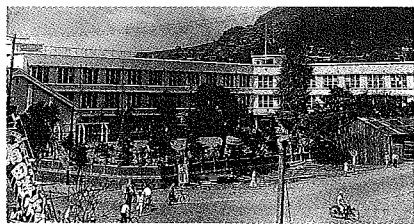


Nagasaki Laboratory Observes 50 Years of Community Cooperation



ABCC was first housed at the Shinkozen Elementary School (now Nagasaki Municipal Suwa Elementary School), where the First Clinic of the Nagasaki Medical College (now Nagasaki University School of Medicine) was relocated after the bombing. (ABCC file photo)

Fifty years ago last summer, on 12 July 1948, the Atomic Bomb Casualty Commission (ABCC) opened its first Nagasaki laboratory, just one year after opening its Hiroshima facility. To observe this golden anniversary, RERF's Nagasaki laboratory hosted a commemorative ceremony on 2 November and its second open house November 3. One hundred and seventy guests, including representatives from the Adult Health Study (AHS), atomic-bomb survivors' organizations, the local and regional governments and medical institutions and schools, attended the anniversary presentation, and 260 visitors attended the open house.

See *Nagasaki Anniversary* on page 7

放影研 RERF update

Volume 10, Issue 1, Spring 1999

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放影研 RERF update

Radiation Effects Research Foundation News and Views
Hiroshima and Nagasaki, Japan

Second External Peer Review Examines RERF's Epidemiology Research Program

On 16-18 November 1998, the Department of Epidemiology became the second RERF department to undergo external peer review according to the recommendation of the 1996 Blue Ribbon Panel. (The Department of Radiobiology was reviewed in January 1998.) Dr. Richard Monson, professor of medicine at the Harvard University School of Public Health, chaired a panel of seven



Dr. Monson (third from left), panel chair, was joined on the panel by (from left to right) Dr. Tsutomu Hashimoto, professor of Public Health at the Wakayama Medical College in Wakayama City; Dr. Lars-Erik Holm, director general of the Swedish Radiation Protection Institute (SSI) in Stockholm; Dr. Tomio Hirohata, professor emeritus of public health at the Kyushu University Faculty of Medicine in Kasuga City; Dr. Kei Nakachi, principal researcher at the Saitama Cancer Center Research Institute in Saitama Prefecture; Dr. Shirley A. Fry, scientific director of the International Consortium for Research on the Health Effects of Radiation, based in Oak Ridge, Tennessee; and Dr. Hiroyuki Shimizu, professor of public health at the Gifu University School of Medicine in Gifu City. (Photo by Junso Takayama)

epidemiologists from Japan, Sweden, and the United States, who were assigned the task of reviewing the department's overall program, including its current and projected activities, evaluating staff performance, and examining management issues related

to intra- and interdepartmental and external collaborations. Dr. Monson was joined on the panel by Dr. Shirley A. Fry, scientific director of the International Consortium for Research on the Health Effects of Radiation, based

See *Peer Review* on page 3

Clinical Genetics Workshop Discusses F₁ Study by Norio Takahashi, Chief, Laboratory of Biochemical Genetics, Department of Genetics

RERF conducted a clinical genetics workshop on 3 and 4 March 1999 in its Hiroshima laboratory auditorium to acquire basic information for the conduct of the proposed health study of the children of A-bomb survivors (F₁ health study). The objectives of the workshop were: (1) to offer advice for the F₁ health study now being planned; (2) to clarify the characteristics of the study population; (3) to give examples of the ongoing molecular genetics studies related to the multifactorial diseases that will be studied under the F₁ health study and indicate the problems involved; (4) to

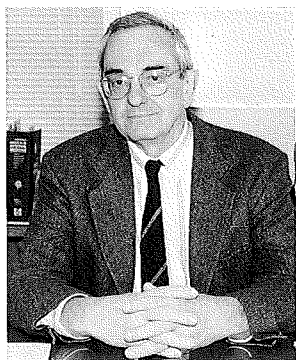
evaluate the significance of the health study from the standpoint of radiation genetics; and (5) to highlight ethical issues that should be considered in the conduct of the study. About 60 people attended the workshop, including researchers from Japan, the Netherlands, and the United States.

After RERF Chairman Shigenobu Nagataki's opening address, Dr. Charles J. Epstein, workshop chairman, described the workshop objectives, and former RERF Chief of Research Seymour Abrahamson then spoke on "The

See *Clinical Genetics Workshop*, p. 4

Epidemiologic and Clinical Follow-up and Interdisciplinary and Collaborative Research to be Emphases in the Coming Year

by Clark W. Heath, Jr., Associate Chief of Research and Editor-in-Chief, RERF Update



Newly arrived at RERF with the new year, I am pleased to serve as editor for *Update*, following in the footsteps of Seymour Abrahamson. Over the years, I have enjoyed reading the news of current RERF activities that *Update* brings, as well as vivid recollections of past ABCC/RERF work and biographic notes about the many staff members,

Japanese and American, who have made the Foundation the distinguished international research institution it is. Having served on the Scientific Council for eight years (1990-1997), I had come to appreciate not only the quality and diversity of RERF research, but its enduring importance for radiobiologic knowledge and radiation safety throughout the world. I also was witness to the administrative and financial difficulties that the Foundation has had to face in recent years. Hopefully, those days are past, and steady support from both Japan and the United States, enhanced by collaboration-based grant funds, will sustain RERF well into the future. With 95% of A-bomb survivors still alive who were under age 10 at the time of bombing, it will be most important to continue follow-up of the Adult Health and Life Span cohorts, as well as the F₁ generation, for some decades to come. It will also be increasingly important to pursue interdisciplinary genetic and immunologic studies, using RERF's rich collection of

biologic specimens to investigate the cellular and molecular mechanisms by which radiation causes cancer and other diseases.

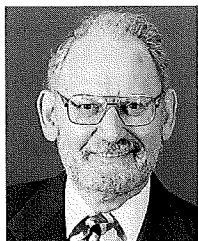
When I retired from the American Cancer Society (ACS) last year, it did not occur to me or to my wife Janet that a year later we would find ourselves living in Hiroshima (accompanied by our basenji dog and my violincello). I had directed epidemiologic research at the ACS since 1988, and Janet had been in charge of measles diagnostic work at the Centers for Disease Control. We had moved to rural south Georgia, near the Atlantic coast, mixing leisure with my occasional epidemiologic and environmental health consultation work. But, discussions with the National Academy of Sciences soon refocused my attention on RERF and on the unique opportunities here to provide on-site support for molecular epidemiology and A-bomb survivor research. This interest, in retrospect, may not be surprising. Its roots may spring from my years of clinical training at the Boston City Hospital, two of which (1964-65) were spent learning hematology from William C. Moloney. Dr. Moloney (who died this past year at the age of 90; see page 27) played a prominent role at ABCC in the 1950s when the relationship of A-bomb radiation to leukemia risk was first being described. He spoke often with us of that work and of his Japanese experiences.

So, the work continues. In addition to ongoing epidemiologic and clinical follow-up of the survivor cohorts, the coming year will see increasing emphasis on interdisciplinary and collaborative research, much of it centered on detailed prospective studies of the F₁ generation. The directions this work is likely to follow are reflected in the

See *Heath* on page 26

Associate Chief of Research Seymour Abrahamson Retires for Fourth Time

December 31, 1998, Associate Chief of Research Seymour Abrahamson retired from RERF for the fourth time, having served almost six years in total. He first came to RERF as a permanent director and chief of research in July 1988 and then served for some time as vice chairman as well. Dr. Abrahamson returned January 10 last year to help out during an extensive administrative transition, after being away only a few months.



In 1997, Dr. Abrahamson took part in the 50th anniversary celebration of ABCC-RERF in Washington that preceded the retirement of Chairman Itsuzo Shigematsu, after 16 years, and the inauguration of Shigenobu Nagataki as RERF's new leader. In December

1996, Sheldon Wolff had taken over as vice chairman and chief of research, and in August 1997, Dr. Senjun Taira filled in the permanent director vacancy left by Dr. Nagataki when he became chairman. In this context, Seymour Abrahamson returned in 1998. In six years here, he interacted with some eleven permanent directors and even more visiting directors.

During his four terms at RERF, Dr. Abrahamson was involved in and witness to some major events and changes that will impact the Foundation for years to come. Among these was the 1996 review by the Blue Ribbon Panel, which examined RERF's history and its current research programs with the purpose of advising the Foundation regarding future research and collaborations in the study of A-bomb survivors. The Panel particularly identified first generation (F₁) genetic effects and low-dose exposures as important research priorities. It also suggested revisions

in the scientific peer review process (leading to last year's reviews of the radiobiology and epidemiology programs) and underscored RERF's international contributions to the investigation of radiation health effects. In its final report, the Panel emphasized that RERF research is important to the entire international community, not just to the Japanese and American governments that fund the organization, a finding that Dr. Abrahamson emphasized as he left RERF in December.

Among other significant events taking place during Dr. Abrahamson's years at RERF were a number of workshops convened to deliberate such topics as immunology, radiation carcinogenesis, aging, and human germline mutagenesis, to name a few, workshops attended by international experts in the respective areas of concern. Even since his December departure, Dr. Abrahamson has returned to RERF to present at yet

See *Abrahamson* on page 22

Peer Review, continued from page 1
in Oak Ridge, Tennessee; Dr. Tsutomu Hashimoto, professor of Public Health at the Wakayama Medical College in Wakayama City; Dr. Tomio Hirohata, professor emeritus of public health at the Kyushu University Faculty of Medicine in Kasuga City; Dr. Lars-Erik Holm, director general of the Swedish Radiation Protection Institute (SSI) in Stockholm; Dr. Kei Nakachi, principal researcher at the Saitama Cancer Center Research Institute in Saitama Prefecture, and Dr. Hiroyuki Shimizu, professor of public health at the Gifu University School of Medicine in Gifu City.

Following Dr. Shigenobu Nagataki's greetings, Dr. Sheldon Wolff presented an overview of RERF, Dr. Kiyohiko Mabuchi, department chief, Hiroshima, outlined the Hiroshima epidemiology program, and Dr. Yoshisada Shibata, department chief, Nagasaki, the Nagasaki program. Ten researchers then made presentations, each of which was followed by a brief discussion period: Dr. Yukiko Shimizu spoke on *Life Span Study [LSS] cancer mortality*; Dr. Mabuchi, on *In utero and F₁ follow-up*; Dr. Kojiro Koyama, on *Skin cancer*; Dr. Yasuyuki Fujita, on *Tumors of the central nervous system*; Dr. Midori Soda, on *Colorectal cancer in the Nagasaki survivors*; Dr. Donald Pierce, on *Mechanistic implications of the age-time patterns of radiation-related cancer*; Dr. Dale Preston (Department of Statistics), on *Radiation risk assessment*; Dr. Gerald Sharp, on *Liver cancer*; Dr. Charles Land (National Cancer Institute and RERF expert advisor), on *Breast cancer and BRCA genes*; and Dr. Shibata, on *The F₁ mail survey*.

Following the formal presentations, on the afternoon of the second day, review panelists toured the department's facilities and the tumor and tissue registries before preparing their final list of 24 recommendations. Their formal recommendations were submitted to Dr. Wolff and will be reviewed by the science councilors at their April meeting.

The panel's recommendations encompassed six categories, the Life Span Study sample, the *in utero* cohort, the F₁ cohort, molecular epidemiology, risk assessment, and organization and performance.

