39	20	0.09
	Presence (n)	11	1	
	Frequency (%)	22	5	
BRAF^{V600E} mutation	Absence (n)	22	4	0.06
	Presence (n)	28	17	
	Frequency (%)	56	81	

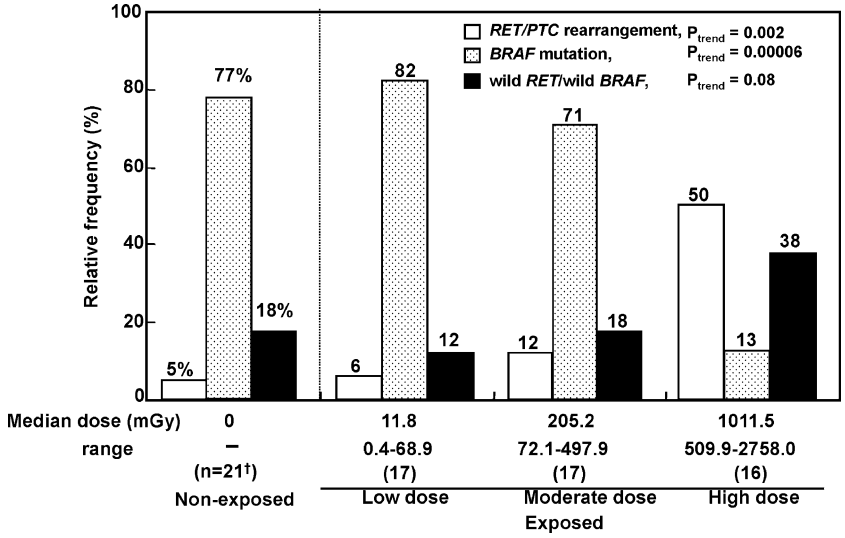

Figure 2. A relative frequency of *RET/PTC* and *BRAF*^{V600E} alterations in papillary thyroid cancer patients grouped by radiation exposure dose levels (non-exposed and dose tertiles). Exposed papillary thyroid cancer patients were divided into three groups by dose tertiles. †One case in the non-exposed group had both *RET/PTC* and *BRAF*^{V600E}. Relative frequency of genes in the non-exposed group was calculated by using 22 for the number of gene alterations. The open, dotted, and closed bars indicate PTC with *RET/PTC* rearrangement, with *BRAF*^{V600E} mutation, or with other unknown alterations, respectively.

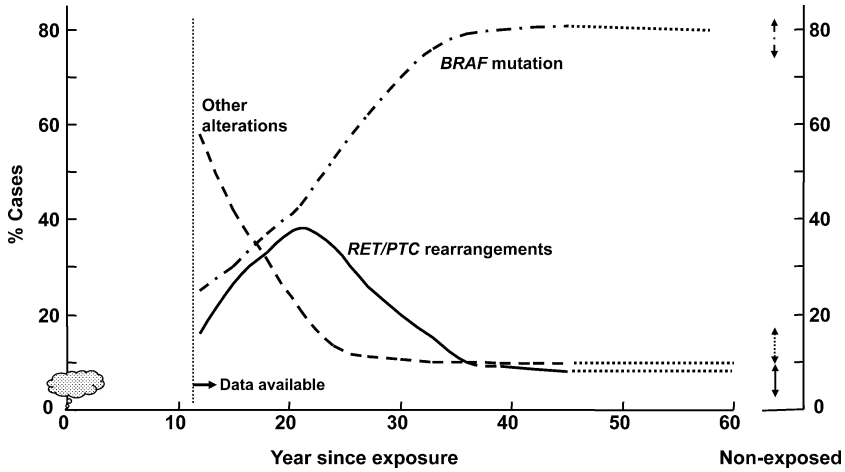

Figure 3. A scheme of gene alteration types in adult-onset papillary thyroid cancer among A-bomb survivors varying with year elapsed since radiation exposure.

Discussion

In papillary thyroid carcinogenesis, constitutive activation of the MAP kinase-signaling pathway, namely rearrangements of *RET* and *NTRK1* tyrosine kinase receptor genes and mutations in *RAS* and *BRAF* oncogenes, seems to be required for transformation.[26] Recent *in vitro* and *in vivo* experiments have also demonstrated the requirement of activation of the RET/PTC-RAS-BRAF-MAPK pathway in thyroid tumorigenesis.[27–29] Interestingly, mutual exclusion of these genetic alterations in the MAP kinase-signaling pathway was reported; one event among *BRAF* mutation, *RAS* mutations, and *RET/PTC* rearrangements[4,5,20] or one among *BRAF* mutation, *RET/PTC* rearrangements, and *NTRK1* rearrangements[6] was singularly found, indicating that one such gene alteration is an important early event in development of papillary thyroid cancer. Further-