With regard to the LSS, they em-

phasized the need for continued surveillance of the LSS and Adult Health Study (AHS) populations with particular attention to cancer incidence; consideration of the interaction of lifestyle variables, infections, and genetic factors with radiation exposure; further investigation of noncancer diseases, particularly cardiovascular diseases, with the added recommendation that a noncancer workshop be convened to involve outside experts; continued interdepartmental interaction and study collaboration, such as the current work being done on primary liver cancer; and genetic and molecular epidemiological exploration of early-onset breast cancer risk in women exposed prior to age 20.

The reviewers recommended sustained follow-up of the *in utero* cohort, those persons who were exposed to either bomb while in their mother's wombs, for at least 20 more years. They noted the particular importance of the *in utero* data in the work of such organizations as the International Commission on Radiological Protection (ICRP) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).

In this same regard, the panel remarked that the F₁ cohort is the primary source of human data on heritable disease risk in the children of radiation-exposed populations and that follow-up continues to be crucial. The F₁ cohort comprises individuals born more than nine months after the bombings to parents, one or both of whom were exposed to radiation at the time of the bombings.

The peer reviewers made a number of recommendations concerning F₁ follow-up and expressed their concern for the scientific and ethical issues involved. They suggested consultation with an ethical advisory committee prior to initiating future studies and that epidemiologists be included in the committee's makeup. In identifying specific study components, they recommended that a nutritional epidemiologist be included in the study's scientific advisory committee so that interactions between diet and radiation exposure could be adequately considered, and they cautioned that "a strong scientific justification must be developed" prior to any exploration of the psychological health of the F₁ cohort. The panel also suggested that particu-

lar efforts "be made to obtain risk estimates for radiation-induced hereditary effects, especially for multifactorial diseases and late-occurring dominant mutations."

In addition, the panel highlighted the importance of informing study participants and interested parties about the intended use of data to be collected prior to undertaking the investigation, and they pointed out that from the onset, it would be important to identify how initial cross-sectional data might be used to assess causal hypotheses in contrast to the use of later follow-up data.

The reviewers further recommended a feasibility study of several hundred individuals to help sharpen study design and indicated that inclusion of all controls, rather than just a sample, in the investigation would strengthen the statistical power of findings.

Turning to the issue of molecular epidemiology, the peer review panel called for the development of a strategic plan for molecular epidemiologic research in the hope that such research would encourage internal and external collaborative endeavors encompassing specialists in diverse areas.

In the area of risk assessment, the panel's report commented on the limitations imposed on cancer incidence data by the lack of a national tumor registry and recommended that future risk assessment be based on incidence and mortality, taking into account the inherent limitation of the cancer incidence data. They also recommended risk assessment of other diseases.

In conjunction with data analysis, the development and use of mathematical models coupled with ongoing testing of assumptions underlying such models was seen as important to the investigations conducted by the department.

In their final recommendations, the peer reviewers considered issues of organization and performance and especially the role of interdisciplinary collaboration in the department's and RERF's future. They strongly recommended that academic affiliations be developed that would enable the training of doctoral students and postdoctoral fellows and that a grant program be created so that RERF data could be used in

See *Peer Review* on next page

4 Clinical Genetics Workshop, Peer Review

Clinical Genetics Workshop, from p. 1
problem: What is being asked? Can the F_1 be used to assess effects of radiation-induced mutations in multifactorial diseases?," shedding light on the question embracing the entire workshop. RERF Vice Chairman and Chief of Research Sheldon Wolff then introduced the RERF program, and the following five presentations rounded out the morning session: Dr. Nori Nakamura, *What has been done in the past*; Dr. Saeko Fujiwara, *Clinical studies in the AHS*; Dr. William J. Schull, *The cohort: Strengths and weaknesses*; Dr. Dale Preston, *The nature of the study population*; and Drs. Kojiro Koyama and Michiko Yamada, *Plans for F_1 mail and clinical studies*.

In the afternoon, molecular genetics studies for each of the major multifactorial diseases were reported: Dr. Epstein, *General aspects*; Dr. Kishio Nanjo, *Diabetes mellitus*; Dr. Akira Hata, *Hypertension*; Dr. Norio Takahashi, *RERF hypertension study*; and Dr. Eric Boerwinkle, *Coronary heart diseases*.

On the second day, Dr. K. Sankaranarayanan explained the issues involved in the use of multifactorial diseases as markers for the evaluation of radiation-induced genetic effects by statistical models, and Dr. Aravindra Chakravarti spoke about the effectiveness of the DNA-chip technique ready to be introduced for the detection of gene-related human multifactorial diseases. After Dr. Arno G. Motulsky presented "The genetics of complex human disease: Medical, biologic, and methodologic problems," the F_1 health study was discussed from the medical, biological, and scientific standpoints.

In the afternoon session, after Dr. Hiraku Takebe reported on the ethical issues related to the health study, all participants worked together using a draft prepared by Dr. Epstein to write a summary report and to prepare the workshop's recommendations. The four recommendations made are as follows: 1) A mail survey of the F_1 population should be conducted. 2) A pilot clinical study of the F_1 population is warranted. 3) An extensive clinical study of the F_1 population is justified principally for the purpose of reassuring the children of survivors and the public at large about the risks of radiation-induced genetic



Pictured from left to right, front to back: Row one: Akira Hata, M.D., Ph.D., professor, Department of Public Health, Asahikawa Medical College; Hiraku Takebe, Ph.D., professor, Atomic Energy Research Institute, Kinki University; Eric Boerwinkle, Ph.D., director, Institute of Molecular Medicine and Human Genetics Center, The University of Texas, Houston Health Science Center; Shigenobu Nagataki, RERF chairman; Charles J. Epstein, M.D., professor, Department of Pediatrics, University of California, San Francisco; Sheldon Wolff, RERF vice chairman and chief of research; Arno G. Motulsky, M.D., professor, Department of Medicine, University of Washington; K. Sankaranarayanan, professor emeritus, MGC, Department of Radiation Genetics & Chemical Mutagenesis, Leiden University Medical Centre; William J. Schull, Ph.D., emeritus Ashbel Smith professor of academic medicine, The Human Genetics Center, School of Public Health, The University of Texas, Health Science Center; Row two: Richard D. Sperry, RERF administrative advisor; Yasuyuki Fujita, assistant chief, RERF Department of Epidemiology, Hiroshima; Saeko Fujiwara, assistant chief, RERF Department of Clinical Studies, Hiroshima; Kazumasa Kunitoshi, RERF Secretariat chief; Senjun Taira, RERF permanent director; Michiko Yamada, senior scientist, RERF Department of Clinical Studies, Hiroshima; Toru Nabika, M.D., Ph.D., assistant chief, Department of Clinical Medicine, Shimane Medical University (observer); Evan Douple, Ph.D., director, Board on Radiation Effects Research, Commission on Life Sciences, National Research Council, National Academy of Sciences (observer); Norikazu Yasuda, Ph.D., chief, Division of Information on Genetic Diseases, Research Center for Biological Information and Resources (observer); Row three: Midori Soda, acting chief, RERF Department of Epidemiology, Nagasaki; Yukiko Shimizu, acting chief, RERF Department of Epidemiology, Hiroshima; Seymour Abrahamson, Ph.D., emeritus professor, Department of Zoology, University of Wisconsin; Aravinda Chakravarti, Ph.D., professor, Department of Genetics and Center for Human Genetics, Case Western Reserve University School of Medicine; Norio Takahashi, chief, Biochemical Genetics Laboratory, RERF Department of Genetics; Masazumi Akahoshi, assistant chief, RERF Department of Clinical Studies, Nagasaki; Kishio Nanjo, M.D., Ph.D., professor and chairman, The First Department of Medicine, Wakayama Medical College; Row four: Shoichiro Fujita, assistant chief, RERF Department of Statistics; Kojiro Koyama, chief, RERF Tumor and Tissue Registry Office; Nori Nakamura, chief, Department of Genetics; Kazunori Kodama, chief, RERF Department of Clinical Studies, Hiroshima; Akio Awa, RERF associate chief of research; Clark W. Heath, Jr., RERF associate chief of research; Yoshisada Shibata, D. Eng., professor and chairman, Department of Radiation Epidemiology, Radiation Effects Research Unit, Atomic Bomb Disease Institute, Nagasaki University School of Medicine (observer); and Dale Preston, chief, RERF Department of Statistics. Not pictured: Norihiko Hayakawa, M.D., Ph.D., professor, Division of Social Medicine, Department of Epidemiology, Research Institute for Radiation Biology and Medicine, Hiroshima University (observer). (Photo by Junso Takayama)

disease. This study should be designed and appropriate samples stored so as to maximize the information that can be obtained. 4) All studies should be designed and carried out with ap-

propriate ethical guidance.

I would like to express my sincere appreciation to the panelists, some of whom came a very long way, who made this workshop a success.

Peer Review, continued from page 3

studies with other research organizations and universities. Within RERF, a high priority was assigned to the department's participation in any epidemiologic investigation undertaken by other departments.

The panel members were especially concerned with data maintenance issues and recommended that resources be secured so that data entry into RERF's computer files can be carried out as soon as possible after collection and that backup files be maintained off-site to avoid any unforeseen mishap. Also in this regard, the panelists were concerned that staffing be maintained at a level that

will guarantee "optimum use of existing data."

Finally, with the resignation of Dr. Shibata and impending retirement of Dr. Mabuchi, the panel called for "balancing the needs of scientific interaction and community communication" in the choice of replacements to head the two departments.

Though external peer review of RERF's research departments is intended to be an annual occurrence, the first two happened to fall within the same calendar year. Selection of the next department for evaluation and the date of that review will take place after the scientific council meets in April and discusses the recommendations of the epidemiology review panel.

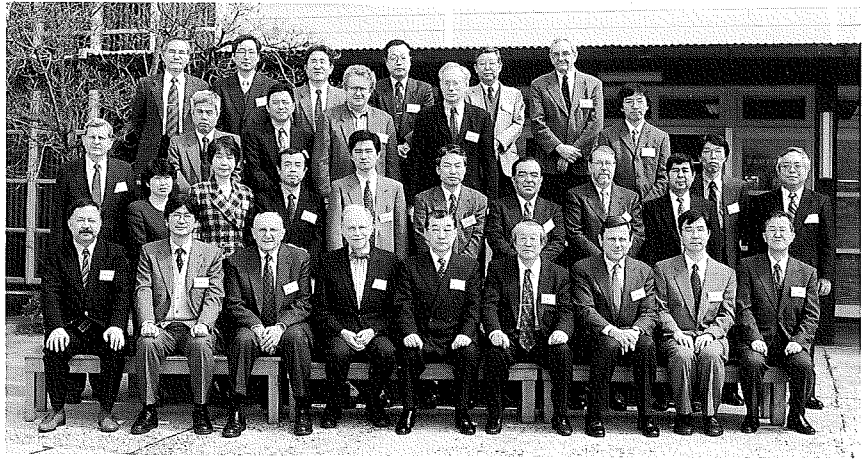
March Workshop Seeks Immunological Approach to Mechanism of Radiation-Induced Diseases

by Seishi Kyoizumi, Chief, Laboratory of Immunology, Department of Radiobiology

On 10 and 11 March 1999, RERF hosted an immunology workshop entitled "T cell function and disease development: Implications for future immunological study on A-bomb survivors" at its Hiroshima laboratory. Recent developments in immunological science have paved the way in explaining many human diseases as abnormalities in the immune system. The purpose of the workshop was to seek advice regarding the direction and focus of our research on clarifying how immunological host-defense mechanisms are involved in the onset and progression of radiation-related diseases among A-bomb survivors. About 50 people attended the workshop, including invited speakers, RERF department chiefs and research scientists, visiting Russian and Japanese scientists, and press members.

The workshop focused on T-cell immunity, which may play the most important role in the disease development of A-bomb survivors. RERF immunologists proposed the hypothesis that a long-lasting imbalance of helper-T cell, a commander of the immune system, could eventually result in various diseases in the survivors (*See Update 9[2]: 10-11,15, 1998*). Workshop members agreed that the hypothesis is valid and should be tested. Discussion by invited speakers and RERF staff generated many ideas on infectious immunity, autoimmunity, and tumor immunity, which were very valuable and important to the exploration of future immunological studies on the survivors.

The two-day workshop was organized by RERF Vice Chairman and Chief of Research Sheldon Wolff and Immunology Laboratory Chief Seishi Kyoizumi and was divided into five sessions: an overview of RERF studies, chaired by Dr. Wolff; cytokine regulation of T-cell immunity, chaired by Dr. Takashi Nishimura, of the Department of Immunology at Tokai University School of Medicine in Isehara; T-cell immunity in infectious disease, chaired by Dr. Kikuo Nomoto, of the Medical Institute of Bioregulation of Kyushu University in Fukuoka; T-cell immunity in autoimmune disease, chaired by Dr. Shimon Sakaguchi, of the Institute of Frontier Medical Sciences of Kyoto University; and T-cell immunity and tumor development, chaired by Drs. Yasuharu Nishimura,



Pictured from left to right, front to back: Row one: Dr. Y. Nishimura, Dr. T. Nishimura, Dr. S. Wolff, Dr. J. T. Grayston, Dr. S. Nagataki, Dr. K. Nomoto, Dr. G. Trinchieri, Dr. S. Sakaguchi, Dr. K. Eguchi; Row two: Mr. R. D. Sperry, Dr. Y. Shimizu, Dr. S. Fujiwara, Dr. M. Hakoda, Dr. Y. Nakamoto, Dr. S. Kyoizumi, Dr. S. Taira, Dr. E. Douple (observer), Mr. K. Kunitoshi, Dr. K. Hamatani, Dr. M. Akahoshi; Row three: Dr. Y. Fujita, Dr. T. Hayashi, Dr. D. Preston, Dr. G. Sharp, Dr. T. Tominaga; Row four: Dr. S. Fujita, Dr. Y. Kusunoki, Dr. N. Nakamura, Dr. K. Kodama, Dr. A. Awa, Dr. C. W. Heath, Jr. (photo by Junso Takayama)

of the Division of Immunogenetics of the Department of Neuroscience and Immunology at Kumamoto University Graduate School of Medical Sciences, and Dr. Kyogo Itoh, of Kurume University School of Medicine. The following presentations were given:

Overview of RERF studies: Dr. Wolff, *RERF overview and workshop objectives*; Dr. Dale Preston, chief, RERF Department of Statistics, *Summary of cancer and noncancer mortality risks in the Life Span Study*; Dr. Kazunori Kodama, chief, Department of Clinical Studies, Hiroshima, *Noncancer diseases in A-bomb survivors*; and Dr. Kyoizumi, *Late effects of A-bomb radiation on the hemolymphoid system*.

Cytokine regulation of T-cell immunity: Dr. T. Nishimura, *The pivotal role of Th1/Th2 balance in immune diseases*; Dr. Yoichiro Kusunoki, associate senior research scientist, RERF Department of Radiobiology, *Possible polarization towards Th2 in A-bomb survivors*; and Dr. Giorgio Trinchieri, Wistar Institute, Philadelphia, Pennsylvania, USA, *Innate and adaptive mechanisms in the antitumor activity of Interleukin-12*.

T-cell immunity in infectious disease: Dr. Nomoto, *Selective commitment and differentiation of T cells in infectious immunity*; Dr. J. Thomas Grayston, University of Washington, Seattle, USA, *Current knowledge about the role of Chlamydia pneumoniae in atherosclerosis*; and Dr. Kusunoki and Dr. Masaki Shimizu, research scien-

tist, RERF Department Clinical Studies, Hiroshima, *Proposal for a new study of Chlamydia pneumoniae infection in A-bomb survivors*.

T-cell immunity in autoimmune disease: Dr. Sakaguchi, *Autoimmune disease induced by manipulation of T-cell immune system: Ionizing radiation as a cause of autoimmune disease*; Dr. Katsumi Eguchi, Nagasaki University School of Medicine, *Apoptosis in the thyroid gland in patients with autoimmune thyroid diseases*; and Dr. Kiyohiro Hamatani, research scientist, RERF Department of Radiobiology, *Autoimmune disease and cancer in thyroid of A-bomb survivors*.

T-cell immunity and tumor development: Dr. Nakamoto, *Immune pathogenesis of hepatocellular carcinoma*; Gerald Sharp, research scientist, RERF Department of Epidemiology, Hiroshima, *The role played by A-bomb radiation and hepatitis viruses in the etiology of primary liver cancer*; Dr. Tomonori Hayashi, research scientist, RERF Department of Radiobiology, *MHC class II polymorphism in A-bomb survivors*; Dr. Yasuharu Nishimura, Kumamoto University Graduate School of Medical Sciences, *Analysis of human CD4⁺ T cells reactive to tumor-associated antigens*; Dr. Kyogo Itoh, Kurume University School of Medicine, *Genes encoding antigenic peptides of human epithelial cancers recognized by cytotoxic T lymphocytes*; and Dr. Kyoizumi, *Implications for future study on A-bomb survivors*.

RERF Hosts Foreign Ministry International Chernobyl Symposium

by Kazuo Neriishi, Chief, Division of Medicine, Department of Clinical Studies, Hiroshima

The Japanese Ministry of Foreign Affairs hosted an open symposium entitled "Health Condition of Residents after the Chernobyl Nuclear Plant Accident" on 18 and 19 February 1999 at RERF. The program was cosponsored by the Hiroshima International Council for Medical Care of the Radiation-Exposed (HICARE), the National Institute of Radiological Sciences (NIRS), the Hiroshima University Research Institute for Radiation Biology and Medicine (RIRBM), and the Nagasaki University School of Medicine as well as RERF. The 40 symposium participants from Belarus, Russia, Ukraine, and Japan included Foreign Ministry Assistant Division Chief Akira Maejima, representatives from various institutions, researchers invited from the new independent states (NIS), trainees from the Commonwealth of Independent States, and researchers from Chiba, Hiroshima, Nagasaki, and Tokyo, who shared the latest scientific information related to dosimetry and epidemiology, hematology, thyroid disease, and data processing.

Dr. Kunio Shiraiishi, of NIRS, in Chiba, chaired the first morning session, on dosimetry and epidemiology, which included presentations by: Dr. Pavlo V. Zamostyan, of the Radiation Hygiene and Dosimetry Department of the Research Center for Radiation Medicine of the Academy of Medical Science of Ukraine, *An analysis of the dynamics of internal exposure of the Ukrainian population from ingestion of food contaminated by radionuclides after the Chernobyl accident*; Dr. Marat A. Maksimov, laboratory head at the Medical Radiological Research Center of the Russian Academy of Medical Sciences (RAMS) in Obninsk, *Basic outcomes of the radiation and epidemiological investigations of the Russian medical and dosimetric registry between 1986 and 1998*; and Dr. Yuri Konstantinov, visiting professor at RIRBM, *Radiation doses to the population in the western districts of the Bryansk region following the Chernobyl accident*.

That afternoon, Dr. Nanao Kamata, of RIRBM, chaired the hematology presentations: Dr. Nobutaka Imamura, of RIRBM, *Establishment of the Japanese Ukrainian Leukemia/Lymphoma Study Group (JULSG)*; Professor D. F. Gluzman, of the Department of Immunocytochemistry of the R. E. Kavetsky Institute of Experimental Pathology, Oncology, and Ra-

diobiology of the National Academy of Science of Ukraine (Kavetsky Institute/UNAS), *Six-year experience of the Ukrainian Reference Laboratory in morphological, cytochemical, and immunocytological diagnostics of malignant diseases of hemopoietic and lymphoid tissue*; and Dr. I. V. Abramenko, also of the Kavetsky Institute/UNAS, *Immunophenotypical patterns of acute leukemias in the children of Ukraine living in regions of radiological control*.



Japanese Foreign Ministry Assistant Division Chief Akira Maejima greets symposium participants. Seated from his left are RERF Chairman Shigenobu Nagataki, Vice Chairman and Chief of Research Sheldon Wolff, and Associate Chief of Research Clark W. Heath, Jr.

The second day began with three thyroid disease presentations in a session chaired by Dr. Ichiro Sekine, of the Nagasaki University School of Medicine Atomic Disease Institute (NUSMADI): Professor A. E. Baranov, of Moscow's Institute of Biophysics, *Medical management and victim treatment of Chernobyl and non-Chernobyl radiation accidents in Russia*; Professor G. Gerasimov, of Moscow's Institute of Clinical Endocrinology, *Iodine deficiency and radiation-induced thyroid diseases*; and Professor Shunichi Yamashita, of NUSMADI, *1998 Japanese thyroid screening in the area surrounding Chernobyl*.

In the final afternoon session, RERF Associate Chief of Research Clark W. Heath, Jr., chaired three presentations concerning data processing: Dr. Andrei Nadejine, of Moscow's Institute of Biophysics, *A system for monitoring the health status of people exposed to ionizing radiation from radiation accidents*; Dr. V. M. Drozd, of the Department of Endocrinology of the Research Institute of Radiation Medicine and Endocrinology, in Minsk, Belarus, *Ultrasound particularities of radiation-induced thyroid cancer in children of Belarus*; and RERF's Kazuo Neriishi, *Subclinical*

inflammation in the A-bomb survivors.

This was the first symposium to come out of a project planned after Soviet Union President Mikhail Gorbachev's 1991 Japanese visit, when the two countries envisioned "a conference of Japanese and Soviet experts on the Chernobyl Power Plant accident." In the early years of the project, Japanese representatives and their areas of expertise were: then-RERF Chairman Itsuzo Shigematsu, registry and epidemiology; then-NIRS Director-General Hiromichi Matsudaira, dosimetry; then-Research Institute for Nuclear Medicine and Biology (today RIRBM) Director-General Jun Kuramoto, hematology; and then-Nagasaki University medical school dean and professor and current RERF Chairman Shigenobu Nagataki, thyroid study.

Soviet representatives and their areas of expertise were: Dr. Leonid A. Ilyin, of the Moscow Institute of Biophysics, radiation hygiene, epidemiology, and radiology; Dr. Pavel V. Ramsaev, of the Institute of Radiation Hygiene in St. Petersburg, radiation hygiene; Dr. Anatoly F. Tsyb, of the Medical Radiological Research Center, RAMS, in Obninsk, endocrinology, oncology, radiology, and epidemiology; Dr. I. I. Dedov, of Moscow's All-Russian Research Center of Endocrinology, endocrinology; Dr. Eugeny P. Demidchik, of the Republican Center of Thyroid Oncology, in Minsk, oncology; Dr. Larisa N. Astachova, Department of Thyroid Pathology, Republican Hospital, Minsk, Belarus, pediatrics and thyroidology; and from Kiev's Research Center for Radiation Medicine, Drs. Anatoly E. Romanenko, radiation medicine; Nikolai D. Tronko, oncology and thyroid surgery; and Ilja A. Likhtarev, dosimetry.

This February symposium provided the first opportunity for many of the three new independent state (NIS; Belarus, Russia, and Ukraine) investigators to meet since the breakup of the Soviet Union. Because the socioeconomic situation remains poor in NIS countries, the exchange program is vital as an information source on recent developments. The data base of Chernobyl patient medical records is well established and ready for analysis. Earlier project efforts included only exchanges of researchers; this was the first symposium, and another is planned for about the same time next year.