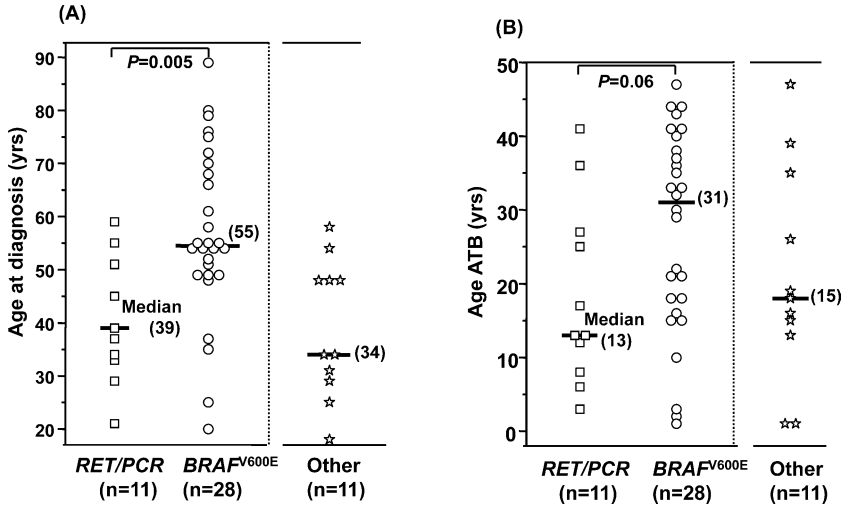

Figure 4. Comparison of age at diagnosis (A) and age ATB (B) by gene alteration status. The square and circle indicate *RET/PTC* rearrangement and *BRAF*^{V600E} mutation, respectively. The star shows wild-type *RET* and *BRAF*.

more, a recently identified *AKAP9-BRAF* rearrangement did not coexist with *BRAF* mutation in radiation-associated papillary thyroid cancer.[21] Those data suggest that a single genetic event in the MAP kinase-signaling pathway may be sufficient for thyroid cell transformation and tumorigenesis.

In this study, pathological and epidemiological characteristics, specifically radiation-related ones, of papillary thyroid cancer having *RET*/*PTC* rearrangements contrasted clearly with those of papillary thyroid cancer having *BRAF*^{V600E} mutation. Noting that 17 (81%) and 1 (5%) of 21 non-exposed papillary thyroid cancer patients having *BRAF*^{V600E} mutation and *RET*/*PTC* rearrangement in this study, respectively, are in agreement with other data on non-exposed adult-onset Japanese papillary thyroid cancer,[12,17,30–32] we for the first time have shown that *RET*/*PTC* rearrangements showed significantly increased frequency with increased radiation dose. In contrast, *BRAF*^{V600E} mutation was less frequent in cases exposed to higher radiation dose. Papillary thyroid cancer subjects harboring *RET*/*PTC* rearrangements developed this cancer earlier than did cases with *BRAF*^{V600E} mutation. Taken together, our findings imply that *RET*/*PTC* rearrangements, not *BRAF*^{V600E} mutation, are closely associated with radiation-associated adult-onset papillary thyroid cancer. Furthermore, these findings have suggested that radiation did not alter basic pathways, but preferentially induced specific events: e.g., preferential occurrence of *RET*/*PTC* rearrangements in the early stage of papillary thyroid carcinogenesis.

The existence of a molecular mechanism other than *RET*/*PTC* rearrangement is suggested from Figures 2 and 3: Unidentified gene alterations other than *RET*/*PTC* and *BRAF*^{V600E} tended to be more frequent with increased radiation dose. *RET*/*PTC* rearrangements showed a peak at 20 to 30 years since radiation exposure and relatively low frequency of 20% in <20 years since exposure, in contrast to 53% of other unidentified gene alterations. Because *RET*/*PTC* and *BRAF*^{V600E} account for 82% of non-exposed papillary thyroid cancer and about 60–70% of papillary thyroid cancer in the Japanese general population,[12,17,30–32] this increase of unidentified alterations in <20 years is thought to be caused by radiation. This unidentified mechanism may be involved in radiation-associated papillary thyroid cancer, which occurred earlier after radiation exposure than did papillary thyroid cancer having *RET*/*PTC*. Figure 5 summarizes our hypothesis of development of radiation-associated adult-onset papillary thyroid cancer among A-bomb survivors.

We anticipate that our molecular oncology study will not only contribute to understanding mechanisms of radiation thyroid carcinogenesis but also linked to "molecular event-based risk estimation" of papillary thyroid cancer in A-bomb survivors, e.g., radiation-induced risk of papillary thyroid cancer with *RET*/*PTC* rearrangements.