Nagasaki Anniversary, continued from page 1

Commemorative Ceremony

At the anniversary ceremony, following congratulatory greetings from the Ministry of Health and Welfare, Nagasaki University, the prefectural governor, and the city's deputy mayor, RERF Chairman Shigenobu Nagataki presented certificates of appreciation to those individuals and groups who have supported ABCC-RERF's mission through the years. Recipients included representatives of the Adult Health Study, Nagasaki University, the Nagasaki University School of Medicine, Nagasaki University Hospital, Nagasaki University School of Medicine's Atomic Disease Institute, the Nagasaki city and prefectural medical associations, the Nagasaki Prefectural Nursing Association, and ABCC-RERF's retirees. Nagasaki University President Takayoshi Ikeda then gave the keynote speech, and guests were invited to attend a reception following the ceremony.

Dr. Ikeda: "Expectations for RERF's Future"

Looking to the Foundation's future, Dr. Ikeda spoke of how RERF's mission, "to conduct research and studies for peaceful purposes on the medical effects of radiation on humans with a view to contributing to the health and welfare of atomic-bomb survivors and to the enhancement of the health of all mankind," plays out internationally as the radiation from nuclear testing and accidents and other sources makes the elucidation of radiation-induced disorders and their mechanisms of universal concern in finding appropriate therapies for potential health problems. Dr. Ikeda underlined the uniqueness and value of the data that have been compiled in 50 years for the many survivors in the RERF cohorts, data that have been used for hundreds of investigations to date and which will prove of further value as the study population ages and new relationships may be ascertained.

He emphasized the need to continue the data collection and the follow-up of survivors and their offspring, calling for RERF to plan its studies "with prospects for the next 50 years." He also called for the continued collection and maintenance of biological specimens, again noting the potential value of those materials for studies that may be conducted in the future, after new scientific methods are developed that can use the materials for as yet impossible investigations. With respect to all of its data and tissue collection activities, Dr. Ikeda underscored the relationship that has been established between RERF and its study participants, a relationship founded in trust and nurtured by the caring manner in which RERF staff have treated those participating in its research. Dr. Ikeda further noted that it will be of even greater importance that RERF maintain its close relationship with outside medical institutes as the population ages and participants find themselves hospitalized for various health problems, also a consideration for successful maintenance of the local cancer registries.

Open House

The November 3 (Culture Day in Japan) open house, the Nagasaki's laboratory's second since ABCC's reorganization as RERF in 1975, provided an opportunity

Continued on next page



Relocation to the Kyoiku Kaikan (Education Center) owned by the Nagasaki Prefectural Education Maintenance Foundation was complete by 1 July 1950. The larger facility provided much needed space to ABCC's growing activities and allowed for more in-depth studies to be undertaken. (ABCC file photo)



On 1 April 1975, ABCC was reorganized and the Radiation Effects Research Foundation was established with equal funding to be provided by the Japanese and American governments. Nagasaki acting laboratory chief, Sadahisa Kawamoto (left) and Director Raisuke Shirabe (right) make adjustments to new nameplate. (RERF file photo)



Construction of the RERF-Nagasaki Prefectural Education Maintenance Foundation building, RERF Nagasaki's current home was completed 17 September 1982 despite a July storm that produced torrential rains and flooding, killing more than 300 people and destroying numerous homes, buildings, and roads. (This drawing is the work of Tadashi Nakaoka, who retired from the Nagasaki Secretariat in June 1996.)

8 Nagasaki Laboratory Golden Anniversary

Continued from previous page

to educate the public and perhaps assuage any uncertainties they might have regarding the foundation's activities and to bolster community support. Among other activities, guests were invited to view panels offering a pictorial history of RERF and explanations of studies and study results, to inspect ultrasound equipment used in thyroid examinations and observe the operation of a blood analyzer, to compare normal and cancerous cells under a microscope, and to have their blood pressure taken and body fat calculated. Questionnaires completed by visitors at the open house were encouraging, reflecting the attitudes that RERF's efforts have been well received and that the community appreciates the opportunity to look more closely at our laboratories and research and that participants in our studies are pleased to understand how their biennial examinations contribute to study results that have international impact.

Japanese Newsletter Commemorative Edition

As an earlier commemorative activity, a special issue of RERF's *Japanese Newsletter*, published 28 August, recorded the congratulatory remarks and reminiscences from RERF's current directors, former ABCC associates, a representative of the AHS cohort, and the chairman of the Nagasaki Association for Hibakushas' Medical Care (NASHIM), who is also president of the Nagasaki Prefecture Medical Association. Following is a condensation of some of that material.

A Brief History of Nagasaki's RERF Laboratory

In March 1947, with funding from the U. S. Atomic Energy Commission, ABCC was established following the 1946 directive of American President Harry S. Truman to the National Academy of Sciences to undertake long-term evaluation of the health effects from radiation from the Japanese atomic bombings. President Truman was responding to the recommendation of a joint commission of American and Japanese specialists who had carried out a detailed investigation of the acute health effects experienced by residents of the two bombed cities.

ABCC's first Nagasaki home in July 1948 was space rented in the Shinkozen Elementary School from the first hospital of the Nagasaki Medical College, which had relocated there after the bombing (cover picture). However, that space was limited and ABCC relocated to the Nagasaki Prefectural Education Center 1 July 1950, where it remained for more than 30 years. Finally, a new building was constructed that has been the laboratory's home since 1 October 1982. (*Each of these facilities is pictured on previous page.*)

The Nagasaki laboratory developed from the unique needs of the atomic-bombing survivors in that community. Different types of bombs exploded over the cities, and the topography and bombing hypocenters were different, affecting each city in different ways. The August 9 plutonium bombing of Nagasaki three days after the uranium bombing of Hiroshima in 1945, left 73,884 dead and 74,909 injured. (This is an estimation as of 31 December 1945 as surveyed in 1950 by the Nagasaki City A-bomb Archives Committee.) According to the 1950 Japanese national census survey, 124,901 persons, 58,920 males and 65,981 females, were exposed to the bombing in Nagasaki, including ten who were also exposed to the uranium bomb in Hiroshima.

Through the years, about half of the Nagasaki survivors have died, and others have been lost to clinical follow-up through migration from the area. The average age of those remaining is approaching 70. However, in Nagasaki, 1,072 survivors have participated in every examination cycle, an impressive number. The biennial health examinations constitute the core of ABCC-RERF clinical studies, and their success depends on the faithful participation of such survivors.

In his comments for the commemorative newsletter, RERF Chairman Shigenobu Nagataki, who is the former dean of the Nagasaki University School of Medicine, identified an underlying key to the continued trust and participation of survivors as ABCC-RERF's long-term collaborative efforts with the Faculty of Medicine of the Nagasaki University. In particular, he cited the school's history prior to the bombing, its proximity to the hypocenter, and ABCC's presence as an educational institution providing Nagasaki University professors with access to the latest scientific papers and state-of-the-art research techniques. A second factor in the Foundation's success pointed out by Dr. Nagataki was the former RERF directorship of Professor Raisuke Shirabe (*pictured on previous page*), an atomic-bombing survivor himself and authority on radiation medicine, an individual well respected by the Nagasaki community.

Nagasaki University President Ikeda, who was medical school dean and a professor in the First Department of Pathology there when he wrote for the special newsletter last summer, began his affiliation with ABCC in 1960, when he helped perform autopsies at ABCC as part of his duties as an assistant at Nagasaki University. As Dr. Nagataki noted, ABCC had the largest collection of foreign journals then available, and Dr. Ikeda took full advantage of the opportunities that provided. Dr. Ikeda reported that he, like many others, was appreciative of the many resources available at ABCC.

However, according to Dr. Ikeda, with the reorganization of ABCC into RERF in 1975, changes were made that affected the community's perceptions of the Foundation. With a tightening of the budget came the discontinuation of ABCC-RERF's long-standing histological and pathological autopsy activities, an event Dr. Ikeda said led to a certain distrust because the decision was one-sided and the local medical associations and the university medical school were not in agreement.

As in his keynote address, Dr. Ikeda also cited the significance of ABCC-RERF's contribution to the work of the Nagasaki City Medical Association's cancer and tissue registries along with that of the Nagasaki University School of Medicine. Dr. Ikeda explained that the local tumor tissue registry began in 1974 with funds from the U. S. National Cancer Institute and that it continues to be operated by RERF and the Nagasaki University School of Medicine though it belongs to the Nagasaki City Medical Association and the prefecture. (In fact, a tumor statistics committee was established in the Nagasaki City Medical Association in 1958.) Dr. Ikeda is concerned now that ongoing cutbacks may threaten the cancer registry.

Nagasaki Association for Hibakushas' Medical Care (NASHIM)

Dr. Tetsuya Iseki, NASHIM chairman and president of Nagasaki's prefectural medical association, offered words of gratitude for ABCC-RERF's 50 years of continuous

support of the health and welfare of the hibakushas (atomic-bomb survivors) and RERF's participation on NASHIM's board of directors and operating committee since the organization's establishment. He particularly thanked Dr. Nagataki, who has been the group's vice chairman from its beginning.

NASHIM comprises representatives from RERF, Nagasaki University, and the city and prefectural medical associations and offices, and it is involved in training and dispatching medical specialists around the world, supporting A-bomb survivors outside Japan for medical care in Japan, disseminating information to educate the public, and publishing books and journals related to the medical care of the survivors. Recently, it has conducted an international symposium and established an annual international peace memorial award.

Dr. Iseki expressed his appreciation for RERF's active role in accepting trainees from abroad, including countries in the former Soviet Union, and he praised RERF as a model to be followed internationally for its pioneering efforts on behalf of the hibakushas.

Interview with an A-bomb Survivor and RERF Adult Health Study (AHS) Participant

Mr. Yoshiji Kajihara, an AHS participant for more than 40 years and president of the town association where the Nagasaki laboratory is located, answered questions describing his experiences with ABCC-RERF through the years in an interview for the special newsletter. The morning of 9 August 1945, Mr. Kajihara recalled, he took refuge in an air-raid shelter at his place of employment, Mitsubishi Heavy Industries, following air-raid sirens and the order to seek shelter. He said that "people remaining outside had their hair, eyebrows, and faces burned," that the "Urakami area was a sea of fire and invisible." "On every street," he remembered, "lay people's charred bodies," and then he added, "I wonder now how I could have survived."

In response to a question regarding the 1975 reorganization, Mr. Kajihara turned to his involvement with ABCC-RERF, pointing out that the organization's name change, from the English Atomic Bomb Casualty Commission to the Japanese Hoshasen Eikyo Kenkyusho, made the Foundation's activity easier to understand. Elaborating, he said, "Some atomic-bomb survivors criticized that ABCC was examining study subjects to determine the effects of the atomic bombs dropped by the United States on human beings." However, he remarked, "leaving aside the question of whether this is good or bad, I feel it is proper for the sake of mankind to study the effects of the atomic bombs on the human body." In this regard, in answer to a later question, Mr. Kajihara noted, "As an A-bomb survivor, the biennial examination I undergo here is my moral support." As to the benefits he has experienced as a study participant, Mr. Kajihara said, "There is no need for me to have a complete medical examination elsewhere because I receive a more detailed examination here. It gives me much hope and peace of mind, and I am thankful."

Though RERF's relocation to its current location presented some difficulty just after Mr. Kajihara became president of the town association ("A request was made to supplant the road running through the proposed site."), he said that the town ultimately "felt that it was desirable

to have a facility like RERF in the community." And, now, with regard to RERF holding open houses, Mr. Kajihara opined, "I think it is desirable for RERF to open its facilities to the public and explain what it is doing."

RERF's Future

In recent years, with a reduction in funding has come a reduction in staff at both RERF laboratories; Nagasaki has lost one-third of its research scientists and half of its general employees. These are issues of general concern. However, in the last year, with the reactivation of the Nagasaki Local Liaison Council and the Nagasaki laboratory's first open house since ABCC was reorganized into RERF, the Nagasaki laboratory is being revitalized.