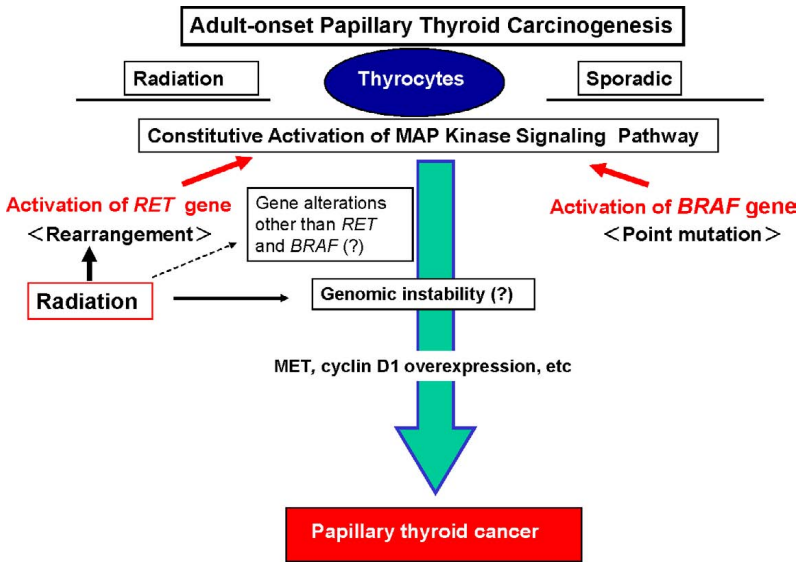

Figure 5. A hypothetical scheme of the development of radiation-associated papillary thyroid cancer among A-bomb survivors.

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Start of Health Examinations of A-bomb Survivors Overseas

Akio Awa, Former Associate Chief of Research

More than 30 years have already passed since health examinations of A-bomb survivors living in the United States were initiated in 1977 by specialists in Hiroshima and Nagasaki. I presume that not many people know the developments that lead to initiation of the project. I describe here, as long as my memory permits, the two episodes before initiation of the medical project. I hope that the stories will be of some help for future generations.

Episode 1

When I was a graduate student at Hokkaido University, I studied in the United States for two years from the spring of 1960. I joined the Tissue Culture Laboratory (professor in charge: Dr. Charles Marc Pomerat) of the Department of Anatomy at the University of Texas Medical Branch at Galveston, Texas. My main theme was a chromosome study using tissue culture procedures. In those days, Dr. Pomerat, my advisor, was a leading expert in research on tissue culture in the United States. With the use of microphotography for taking images of cultured cells alive, Dr. Pomerat had no equal in terms of research on cellular morphology or activity. Dr. Pomerat was also one of the founding members of the American Tissue Culture Society, and served as president of the society. Unfortunately, however, Dr. Pomerat stayed in Galveston only about three months. He was reportedly not on good terms with the dean of the medical branch.

Dr. Pomerat had to look for a position at a different laboratory. Arrangements were then made by one of Dr. Pomerat's previous students to have the professor transfer to the Pasadena Foundation for Medical Research (PFMR), to which this student belonged. All necessary laboratory facilities were transferred to PFMR. On July 4, 1960, an Independence Day, I moved to Pasadena, following my mentor. Thereafter, for one year and nine months until the end of March 1962, I continued my research at PFMR.

Pasadena is located about 20 km northeast of Los Angeles (LA), in the north of which stands Mt. Wilson, which is the site of a famous observatory. In those days, having many beautiful Spanish-style buildings, Pasadena was famous as a place where many California millionaires lived. Donations from those millionaires were sufficient for covering costs for the operation of PFMR. Because of its affluence, Pasadena was known as a beautiful small city with well-maintained cultural-arts facilities. On New Year's Day, an annual event called the "Rose Parade" was held on the main street (Colorado Boulevard). Many floats decorated with roses and carrying beautiful girls paraded through the city, and subsequent college football games sent football fans into a frenzy.

On the other hand, since smog produced from excessive motorization at LA's city center drifted with the southwest wind into the Pasadena Valley, the air in the city was polluted, which made the sun always look dull. By the way, the term "smog" is a compound of smoke (= exhaust gas) and fog, and was first used in this area. Now, smog is a familiar term, symbolizing environmental pollution.

As part of its program for providing scientific contributions to medicine and society, PFMR holds a tissue culture training course for about one week every summer. Dr. Pomerat was an excellent educator, and his lectures were quite easy to understand. In addition, having remarkable skills of watercolor painting, Dr. Pomerat could draw with ingenuity various biomedical illustrations on the blackboard. Many students from Japan visited Dr. Pomerat's laboratory for his guidance. When I was at PFMR, there were two Japanese researchers other than myself (the three of us were all graduates from the same university).

Because of limited staff and space, only eight people participated in the tissue culture course in the summer of 1961. Training was conducted on a one-to-one basis, starting with the basics of tissue culture. I was involved in the training regarding chromosome analysis methods using cultured cells. In this training course, I met a person who is the main character of this episode.

The person was one of the trainees, Dr. Thomas Noguchi. Dr. Noguchi was born on January 4, 1927. He was eight school-years older than me. Dr. Noguchi was a very hardworking person. After graduating from the Nippon Medical School, he visited the United States and further studied medicine (pathology and anatomy). Mrs. Noguchi was an American of Japanese ancestry. In the summer of 1961, when he underwent training at PFMR, Dr. Noguchi had the position of pathological autopsy expert at Loma Linda University, LA and judicial autopsy expert at the LA County Medical Examiner's

Participants of the first tissue culture course at PFMR in the summer of 1961. Dr. Thomas Noguchi is the fourth person from left in the second row.

Office. In the training course, Dr. Noguchi often helped me when I found it difficult to make explanations in English. This was the start of exchanges both in public and private between the Japanese scientists who studied at PFMR and Dr. Noguchi. I learned various aspects of the United States from Dr. Noguchi. This broadened my perspective regarding the United States, which was very useful for my stay in that country.