Looking into the 21st century, Dr. Taira, RERF director in charge of the Nagasaki laboratory, remarks upon the need for an increased number of researchers in Nagasaki to conduct studies in close cooperation with Nagasaki University and the Atomic Bomb Institute of its medical school. As new techniques are developed, Dr. Taira looks forward to the development of new research programs never before possible.

New Software Simplifies Data Access

by Eric Grant, Research Scientist, Epidemiology

In response to the need for simple, unimpeded access to RERF data, we have developed a new application, which we call Easy Click. It automatically assembles requested data in a form with which researchers are familiar and that they can use immediately.

RERF's database system plays a central role in the Foundation's research efforts. Managed by the Information Technology Department, the system is charged with archiving all data collected since ABCC's inception in addition to managing and storing new information as it is collected from a variety of sources.

RERF uses a relational data base, which structures data into many tables with small numbers of variables that are related to one another by links or keys. This contrasts with a design of fewer larger stand-alone tables with many variables. Advantages to the relational design include easier maintenance, capability to extend the data base for future projects without disrupting existing tables, data consistency, and lockout of private data that should not be available for general access. However, as a consequence of having the data spread out over many tables, putting the data back together in response to an investigator's request becomes more complex. A user must: (1) have an understanding of the data location (table names) and variable names; (2) know the key(s) that relate the different tables; and (3) know how to write a command to assemble these tables and variables. Without aid, the researcher's efforts might be impeded, forcing reliance on database experts to perform these tasks.

Easy Click provides a list of RERF's most common variables via a point-and-click interface. The user selects which variables and cohort they are interested in and supply a password, and Easy Click dynamically generates and dispatches a command statement to create a new table with these variables. The relational database server creates the new table in response to the request. This process is fast because the server is designed to quickly handle such requests and there is little network traffic involved in this process. In addition to these features, Easy Click

See New Software on page 21

A Short Review on the Development of Radiation-Induced Cancers in Humans: Molecular Lessons from the Atomic-Bomb Survivors

by Keisuke S. Iwamoto, Senior Scientist, Department of Radiobiology

Introduction

Ionizing radiation is known to cause cancer in humans, though the mechanisms are unclear. The current understanding of cancer development centers around the multi-stage theory of carcinogenesis, where a number of genetic and epigenetic events are required before a normal cell becomes a cancer cell.¹ To begin to understand the role of ionizing radiation in cancer development, it is important to recognize the types of changes incurred in an irradiated cell. In broad terms, the changes can be categorized as physical and biological.

One of the major cellular targets of ionizing radiation is DNA. The most important damage that ionizing radiation can inflict on DNA is the double-strand break.² Unrepaired or imperfectly repaired double-strand breaks can lead to gross alterations of chromosomes, such as deletions, translocations, and inversions, or to more subtle changes, such as point mutations.

This article briefly summarizes work done in the Department of Radiobiology demonstrating, first, that ionizing radiation can dose-dependently induce DNA damage in cancer-related genes, the physical aspect; second, that such induced damage is selectively determined by cellular factors, the biological aspect; and third, that during the long process of human radiation-carcinogenesis, further biologic changes are actively induced long after actual radiation exposure. The evidence supporting these hypotheses has been generated through *in vitro* and *in vivo* systems and through molecular epidemiological investigations using archival tissues from the atomic-bomb survivors.

Creation of cancer-specific gene damage: *In vitro*^{3,4}

Specific translocations, such as *BCR-ABL*, and inversions, such as *H4-RET*, are well recognized fusion genes in radiogenic cancers, such as chronic myelogenous leukemia (CML) and papillary thyroid carcinoma, respectively. To determine whether such characteristic aberrations can be induced in cells irradiated *in vitro*, Daudi (Burkitt's lymphoma), HT1080 (fibrosarcoma), and 8505C (thyroid carcinoma) cell lines were irradiated to doses of 10, 50, and 100 Gy. *BCR-ABL* was examined in the Daudi, HT1080, and 8505C cells, and *H4-RET* was examined in HT1080 and 8505C cells using reverse transcription polymerase chain reaction (RT-PCR). Independent of cell origin, both the *BCR-ABL* translocation and the *H4-RET* inversion were detected in a dose-dependent manner 48 hours after irradiation (Fig. 1). These results demonstrate that ionizing radiation can indeed create cancer-related gene alterations, albeit at low frequency and randomly.

Selection of tissue-specific cancer genes: *In vivo*⁵

Then, why do radiation-induced CMLs possess *BCR-ABL* but not *H4-RET*, and why do papillary thyroid carcinomas possess *H4-RET* but not *BCR-ABL*? At this point, biology must be taken into greater consideration. To il-

lustrate this *in vivo*, human thyroid tissue grafted into severe combined immunodeficient (SCID) mice were irradiated and the tissues examined again for *BCR-ABL* and *H4-RET*, allowing 48 hours, seven days, and two months for the tissues to respond to the insult (Fig. 2, bottom, next page). As expected, neither fusion gene was detected in the unirradiated controls, and both fusion genes were detected in the tissues 48 hours postirradiation, which confirmed the 48-hour *in vitro* experiment. Moreover, in the tissues harvested at 48 hours, atypical (those not associated with the particular cancer) and typical (those associated with the particular cancer) forms of *BCR-ABL* and *H4-RET* were found. Interestingly, the *BCR-ABL* gene could no longer be detected in the irradiated thyroid tissues seven days and two months postirradiation, but the *H4-RET* gene remained and, in fact, increased in frequency. Moreover, the atypical forms found at 48 hours had disappeared and only a high frequency of typical forms were left. These results illustrate that the biological selection of randomly induced lesions is one factor important in radiation carcinogenesis.

However, not all radiation-induced human cancers have known translocations or inversions associated with them, though many cancers do exhibit loss of heterozygosity, which indicates the deletion of a gene or genes. And, as mentioned earlier, deletions are one of the most frequently observed damages following ionizing irradiation. The most likely target genes to deletions are tumor suppressor genes because loss of function of these genes is all that is required to advance the carcinogenic process. Thus, investigation of one of the radiogenic cancers in the atomic-bomb survivors was initiated.

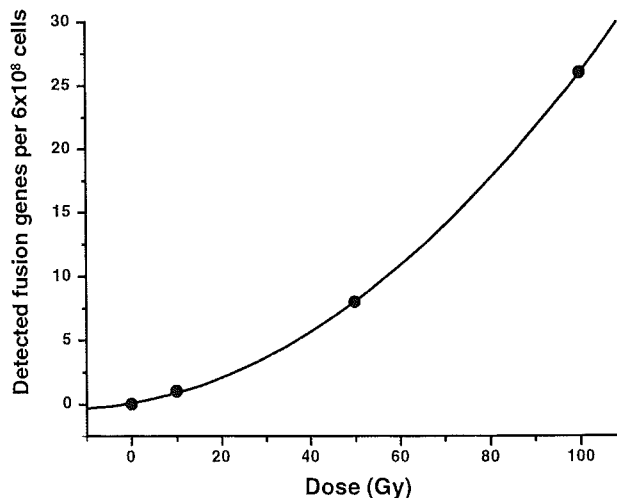


Figure 1. Dose-dependent increase in the number of fusion genes detected. Either *BCR-ABL* or *H4-RET* fusion genes were counted and summed. Gene analysis was done 48 hours after irradiation.

p53 mutations in hepatocellular carcinomas: Atomic-bomb survivors⁶

The mechanism of liver carcinogenesis is unclear, although it is believed to involve multiple endogenous and exogenous genetic alterations. One form of liver cancer, hepatocellular carcinoma (HCC), is particularly common in Africa and Asia, including Japan.⁷ Studies have demonstrated a strong association between HCC and hepatitis B and C virus infections.⁸ The HCC cells also exhibit frequent allelic losses on specific chromosomal arms in their nuclei, particularly losses in the single most commonly mutated gene in human cancers, the tumor suppressor gene *p53*.⁹

Because of the relatively long latency period, the mechanistic role of ionizing radiation in the dose-dependent increased frequency of HCC among the atomic-bomb survivors of Hiroshima and Nagasaki is not clear.¹⁰ To shed some light on the molecular events that may, in part, help to explain the heightened risk of atomic-bomb-induced HCC, the *p53* gene was analyzed in the HCC tissue samples from 120 survivors of the atomic-bomb explosions, who were exposed to various doses of radiation.

There was no difference among the four groups with respect to frequency of deletions. Restriction-fragment-length polymorphism analysis demonstrated loss of heterozygosity in 32% of the informative samples.

However, there was a statistically significant dose-response relationship in the percent of HCC samples harboring a *p53* point mutation in the tumor tissues (Fig. 3). The background frequency of 46% that we found is similar to the frequency in the general Japanese population reported by Oda *et al.*⁹ It is striking that there was a dose-response relationship for point mutations but not for deletions, which are one of the major types of DNA damage thought to be caused by ionizing radiation.² One consider-

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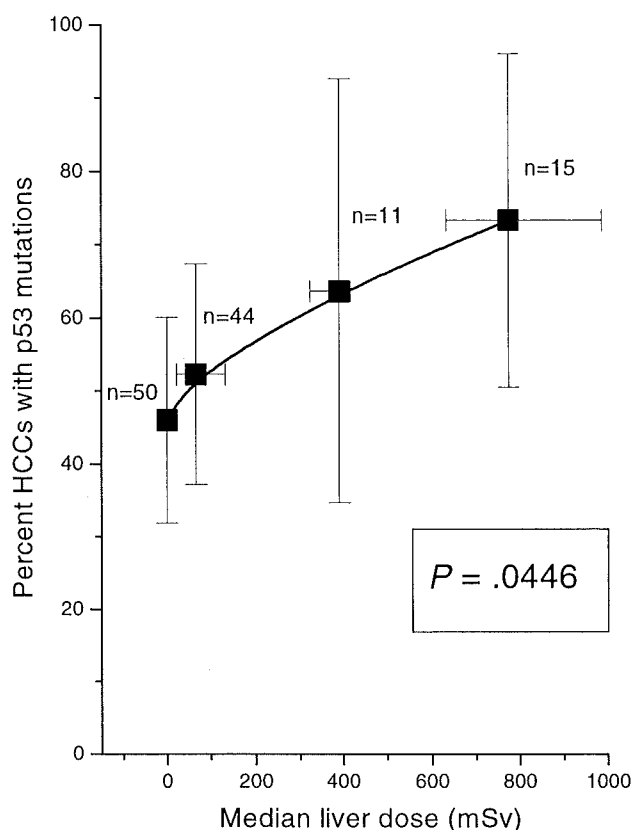


Figure 3. Percent of hepatocellular carcinoma (HCC) samples with p53 mutations as a function of the dose of atomic-bomb radiation to the liver. Statistical analysis was applied to the ungrouped data. The error bars for the percent of HCCs with p53 mutations denote two standard errors, and the error bars for the median liver dose denote the 25th and 75th quartiles of the dose-grouped data. The P value is two-sided. (Figure adapted from reference 6.)