After I returned to Japan in 1962, significant events that made Dr. Noguchi a "man in the news" developed one after the other, by which he drew attention from the world. The first incident was the suicide of Marilyn Monroe, a Hollywood star, in August 1962. Since Dr. Noguchi conducted a postmortem, he attracted attention from the entire nation. The second incident that made him even more famous was the assassination in LA in July 1968 of Robert Kennedy, then Democratic presidential candidate and younger brother of the late John Kennedy. In this incident also, Dr. Noguchi, Chief Medical Examiner for the county, was responsible for the postmortem, and his every move attracted much attention from the public. Even before and after those incidents, he conducted autopsies for many Hollywood stars. He was therefore given a nickname "the coroner to the stars" by the British press. After resigning from his position as Chief Medical Examiner of LA County in 1982, Dr. Noguchi served as professor of pathology at the University of California in Los Angeles (UCLA) and the University of Southern California (USC), prestigious universities on the West Coast. He thus had a successful career as an outstanding pathologist/autopsy expert until he retired in 1999.

Episode 2

During the three days from November 30, 1975, an international symposium titled "Automated Cytogenetics" was held in Pacific Grove, a place of scenic beauty near San Francisco. I was invited to the symposium, which was organized by Dr. Mortimer Mendelsohn, former Vice Chairman and Chief of Research of the Radiation Effects Research Foundation (RERF). I made a presentation titled "Cytogenetic study of A-bomb survivors and their children in Hiroshima and Nagasaki." After finishing the presentation, I visited Pasadena for the first time in 13 years and six months. At that time, Dr. Yasushi Ohnuki, two years my senior at college, and Dr. Tohru Okigaki, my contemporary at college, were on the permanent staff of PFMR. In addition, I found that many of the staff members whom I had known during the period of my assignment at PFMR were still working there, making this revisit a more pleasant occasion. During PFMR's seminar in the afternoon of December 4, I made a presentation on a topic similar to the above-mentioned international symposium presentation. The seminar was covered in detail with photos by a local newspaper, the *Pasadena Independence Star News*.

Not long after I returned from Pasadena, I received an airmail letter. The sender was Ms. Katsu (correctly, Kazue) Sueishi. The letter was beautifully written using a writing brush on traditional Japanese paper. I describe the essential points of the letter as follows:

> "I read an article in the *Pasadena Independence Star News* covering recent findings on follow-up health-examinations of A-bomb survivors and their children at the Atomic Bomb Casualty Commission (ABCC) and RERF. I was exposed to radiation from the atomic bomb in Hiroshima, but I am now living in LA. Despite my concerns about health disorders related to the atomic bomb, I cannot undergo health checkups as regularly as A-bomb survivors living in Hiroshima and Nagasaki. In LA, there are few physicians who have enough information regarding atomic bombs. Whenever I see a doctor, he/she finishes his/her examination by saying, 'Your concerns over your health may be due to psychological reasons.' In addition, medical expenses here are very high, which makes me refrain from seeing doctors regularly. This is the biggest problem for us, the members of A-bomb survivors' group in LA. Isn't there any sensible resolution for our problem?"

I wondered how I could respond to this earnest appeal. No concrete solutions came to my mind. I therefore wrote a letter to my friend at PFMR, asking him whether he can discuss this matter with those involved in medicine in the United States, including Dr. Noguchi. I also wrote a similar letter to Ms. Sueishi. Thereafter, I exchanged airmail letters with Ms. Sueishi several times. I believe that she reported on subsequent progress of the matter, but I do not have a clear memory about it. In those days, I was

extremely busy and could not provide Ms. Sueishi with substantial support. Although I may sound apologetic, that was the time shortly after reorganization of ABCC into RERF, and I was very busy in drafting a budget for the first fiscal year for RERF.

In July 1976, Dr. Noguchi and Ms. Sueishi visited Hiroshima. They also came over to RERF. Although this was the first time that I met Ms. Sueishi, I felt that I had already met her several times before. I have heard that the two visited the local governments and medical associations of Hiroshima Prefecture and Hiroshima City and made their best effort for the realization of the health-examination project for A-bomb survivors living in the United States. Thanks to the effort of Dr. Noguchi and Ms. Sueishi, as well as the untiring effort of those concerned in various circles in Hiroshima, in the summer of 1977, specialists from Hiroshima visited the West Coast, including LA and San Francisco, where many A-bomb survivors lived, for interviews and medical examinations. From RERF, dosimetry experts participated in this project for the estimation of radiation doses of A-bomb survivors living in the United States. The project has greatly contributed to eradication of concerns over health among those survivors.

Now, I want to describe my personal views regarding the project. Needless to say, the health-examination project for those living in the United States started with personal efforts of Dr. Noguchi and Ms. Sueishi. The effort subsequently made by the medical associations of Hiroshima and Nagasaki and medical administrative specialists greatly contributed to the implementation of this project. This attests to the fact that the power of a small thing like an ant, if supported by enthusiasm, can become big enough to move a large rock. The health-examination project has been expanded over the years, and now even A-bomb survivors living in Brazil can undergo relevant examinations. It is gratifying that the medical project is still helpful in maintenance of the health of A-bomb survivors abroad and alleviation of their psychological concerns. I feel proud that I provided some help, even though a small amount, to the great efforts made by Dr. Noguchi and Ms. Sueishi. The above is my subjective report, which, to my regret, may lack objectivity. I would like to ask those well-versed in this project to indicate my mistakes and make necessary corrections.