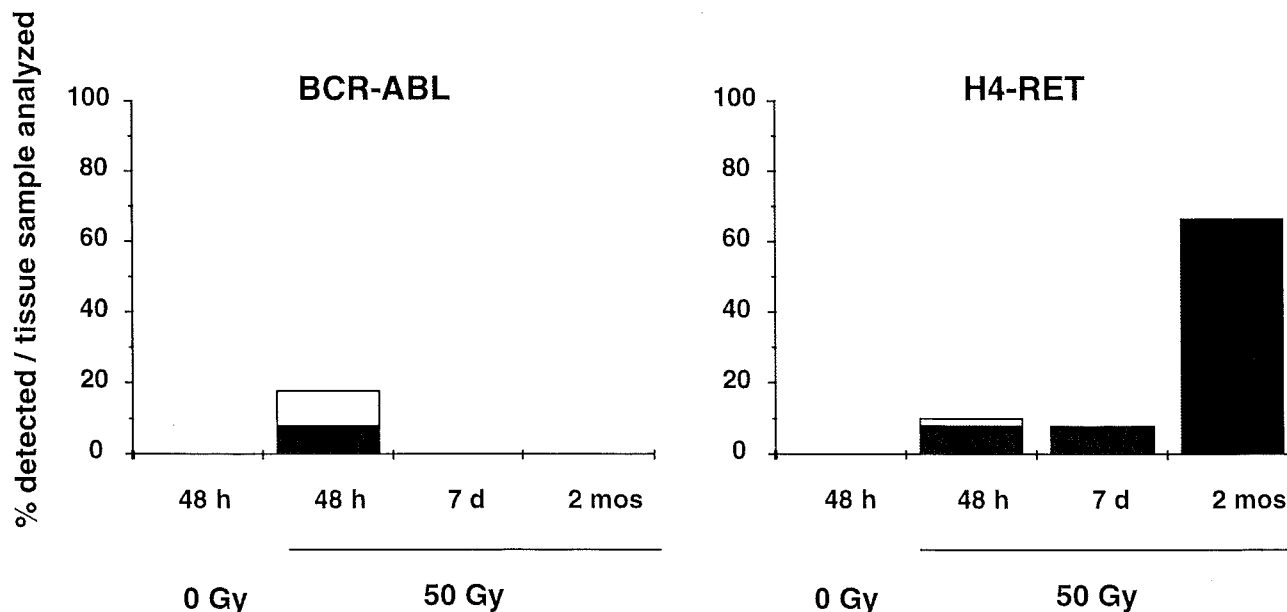


Figure 2. Selection of tissue-specific fusion genes. Creation and continued expression of both BCR-ABL and H4-RET fusion genes were examined in human thyroid tissue grafted into SCID mice at several time points following irradiation. Open bars represent atypical fusions (not associated with the disease), and closed bars represent typical fusions (associated with the disease).

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ation is that cells with deletions could have died early, leading to a negative selection of deletion-type damage.

The dose-dependent enrichment of cells with *p53* mutations in the tumors is probably caused by expansion of cells with *p53* mutations plus mutations in other genes that allow unregulated growth. The direct radiation target is more likely to be a gene that is changed into a mutator by a radiation-induced mutation. The induction of a mutator gene would be expected to increase with dose and would allow a single cell or its progeny to accumulate multiple mutations necessary for the conversion of a normal to a cancer cell.

Supportive evidence for creation of a mutator gene is found in the study by Cha *et al.*,¹¹ who demonstrated that *N*-nitroso-*N*-methylurea exposure was not directly responsible for the mutations in the *H-ras* proto-oncogene that are frequently found in *N*-nitroso-*N*-methylurea-induced rat mammary tumors (and, in fact, that the *H-ras* mutations were shown to pre-exist rather than be generated at a later time). Further support is found from *p53*-knock-out mice that demonstrate enhanced HCC development after exposure to liver carcinogens.¹² Such studies, as well as the one conducted in the Department of Radiobiology, emphasize the importance of conditional mutations whose oncogenic potentials are realized after exposure to a carcinogen and concomitant damage of another gene.¹³ Thus, one would expect a dose-dependent rise in *p53* point mutations in the tumors.

Future studies in the survivor population on the associations of *p53* mutations with hepatitis B and C virus infections (found frequently in the Japanese HCC population), which lead to chronic cycles of cell loss, regeneration, and damage, should provide clearer clues to the etiology of radiation-induced human liver cancers.

Summary

Ionizing radiation can produce a variety of lesions in DNA. The creation of these lesions is more or less random and independent of the type of tissue irradiated. However, certain aberrations can be positively selected if they confer a survival advantage to the cell, which may in large part be determined by the type of cell. Thus, only the *H4-RET* fusion gene was retained in thyroid tissue, although both *H4-RET* and *BCR-ABL* were initially generated because *H4-RET* is important in thyroid carcinogenesis while *BCR-ABL* is only important in CML.

However, these results do not preclude the importance of radiation damage in promoting genomic instability by the damage or deletion of a gene whose dysfunction or loss creates a mutator phenotype. In the HCCs of the atomic-bomb survivors, this mutator phenotype appears manifested by the dose independence of *p53* deletions and the dose dependence of *p53* point mutations.

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This investigation using human archival tissues samples was approved by an institutional review board.

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Multidepartmental Research on Radiation and Liver Cancer

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Since the completion of comprehensive analyses of cancer incidence in the Life Span Study (LSS) of atomic-bomb survivors,¹ the emphasis in studying radiation effects has turned to site-specific investigations. (See "Site-specific Cancer Incidence: An Interim Report," *RERF Update* 7[1]:6, 1995.) This approach allows more thorough analysis of radiation effects with three aims: 1) diagnostic confirmation and determination of histologic subtype of cancer through pathology review, 2) adjustment for possible confounding by other important risk factors, and 3) the testing of possible interactions between radiation and other risk factors. Diagnostic confirmation and measurement of other risk factors are critical in the case of primary liver cancer (PLC) because a large proportion of diagnoses are based on cause of death only and because viral hepatitis plays an important role in its etiology. This article describes the current status of research on primary liver cancer and associated radiation effects by a multidepartmental collaborative working group at RERF.

A number of interesting research needs are being addressed by the RERF site-specific study of liver cancer. Alpha irradiation from Thorotrast, a contrast medium used for medical imaging, is a known liver carcinogen^{2,3,4} primarily linked to an increased risk of cholangiocarcinoma. However, liver carcinogenicity of the predominantly gamma irradiation from the atomic bombs has not been as firmly established as with Thorotrast, nor is it known whether whole-body exposures resulting from atomic-bomb radiation leads to cholangiocarcinoma or to the major form of primary liver cancer, hepatocellular carcinoma. By using cases accepted after careful pathological review, we can more reliably assess the dose response, distinguish hepatocellular carcinoma from cholangiocarcinoma, investigate a possible gender difference in radiation effect, and study possible differential sensitivity by age at exposure. The availability of tissue specimens makes it possible to conduct molecular studies. Hepatitis infection in cases and a set of controls is being assessed through polymerase chain reaction (PCR) for hepatitis B virus (HBV, a DNA virus) and reverse-transcriptase PCR for hepatitis C virus (HCV, an RNA virus). A preliminary report on the PCR work has already appeared in *RERF Update* ("Investigating the Link between Liver Cancer and Hepatitis," *RERF Update* 6[3]:6, 1994). Analysis of the case-control data allows testing for interaction between radiation and hepatitis viruses in the occurrence of liver cancer as well as the examination of other risk factors (smoking, alcohol consumption, and occupation) measured in the LSS mail surveys. Data on mutations at *p53* and other loci can be used to test hypotheses about the relationship of various genes to stage and lethality of liver tumors.

A panel of three pathologists (Toshiyuki Fukuhara, *RERF expert advisor and Department of Pathology, Hiroshima Prefectural Hospital*; Hideyo Itakura, *RERF*

consultant and Department of Pathology, Institute of Tropical Medicine, Nagasaki University; and Masami Yamamoto, *Department of Hospital Pathology, Hiroshima University Hospital*) reviewed 3,902 known or potential cases of primary liver cancer. Eight hundred and thirty cases of primary liver cancer diagnosed in the study period (January 1, 1958 to December 31, 1987) were accepted. A subset of 364 histologically diagnosed cases were the basis of a case-control study and were matched to controls from the RERF autopsy series who had available liver tissue; the pathologists judged case and control slides for evidence of chronic hepatitis and cirrhosis. To date, scientific reports have been produced detailing the pathology review, analyses of primary liver cancer incidence in the LSS cohort, and results of the *p53* mutation study. The remainder of this article will summarize the current findings for incidence and case-control studies and review the work that is in progress.

PLC incidence. In all, 79,894 members of the LSS cohort met the inclusion criteria for the study: 1) in Hiroshima or Nagasaki at the time of the bombings, 2) known whole-body kerma dose under 4 Gray, and 3) alive and not previously diagnosed with cancer at the start of cancer-incidence follow-up (January 1, 1958). Cases were excluded if liver cancer was diagnosed outside of the tumor-registry catchment areas of Hiroshima and Nagasaki prefectures (where ascertainment is incomplete). Follow-up was discontinued for persons with first primary cancer other than liver cancer at the time of first cancer diagnosis. As with all LSS analyses, person-year denominators were adjusted for out-migration as estimated for the AHS subset, and correction for measurement-error bias was made in the dose-response regression.

We detected a significant excess relative risk of primary liver cancer for radiation (0.81 per Sievert; 95% CI 0.32–0.43; Figure 1). There was no evidence of a gender difference in dose response, although the relatively small number of female cases meant few excess (radiation-related) cases would be expected, so there was little power to discriminate a gender sensitivity if one existed. Nevertheless, separate male/female estimates of relative risk were virtually identical. This is contrary to the suggestion of a gender difference in the previous incidence analysis, which we believe is due to a difference in background liver-cancer incidence between proximally and distally exposed surviving women. Age-/time-/city-adjusted liver-cancer incidence in the distally exposed surviving women was 1.6 times higher than the background incidence predicted by the intercept of the dose-response regression. Because a large number of persons in the LSS cohort were exposed to extremely low doses of radiation, the regression intercept is a reliable estimate of background incidence. This estimate is not subject to possible bias from model extrapolation or geographical differences in unmeasured,

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unadjusted factors (such as lifestyle, socioeconomic status, and occupation) that could affect mortality rates between urban and rural populations.

There was a curious peak in radiation sensitivity with age at exposure that occurred in persons exposed during their late teens to early twenties (Figure 2). This result was statistically significant (as compared to monotone age-at-exposure effect modifiers), but its explanation is speculative. One possibility is confounding by hepatitis-B virus (HBV) infection, which has been shown to be related to both radiation dose and age in studies conducted in the Adult Health Study, so that unmeasured HBV infection status in the LSS incidence analysis could induce a relationship between dose and age at exposure. Alternatively, given that most of the liver-cancer cases occurred in males, a report of elevated serum testosterone as a risk factor for hepatocellular carcinoma⁵ suggests another possible explanation if one postulates that the elevated relative risk for radiation during adolescence is limited primarily to males (which cannot be ruled out given the lack of power for discriminating male/female risk).

It was not possible to discern a difference in radiation dose response for hepatocellular carcinoma versus cholangiocarcinoma because of a very small number of cholangiocarcinoma cases. No excess cases of cholangiocarcinoma were observed in the 1+ Sv dose group, but only one excess case would be predicted if the dose response for cholangiocarcinoma were the same as that for hepatocellular carcinoma. This difference (one expected, zero observed) is not statistically significant; therefore, we cannot say conclusively whether cholangiocarcinoma is related to atomic-bomb radiation exposure. However, the small number of observed cholangiocarcinoma cases demonstrates that this is not the predominant form of liver cancer arising from atomic-bomb radiation exposure (i.e., whole-body gamma-neutron exposure), as is the case with Thorotrast.

Case-control study. A case-control study nested within the LSS cohort was designed to measure viral hepatitis infection status in the cases and in a sample of controls. (It would be impossible to use the entire LSS since deceased members can no longer be tested, while living members would have to be contacted and requested to donate serum, an undertaking that would be prohibitively expensive and time-consuming given the tens of thousands of cohort members still alive). To assure availability of liver tissue for the assessment of viral hepatitis and prevalence of cirrhosis, controls were selected from the RERF autopsy series and matched to cases on age/year of death, city, gender, and radiation dose.⁶

The primary motivation for the case-control study was two-fold: 1) to determine the extent of confounding—if any—of the radiation effect on liver cancer by viral hepatitis and 2) to assess whether there is any interaction between radiation and viral hepatitis in the etiology of liver cancer. Unfortunately, because nested case-control studies of interaction generally lack statistical power,⁷ the decision was made to match on radiation dose, which precludes the assessment of confounding. (More recently, designs have been developed that would allow assessment of confounding and provide greater statistical power than matching,⁸ but these designs were not available at the time the liver cancer study protocol was prepared.)