Note: Although the first letter from Ms. Kazue Sueishi had been maintained in my files, its location has been unknown since I transferred my private files to my home at the time of my retirement. I am still trying to locate this letter … It is quite regrettable if I have lost it.

In Memory of Dr. Chiyoko Satoh (1937–2008)

Norio Takahashi, Laboratory of Biochemical Genetics, Department of Genetics

In mid-March, when the cherry blossoms were first starting to bloom, I received news of the death of Dr. Chiyoko Satoh who had once served as Chief of the Department of Genetics. The news was shocking to me, because I had heard only that she was well.

It is true that time flies, and it has been nearly 30 years since I first met Dr. Satoh, when I visited RERF to be interviewed for a job. That was in June 1978.

When I joined the Biochemical Genetics (BGS) Laboratory of the Department of Clinical Laboratories (the laboratory was later incorporated into the Department of Genetics), research on genetic effects of A-bomb radiation using starch gel electrophoresis was at a peak. Everyday, electrophoresis was performed as if the laboratory were some sort of factory. Dr. Satoh was the leader of these studies and, under her guidance, research scientists labored hard to achieve progress in their own experiments and data preparation.

Since DNA research was to be conducted after the electrophoresis studies, we decided to prepare immortalized cell lines using lymphocytes obtained from study participants. Dr. Satoh and I embarked on furthering our education (away from RERF, in Osaka) by studying techniques for cell immortalization and DNA analysis together under Dr. Tasuku Honjo, then Professor at Osaka University. One of my fondest memories is of us engaging in experiments day and night in a laboratory located in Osaka's Nakanoshima district under the guidance of Dr. Mieko Kodaira (currently, Associate Senior Research Scientist at the Department of Genetics). I was impressed with Dr. Satoh, who, while staying at a weekly rental apartment, pushed herself everyday with the aim of introducing the new techniques to our laboratory.

Over the years, Dr. Satoh and I often attended the same international scientific conferences, but we never took the same airplane (even for short-distance trips). She probably was avoiding such a situation out of consideration for her subordinates, to ensure that they could relax by themselves, or she might also have felt that it was easier simply to travel by herself.

What I have written so far may give the impression that Dr. Satoh was a straight-laced woman, with no interests outside of work, but that was not at all the case. All the staff members who worked at RERF for a relatively long time surely know that she played tennis. Not only in the evenings but also during lunchtime, she could be seen in her tennis skirt playing energetically on RERF's tennis court.

Dr. Chiyoko Satoh in 1997 (fourth person from left in front row) with staff members of the Biochemical Genetics Laboratory

Dr. Satoh's spirit of challenging new goals, which showed not only in the area of research but also in her hobbies, might have been the secret to how she maintained her youth. She especially loved scuba diving and often showed me photographs that she had taken while in the water. Even after her retirement from RERF, she apparently remained active in these two hobbies; whenever we heard word of her, the news was often in such context.

Dr. James Neel, Professor at the University of Michigan, who was one of the founders of the American Society of Human Genetics and a giant in the field of human genetics, visited RERF once a year to make detailed review of BGS results. At such times, Dr. Satoh used to exclaim, "Typhoon Neel is coming." However, Dr. Neel has since passed away. Dr. Howard Hamilton (then Chief of the Department of Clinical Laboratories), who used to affectionately call Dr. Satoh "Sugar," has also died. Now, Dr. Satoh is gone, and I truly feel as if the world has become a lonelier place.

On the grounds of Fumon Temple, where Dr. Satoh's funeral was held, blossoms of a weeping cherry tree were in full bloom. I felt they were suitable for bidding farewell to Dr. Satoh, who always had a glamorous air about her. I join my hands in prayer for the repose of her soul.

Mourning the Death of Former Vice Chairman Sheldon Wolff (1928–2008)

Seymour Abrahamson, Former Vice Chairman and Chief of Research

One important measure of a person's life is the beneficial influence he or she has had on the lives of countless others. For Professor Sheldon Wolff (Shelly to all who knew him) that influence has been on a grand scale. To me personally it has lasted over a half century.

Shelly was born in Peabody, Massachusetts, earned his Bachelor of Science Degree, with highest honors, at Tufts College in 1950 and then by 1953 he completed both a Master's and PhD degree at Harvard University. He studied with Professor Karl Sax, one of the pre-eminent cytologists of that era. The Biology Division of Oak Ridge National Laboratory under the direction of Dr. Alexander Hollaender was becoming the international center of research in radiobiology and it was natural for Dr. Hollaender to recruit this highly touted young PhD to the program in 1953.