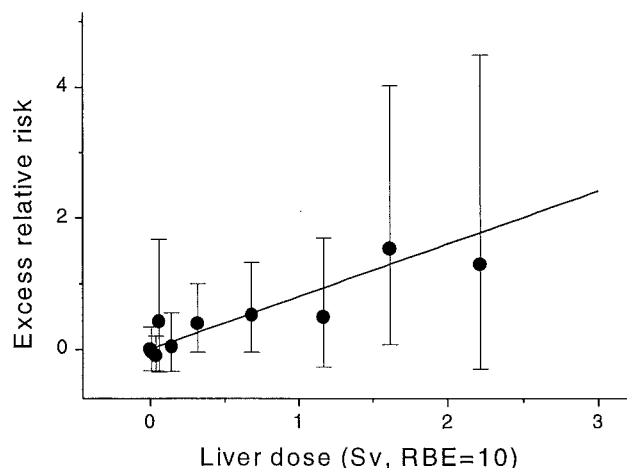


Figure 1. Excess relative risk for primary liver cancer from atomic-bomb radiation. Points are based on collapsing the dose strata used in the incidence analysis to reduce clutter. The line is from a linear-fitted excess relative risk function.

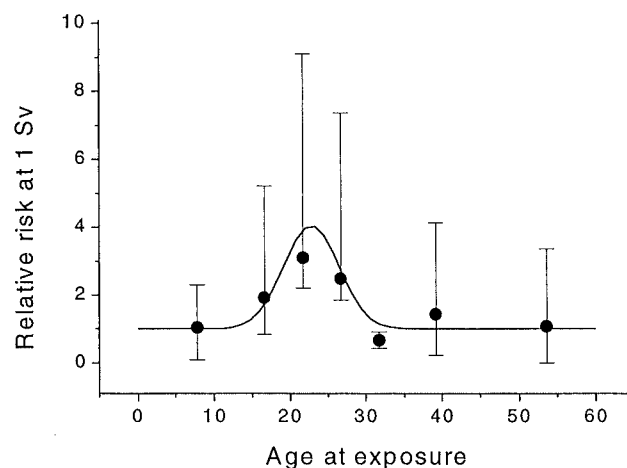


Figure 2. Dependence on age at exposure of the relative risk of primary liver cancer at 1 Sv, averaged over gender. Points are based on collapsing the age-at-exposure strata to reduce clutter. The line is based on an exponential-quadratic function multiplying a linear excess relative risk function.

HBV and HCV infection statuses were ascertained via PCR and reverse transcriptase (RT)-PCR by T.M. (Department of Radiobiology). Twenty-six percent of cases and 5% of controls were positive for HBV, and 46% of cases and 6% of controls were positive for HCV. Because RT-PCR for detecting HCV RNA virus in liver tissue stored for long periods as formalin-fixed and paraffin-embedded tissue blocks is a new technique, we have begun validating tissue-based results using cases and controls for whom serum samples were collected and stored in the Adult Health Study (*RERF RP 1-99, Addendum to RP 5-90*).

Preliminary analyses could not rule out a possible interaction between HCV and radiation but showed no evidence of interaction between HBV and radiation. More sophisticated analyses are currently underway using Charles Land's analytic approach to radiation-matched nested case-control studies.⁹

Other investigations. In addition to studying the risk of liver cancer following radiation exposure, G. S. (Department of Epidemiology) is currently investigating whether radiation exposure is related to survival after diagnosis of cholangiocarcinoma relative to that for hepatocellular carcinoma, after accounting for age at diagnosis and treatment modality (major factors in survival). These analyses will also examine whether viral hepatitis, associated cirrhosis, and/or various patterns of *p53* mutation play a role in survival. Stage is also an important factor in many cancers, but published data from other tumor registries in Japan have shown that stage is not strongly related to survival from liver cancer. Mutations at the *p53* locus were investigated by K.I.—Department of Radiobiology—in a subset of primary liver cancer cases, including all high-dose cases.¹⁰ (See page 10.) Results for analyses of survival so far suggest that survival from cholangiocarcinoma is shorter than from hepatocellular carcinoma and that patients with dual mutations at the *p53* locus (both alleles are non-wild type) appear to have shorter survival.

A study to determine the joint role of radiation and HCV infection on development of chronic liver diseases has been conducted in the AHS population. Although there was no evidence of a dose-response relationship of serum anti-HCV antibody positivity, preliminary results could not reject the possibility that the radiation dose response for chronic liver disease among anti-HCV-antibody-positive survivors may be greater than that among anti-HCV-antibody-negative survivors. Thus, radiation exposure may accelerate the progress of HCV-associated chronic liver diseases that precede cancer. This result is consistent with a possible HCV-radiation interaction in the liver-cancer case-control study and warrants further scrutiny.

Conclusion. Analyses conducted to date based on reviewed primary liver cancer cases have confirmed a relationship between atomic-bomb radiation and hepatocellular carcinoma and suggested an age-at-exposure effect with peak sensitivity around age 20. They have further demonstrated that investigations of the etiology of primary liver cancer should take subtype into account. Why Thorotrast leads predominantly to cholangiocarcinoma whereas atomic-bomb radiation apparently does not is not clearly understood but may be related to the uptake and residence of Thorotrast in connective tissue near the liver bile ducts whereas atomic-bomb radiation exposure should be roughly uniform to the entire liver. However, it is not known whether the radiation effect occurs at the level of precursor cells that give rise to both hepatocytes and bile duct cells or to partially differentiated cells that are committed to become one or the other. Nor is it known at which stage(s) in the pathogenesis of HCC or cholangiocarcinoma the radiation exerts its effect.

The complex nature of carcinogenesis means that epidemiologic studies alone are insufficient to elucidate mechanisms of radiation carcinogenesis. In addition, it is necessary to conduct studies that go beyond analyses of radiation alone in order to make certain of the radiation effects and to have confidence in applying risk estimates derived from the atomic-bomb survivor population because of possible confounding or effect modification by other factors that can vary across populations. The liver-cancer working group brings together scientists within RERF who

have expertise in epidemiology, molecular biology, clinical medicine, pathology, and statistics. By working together, we are now able to jointly examine the roles played by radiation and other risk factors in the etiology of this important cancer and to discern some of the mechanistic events associated with the relationships of these factors to primary liver cancer.

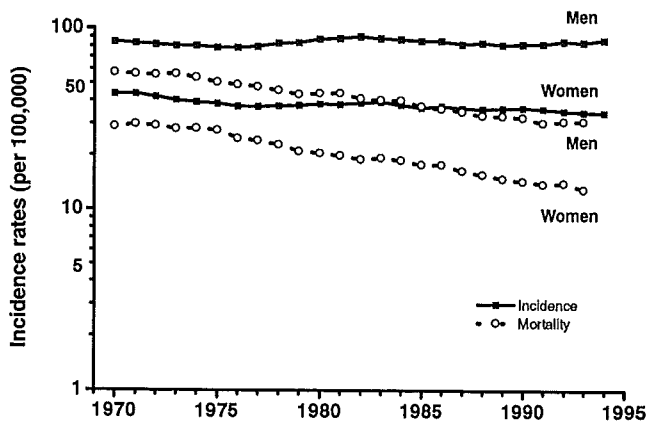
Acknowledgments. Substantial contributions to the design of the primary liver cancer site-specific study were made by Gilbert Beebe and Charles Land at the U.S. National Cancer Institute/Radiation Epidemiology Branch. These studies are under the guidance and overall management of Kiyohiko Mabuchi, chief of RERF's epidemiology department, Hiroshima. We are indebted to Dale Preston, chief, and Don Pierce, of RERF's statistics department, for many helpful suggestions concerning the analysis of the incidence data and radiation dose response.

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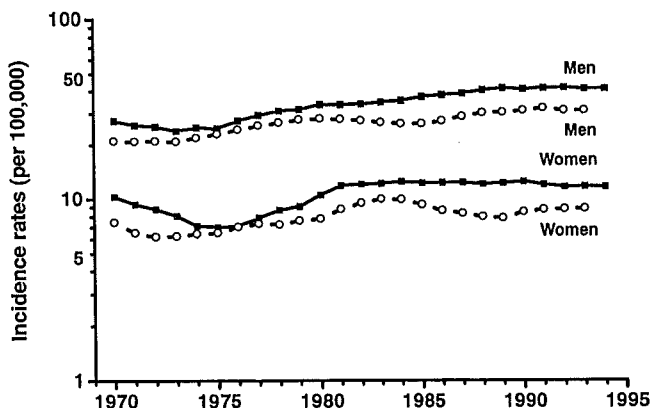
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Incidence and Mortality Trends for Stomach, Lung, and Breast Cancers in Hiroshima City, 1970-94

by Kojiro Koyama, Chief, Tumor and Tissue Registry Office



Stomach cancer. The incidence rate for stomach cancer in men was level throughout the study period (80-90 per 100,000). The rate in women decreased, but not remarkably (from 45.8 in 1970 to 32.1 in 1994). In contrast, marked declines in mortality rates are seen for both men and women over the study period.

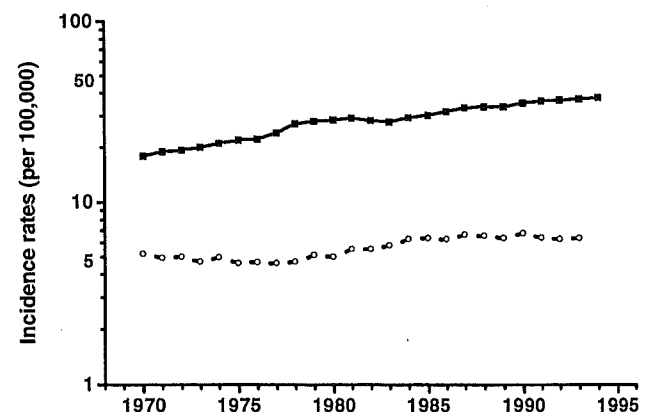


Lung cancer. Incidence rates for men increased by 38% over the 25-year period. For women, a temporary dip seen in the early years was followed by increasing rates over the next five years, with little change after 1980. Lung cancer mortality and incidence trends seem roughly similar for both sexes.

Since 1958, under agreements with the Hiroshima and Nagasaki Medical Associations, ABCC and RERF have been responsible for the routine operation of the Hiroshima and Nagasaki tumor registries. While these population-based registries are closely linked to the Life Span Study (LSS), they have provided important information on cancer incidence in the general population of Hiroshima and Nagasaki.

Incidence and mortality trends for cancers of the stomach, lung, and breast are shown here. Incidence data, not limited to first primary cancers, are from the Hiroshima Tumor Registry, and the study period is from 1970 through 1994. Mortality is based on vital statistics data provided by the Japanese Ministry of Health and Welfare.

City population estimates by age and sex are based on five-year census data with linear interpolation for noncensus years. Incidence and mortality rates were standardized to the International Agency for Cancer Research world standard population. Lines depicted in the figures are smoothed from the plotted raw data points by five-point running averages.



Breast cancer. The incidence rate in 1994 reflected a steady increase over the study period, with the 1994 rate (36.4) about twice that of 1970 (16). Mortality also increased but is less marked than for incidence.