One of Shelly's first publications in *Science* showed that irradiated Vicia fava seeds required oxidative metabolism in order for induced chromosome damage to be repaired. He had used chemicals to block metabolism. (Human cytogenetics research was still more than a decade from practical use. In fact the correct human chromosome number had yet to be discovered.) It was, however, this report by Shelly that allowed me to demonstrate in my PhD thesis that the same held true for the fruitfly, Drosophila. This confirmed Shelly's work. This was the start of our long-lasting friendship.

Shelly spent from 1953 to 1966 at Oak Ridge where he held a Senior Research Staff position and his studies led to international prominence. His laboratory attracted post-doctoral fellows who were to become future leaders in the field as was true of his students at the University of California, San Francisco (UCSF) where he moved in 1966 as Professor of Cytogenetics.

While there he and his students pioneered work on sister chromatid exchange (SCE) in mammalian cells, the chemical techniques that were developed allowed the differentiation of the two chromatids and was an important means of assaying chemical mutagen induced damage. Certain human diseases were also shown to be associated with enhanced levels of SCE's. Three of his publications in this area reached the status of Citation Classics.

Because of our interactions on various scientific committees we were able to co-author two publications that appeared in the journal *Nature*. The first was a demonstration that the larger the DNA content of a species the larger the radiation-induced gene mutation rate. The second was an analysis of the mechanism underlying radiation-induced gene mutations indicating that chromosome deletions or other rearrangements were the primary cause of such mutations in animal germ cells. In a sense, this confirmed the work of L.J. Stadler, the co-discoverer with H.J. Muller of the phenomenon that X rays induced mutations.

Dr. Sheldon Wolff in his RERF office in 1998

In 1983, Shelly became Director of the Laboratory of Radiobiology and Environmental Health at UCSF, a position he held until his retirement from the University. And in 1984, he published another highly influential paper in *Science* on adaptive response induced by low-dose exposure to ionizing radiation. It is a very interesting observation for estimating the low-dose risk, and we do not know as yet whether or not such low-dose exposure itself is detrimental or not.

His honors include but are certainly not limited to: The E.O. Lawrence Memorial Award 1973, Gold Medal recipient and Failla Lecturer of the Radiation Research Society 1992, and the first Leonard Sagan Belle Award in 1998 as a recognition of his research that had previously demonstrated unusual repair mechanisms accompanied by low-dose radiation exposures. In 1980–81, he served as President of the Environmental Mutagen Society (EMS) and Honorary Vice President of the Third International Con-

ference of Environmental Mutagens and was recipient of the EMS Award.

As the readers of this publication know, after his retirement from the University of California, Dr. Wolff was Vice Chairman and Chief of Research of the Radiation Effects Research Foundation from 1996–2000.

Shelly's curriculum vitae involving scientific activities on the national and international level runs to over three and a half pages and includes work for the National Academy of Sciences, National Institutes of Health, many programs of the Department of Energy and a number of different international committees. He also served on the editorial boards of nearly a dozen scientific journals. Shelly had a wonderful sense of humor, a zest for life, and was a connoisseur of fine food, excellent wines, and good cigars.

Shelly died on June 5th 2008 as a result of pulmonary fibrosis. He is survived by Francis, his wife of fifty-four years, his three children, Victor, Roger and Jessica, and three grandchildren.

In Memoriam

The cohort of former employees of ABCC and RERF is aging along with the A-bomb survivors. From time-to-time we receive word that another former employee has died. We plan to report the information that we receive, but often we do not have sufficient knowledge to write a proper obituary. So we will rely on your help to send us the names of any former employee who you know has recently died. Also, please let us know if any of our information in *Update* is incorrect and feel free to provide additional information for RERF's records.

Ray Carl Anderson (September 24, 1917–May 20, 2008)

William "Jack" Schull alerted us to the passing of Ray Anderson who was Jack's predecessor as head of the Genetics Department of ABCC. He served ABCC between 1947–1949. He had been retired from the faculty of the University of Minnesota and spent time between his lakeshore home in Northern Minnesota and a home in Sun City, Arizona. He was 90 when he died this year in Sun City, Arizona. Dr. Anderson was one of the four individuals who organized the ABCC in the autumn of 1947 (along with Dr. James Neel, Dr. Masuo Kodani, and Mr. Richard Brewer). He had a Ph.D. in genetics as well as his medical degree. He lived first in Hiro-machi since there was no housing available in Hiroshima and his office was located in the Red Cross Hospital in Senda-machi and later shifted to the Gaisenkan in Ujina area when the laboratory was constructed there. He left Hiroshima in 1949 and went to the University of Minnesota Medical School where he became a Professor of Pediatrics (Cardiology). His research was associated with Dr. C. Walton Lillehei's surgical group that pioneered open-heart surgery.

Dr. Anderson and his wife Hattie satisfied a 46-year desire to visit Hiroshima in October 1995 when they returned on a cruise ship from Vancouver. By a strange coincidence, and unknown to each other, there was another passenger on the same cruise ship who was also associated with ABCC—Dr. Isolde Loewinger, who was Chief of Pediatrics from 1955–1957. They had never met before. But since Dr. Anderson had written to former RERF Chairman Itsuzo Shigematsu about his arrival and Dr. Loewinger to Mr. Mick Rappaport about hers, both of them while on board were informed in a fax sent by Mr. Richard Sperry that they shared something in common.

Facts and Figures

In *Update* Volume 16 (2005), the Biosample Archive of RERF was summarized in a table that illustrated the large number of archived materials that have been donated and stored at RERF. The article also emphasized the importance of those samples to RERF's research and their potential to be used to improve our basic understanding of late-arising health consequences of prior acute radiation exposures. With evolving analytical methodologies, the samples continue to gain value and require vigilant management and prudent usage in order to optimize their scientific value.

Recognizing the importance of this treasure and its maintenance responsibilities, RERF has a 17-member Committee on Biological Samples (CBS) that has been meeting to assess the collection, storage, and use of biological samples at RERF. During 2007 the CBS activities included: (1) updating inventories of archived biosamples; (2) reviewing the storage methodologies employed by RERF; (3) assessing current storage capacities and projected storage needs; (4) reviewing the status of safeguards; and (5) review of the current management of the archives.

On May 15, 2008 the CBS released a 36-page report: *Committee on Biological Samples: Status Report—2007 and Recommendations*. The report identifies and discusses several issues associated with the archived biosamples at RERF. In addition, the committee reached a number of conclusions, including for example:

- The holdings of the archive have been updated with details and improved accuracy, but improvements could be made in the speed of recovery, frequency of updating, and accuracy of the inventory data.
- Overall growth of the archive is estimated to be in the range of 5% per year, with a projected doubling of the holdings within 15 years.
- Significant improvements have been made in securing uniform coverage of adequate electrical backup for all cold-storage units (mechanical freezers), but improvements could be made in remote monitoring of all of the storage units.
- The Hiroshima Laboratory is extremely limited in space and RERF will need to provide additional renovated space to accommodate the growth of the archives.
- Ten-year projections of the required storage space suggest that the current ~228 m^2 will need to be increased to ~424 m^2, an ~86% increase.
- A restructuring of how the archive is managed could increase the overall quality and utility of RERF's biorepository.
- While elements of quality assurance (QA) and quality control (QC) programs are in place, the programs need to be uniformly applied and practiced.

The report suggested a number of recommendations with respect to improving the archive inventory process, increasing sample safeguards, expanding the storage capacity, designing and implementing a regimented QA/QC program, and restructuring of the archives to include a centralized management and database. Finally, the report included an annex with tables listing the most recent biosample inventories, a summary of biosample preparative protocols, and a report of a visit to the Mayo Clinic in Rochester, Minnesota by Drs. Susan Geyer and Hiroaki Katayama to observe and discuss how that important U.S. research institution collects, stores, and utilizes biosamples.

The CBS strongly recommended that RERF plan a series of international workshops designed to obtain advice from experts on the collection, storage, and utilization of RERF's world-heritage biosamples. The first of such workshops was held in March 2008 (RERF Symposium on Bioinformatics, see page 10). The second was held in RERF October 10–11, 2008, focusing on breast cancer research and will be reported on in the next issue of *Update*. As stated in the past, RERF welcomes any and all constructive input from the scientific community on the nature and use of this unique biosample repository.

Research Protocols Approved in January–September 2008

RP 1-08 Establishment of a Recombinant Mouse Model for Assessment of Genetic Effects of Radiation at Low Doses

Noda A, Hirai Y, Kodama Y, Cullings HM, Nakamura N

In this project, we propose to create genetically modified mice in which mutant cells arising in their body will generate green fluorescence. By using these mice, genetic effects of radiation (transgenerational effects) will be measured in their germ cells; spermatids, spermatocytes, spermatogonia, and oocytes. This approach could pave the way to analyze genetic effects of radiation at low doses without requiring a large number of F_1 animals. To study the possible negative selection of mutant embryos or neonatal mice carrying the mutation, a fraction of mutant germ cells will be used to produce fertilized eggs which will be subsequently transplanted in pseudopregnant mice's wombs to scrutinize the developmental/growth process. Furthermore, mutant cell frequency of somatic cells in F_1 animals born to irradiated mice will be measured to test if genomic instability might be observed as a delayed effect of parental exposure.

RP 2-08 Mail Survey 2008 on Epidemiological Factors in the Extended Life Span Study Population

Nishi N, Nagano J, Grant EJ, Sugiyama H, Sakata R, Hsu WL, Kasagi F, Fujiwara S, Akahoshi M, Moriwaki H, Mabuchi K, Ron E, Suyama A, Kodama K

A mail survey will be conducted on about 47,000 subjects in the Extended Life Span Study cohort (LSS-E85) who are alive at the time this study is initiated, in order to obtain and update information on epidemiological factors such as lifestyles, history of radiotherapy, height, weight, financial situation, disease history, menstruation, and psychosocial factors. Such information will be used as factors that may confound or modify the health effects of radiation. Due to the large size, long-term follow-up, and advanced age of the cohort, an effort to broaden the focus to include overall aging markers is also proposed. Additional targeted data include present and past history of major diseases as well as mental and physical health status. A pilot study has shown that both the validity and reproducibility of the questionnaire are high and its implementation is feasible. To support the approved research protocol entitled "Clinical health study for expanded group of younger A-bomb survivors" (RP 3-07), applicants for the clinical health study will be sought among subjects of the mail survey to increase the number of participants of the Adult Health Study under 10 years old at the time of the bombings, from the current 700 to 2,900.

RP 3-08 Mortality in Relation to Smoking and Other Lifestyle Factors in a Japanese Population

Sakata R, McGale P, Darby S, Grant EJ, Nishi N, Boreham J, Sugiyama H, Soda M, Shimizu Y, Tatsukawa Y, Yamada M, Moriwaki H, Kasagi F, Suyama A, Geyer SM, Kodama K, Peto R

Existing studies of the effects of smoking in Japanese populations suggest that its impact on mortality is smaller than elsewhere, given the amount smoked. At present it is not clear whether this is a reflection of the fact that cigarette smoking became common in Japan somewhat later than in other countries or whether there are other factors that modify the impact of smoking, or appear to modify it. (For example, the lung cancer rate in non-smokers is higher in Japan than in some other countries. Therefore, if the lung cancer rate among smokers were the same in Japan as elsewhere, the relative risk would appear smaller.) It is also not clear what the impact is of using different methodologies to estimate the smoking risk. The proposed study will address those issues in the Life Span Study population (including members of the Adult Health Study) using data already held at RERF. The project will be carried out jointly between staff from RERF and the University of Oxford and it will draw on experience that has recently been gained in analyses of the effect of prolonged smoking in the British doctors' study.

RP 4-08 Investigation of Storage Conditions for Cataract Tissue of A-bomb Survivors, and Its Collection and Storage Program

Neriishi K, Blakely EA, Chang P, Nakashima E, Ohishi W, Fujiwara S, Hida A, Akahoshi M, Hayashi T, Ito R, Nakachi K, Minamoto A, Yokoyama T, Toda S, Uematsu M, Tsuiki E, Kiuchi Y, Kitaoka T, Shirai A, Cucinotta FA, Chylack LT

The goal of this project is to confirm reproducibility of the storage method for cataract tissues from the Adult Health Study (AHS) participants who undergo cataract operations, and to collect and store the tissue for future analyses. A recent study has indicated that the odds ratio at 1 Sv of prevalence for those who underwent cataract operations was 1.39 (95% confidence interval 1.24, 1.55). AHS participants who were young at the time of the bombings are expected to reach the age of cataract operation within the next decades. The removed cataract tissues are expected to contribute significantly to future research on radiation-induced cataract. When enough numbers of tissues are collected, new research protocols, focusing on specific topics, will

be separately prepared.

RP 5-08 Breast Cancer Incidence among Atomic-bomb Survivors, 1950–2005

Yonehara S, Nishisaka T, Nakashima M, Nishi N, Furukawa K, Soda M, Suyama A, Ikeda T, Tokuoka S, Mabuchi K, Land CE, Preston DL, Kodama K, Kasagi F

Several breast cancer incidence studies based on the RERF Life Span Study (LSS) population were conducted during the period from 1950 through 1990. Among those breast cancer cases, a highly significant linear dose response was observed in breast cancer incidence among exposed people; among women exposed at less than 20 years of age, excess relative risk per Sv for those with attained age of 35 or more was around 2, whereas excess relative risk per Sv for those with attained age of 20 years or more and less than 35 was shown to be remarkably high, at 16.8. Further, among women exposed at less than 20 years of age, excess relative risk of bilateral breast cancer per Sv was also shown to be high, which suggested the presence among them of a group highly sensitive to radiation-induced carcinogenesis. However, more recent data indicate that both age at exposure and attained age are important modifiers of the radiation-related risk of breast cancer, and the relative importance of these two factors is dependent on models, background rates, and other assumptions used. We thus need to pursue the risk analysis to better understand the risk patterns in an extended follow-up and try to identify morphological or other features contrasting early- vs. late-onset breast tumors. In this study, we will examine new breast cancer cases occurring in the LSS during the 15 years (from 1991 through 2005) following the previous period and cases that occurred during the previous study period but were registered after that period. Ages at diagnosis of new breast cancer cases occurring during the period from 1991 through 2005 are at least 45 years old. We will examine new findings and compare them with previous findings, and review all breast cancer cases during the entire period since the previous study, by classifying them based on new histological classification criteria of the World Health Organization (WHO).

Recent Publications

(Japanese): the original article is in Japanese.

Adiga SK, Toyoshima M, Shiraishi K, Shimura T, Takeda J, Taga M, Nagai H, Kumar P, Niwa O. p21 provides stage specific DNA damage control to preimplantation embryos. Oncogene 2007 (September 13); 26(42):6141-9.

Asakawa J. Restriction landmark genome scanning for the detection of mutations. Martin CC, ed. Methods in Molecular Biology™—Environmental Genomics. Totowa, New Jersey: Humana Press 2007:pp 153-70.

Asia Pacific Cohort Studies Collaboration (RERF: Nakachi K). The burden of overweight and obesity in the Asia-Pacific region. Obesity Reviews 2007 (May); 8(3):191-6.

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