RERF's Hiroshima Laboratory Opens Doors to 680 Guests

RERF's Hiroshima laboratory held its fourth open house on 23 November, Japan's Labor Thanksgiving holiday, welcoming 680 guests through its doors. The open houses, undertaken in 1995, have been established to inform the public regarding the research activities conducted at RERF.

This year, a photo display traced the Foundation to the early years of the Atomic Bomb Casualty Commission, informational panels prepared by each department described specific research investigations and results and researchers were available to discuss their activities and answer questions, microscopes were set up so that visitors could examine cancer cells, an electron microscope allowed them to visualize DNA, and computers were available for

those interested in exploring the Internet. A chromosome analyzer and cell sorter were also included for inspection.

RERF has been pleased with the reception the open houses have received by the many visitors each year and has planned them on holidays to allow more people to attend. The large number of participants and the presence of many families this year suggests that this has been a successful plan. Comments from those in attendance have indicated that the open houses have broadened their general knowledge of RERF and the scope of its research.

In addition to November open house attendees, another 419 visited the Hiroshima laboratory on 5 and 6 August, in conjunction with A-bomb Day events in the city, the time when RERF held its first two open houses.

My Experience of the Atomic Bomb—Testimony of an Employee Though Barley Was Treaded: Memory of Collective Evacuation

by Tadataka Kuribayashi, retired, Secretariat

Editor's Note: This article is edited and reprinted from an article distributed by RERF and its labor union on the occasion of the 1994 A-bomb anniversary, when the author was asked to share the story he had written some 30 years earlier. Mr. Kuribayashi retired from RERF in June 1995 following almost 35 years of service to ABCC-RERF. During that time, he worked in the business office, the Department of Epidemiology and Statistics, and the accounting and personnel sections of the Secretariat. Here is his story:

I feel a little uneasy, but I am glad to be able to cooperate. The evacuated elementary school students, including myself, have reached the age of 60, and many of us have grandchildren now. I have served at ABCC-RERF for almost 34 years. The six months I spent in Tsutsuga Village in the northern part of Hiroshima Prefecture still remain vividly in my memory even after so many years. It might be difficult for young people to imagine what happened in those days, but I want them to know that there are many people who underwent experiences similar to mine and that they are still very much alive. It is worthwhile, perhaps, to go back once again from the affluent life we are now enjoying to the "starting point" and look behind. (This note was included in "Koho Tsutsuga" [PR journal of Tsutsuga Village, Yamagata County] published in September 1975.)

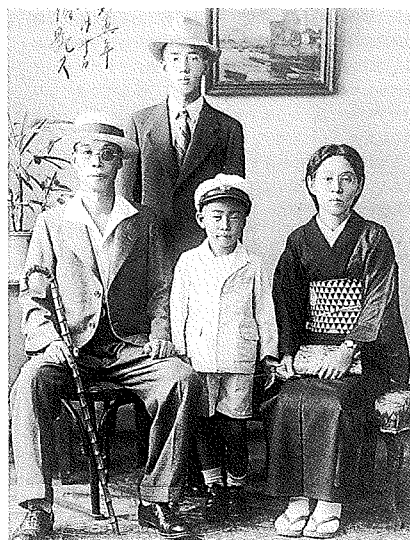
In late June 1966, I decided to visit Tsutsuga Village in Yamagata County for the first time in 21 years. I wanted to do some sketches for an art exhibition. Probably because it was early Sunday morning, the diesel locomotive from Yokogawa to Kake was not crowded. Carefree high school girls in white sailor blouses were talking and smiling. It was a peaceful sight with no trace of darkness.

With the sound of a bell, the diesel locomotive left the platform. As the train pulled out, something touched my heart, and I turned my eyes to the landscape outside the window. The sorrow and loneliness I had felt when I had parted from my mother for collective evacuation on 12 April 1945 came vividly to my mind.

Collective evacuation

On that morning, when I was in the sixth grade in a national elementary school, I went to the school for the last time with my mother. The night before, my father managed to procure from somewhere some sugar, which was extremely scarce and precious in

those days, and my mother made botamochi (sweet rice cake dumpling covered with bean paste) for me. It was a simple dinner by present standards, but it was the last the three of us, my parents and I, had together.



Mr. Kuribayashi's family in 1940. At the center in the front row is the author, then in the first grade of a national elementary school. (Photo courtesy of author.)

I don't remember what the teachers said at school that day. The evacuation was probably a measure to get the children out of town so that they would not become burdens for their parents in air raids, but it saved the lives of thousands of children from the disaster of the atomic bomb. We walked to Yokogawa Station in a line. It was the last time for me to see the old and quiet castle town of Hiroshima.

When the train left Yokogawa Station, parents were not allowed on the platform, so they got together at the ticket gate to see their children off. I tried to find my mother, but I couldn't. The train heartlessly slid out.

Saihoji Temple in Tsutsuga Village

That day, after changing trains several times, I arrived at Tsutsuga Village for the first time. Saihoji, which had handsome copper roofs, was chosen as our lodging house. First I noticed its large main room with several tens of tatami (straw) mats and gilded sculptures inside. The dinner was wonderful sekihan (rice cooked with red beans), but the children, who ate too much on the train, did not eat it up, to their later regret.

The children were happy to see many new things, but at night, because of the parting from their parents, one or two began to cry, and then, the crying spread among many children. The next day, 19 children, boys and girls from the third to sixth grades began their lives in the village. The village people were kind to us. On the first day, they held a welcome party at a school and gave us red and white rice cakes. It was a happy first step for us.

After a while, we began to be troubled by lice. Although it was late April, it was cold in the mountain village. It was very difficult to exterminate these strangely shaped creatures. The matron became busy with the extermination work every day. She was the wife of Mr. Yamakawa, the teacher who led us from Hiroshima, and she helped me in various ways during the half year of my evacuation life.

The Tsutsuga Village National School was not large, but the hallways were always shining from polishing. There were strict ways of cleaning: lift your back while wiping the floor; rub the floor with spirit; and so on. Gradually, I got used to the custom, and after a while, I did not feel the work troublesome. During exercise hours, we always climbed a hill at the back and played war games. Running on the hill was fun, but the hunger that came later was painful.

On holidays, all the children went into the mountains to gather wood for fuel and whatever edible herbs we could find, including butterburs. Sometimes we went to distant villages to get

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A section of Saihoji Temple. Some children hid in the room at the end of the corridor to weep, thinking of their parents. (Illustration by author.)

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potatoes. These holiday events were fun for us.

We also enjoyed the visit by the school teachers, who were strict at school but like kind brothers at the temple. Mr. Mori, a young teacher who often told us ghost stories, was especially popular—and Ms. Nogami who sang songs with her beautiful voice.

The sixth-grade boys were naughty and disobedient. We took defiant attitudes toward the matron on every occasion. There was nothing sweet to eat, so to her surprise, we licked water colors.

After one week of evacuation life, one of the children contracted pneumonia. No rice was left, so Mr. Yamakawa had to visit the agricultural association every day, but the children complained one after another without appreciating the troubles he underwent for them. How I feel sorry for him when I think about it now. I also feel sorry for Ms. Amago, who was assigned to the temple later. She was a young teacher and female and, so, the best victim for the attacks of naughty children.

Reunion with my mother

Under the circumstances, a most delightful day came, a visiting day for parents on 30 June. During the two-and-a-half months since evacuation, we had exchanged many letters, but we were overjoyed at the chance to see our parents.

My mother came. There were strict restrictions on the gifts, and parents were not allowed to bring luxurious foods and goods, but many violated the rules. Though “luxurious foods” in those days were not really luxurious, I had a slight grudge against my mother, who followed the rules strictly and brought only parched sesame seeds mixed with salt, pickled ume (Japanese apricot), and a few other foods. But, I immediately forgot my grudge. In the precincts of the temple, my mother cut my long hair. After me, she cut the hair of one child after another. I still remember vividly my mother with a hair clipper in her hand.

That night, a small reception party was held for the parents. I made simple opening remarks by means of flag signaling. Each child sang a song and a few happy hours passed by. I sang “Ware wa Uminoko (I am a child of the ocean)” in a loud voice.

I wonder what kind of dream I had that night, when I slept with my mother. I didn’t think much about the war or the shortage of food. I was just



Precincts of a shrine adjacent to the national elementary school in Tsutsuga Village. When the atomic-bomb was dropped, the author was being trained in Morse signals. (Photo courtesy of author.)

happy being with her, though I didn’t know when I would be able to see her the next time. However, the visit was short and transient. In the morning, the parents had to leave. We went out to the road to see them off as they prepared to leave in a truck. When the motor started, all the children began to run after the truck, calling after our parents in tearful voices, but the sight of the truck blurred with tears and disappeared.

Hardships in evacuation life

In early July, summer came to this village in the mountains close to the northern border of the prefecture. Not a day passed without potatoes on the dining table, and I more or less enjoyed boiled wild herbs. We had parched soybeans between meals. Everyone was especially anxious about the amount of rice and had a deep attachment to his bowl of rice. We compared the weights of the bowls with both hands, and after choosing the heavier bowl, we then compared it with another. This required patience, but everyone did this carefully. The senior students were allowed to choose first, and the small children could not pick up a bowl before them. However, with parched soybeans, the smaller children were allowed to choose first the bowl they thought contained the largest number of beans.

We came to learn the sutras by heart and chanted them in the morning and evening without looking at scriptures. Someone immediately learned how to make straw sandals, and the technique spread among the children, some of whom became really skillful later. Around that time, instead of lice, children began to have fleas, and the matron continued to have busy days.

At the school, we were busy working in the farm as well as digging pine roots and collecting flax. Children from the town tried to prove that they could work just as hard as the robust village boys. A small river tens of meters away from the temple was the best recreational spot. The feel of cool water under abundant green leaves made me forget the lapse of time.

The fatal day (6 August)

The weather was fine in the village on the morning of 6 August, more than a month since our parents’ visiting day. In the precincts of a shrine adjacent to the school, we sixth-grade boys were undergoing training in Morse signalling. A cool breeze blew under the ginkgo trees, and the cicadas seemed to be singing the joys of summer. Suddenly, I felt something warm on my left cheek and turned around. It seemed like a strong reflection from a mirror. Then, a roaring sound shook the whole village. While I was wondering what had happened, a column of clouds appeared above the mountains in the south. They were not ordinary clouds but of a superb pink color. Gradually, they assumed the shape of a mushroom and rose to the sky.

When I returned to the temple, the matron said she had felt a strong tremor even in the temple. As time passed, the fine sky gradually became dark, and in the late afternoon, a lot of ashes from paper and other things fell from the sky. First a rumor circulated that an arsenal had exploded. I later heard that a fire engine from an adjacent village had gone to Hiroshima City for rescue, but because of the strong fire, it could not go beyond Yokogawa and had to return. Thus, though I was small, I felt something unusual had

happened. However, I didn't even imagine that the big city of Hiroshima had instantaneously become a sheet of fire.

Soon, I heard that many people with severe burns came back to the village. All of these people were from the village and working in Hiroshima. After that, there was no communication from parents. After more than a week, a teacher told us that there had been an important announcement and that Japan had lost the war, but I cannot remember sorrow or anxiety at that time. We might have been too young to have any direct emotion about the big change in the nation. Even though the war ended, we couldn't do anything. No one came to fetch us, and everyone lived anxiously from day to day.

Reception center for A-bomb survivors in Miyajima

At the beginning of September, I received a wrinkled-up postcard. Though my mother's name was mentioned, the handwriting with a pencil, some parts of which were blurred, was not my mother's. The card simply said, "I am in the reception center in Miyajima. Come here immediately," and a simple map of the place was provided. I wondered why my mother had not written herself, but I was glad to know where she was. However, the date on the card showed that many days had passed since it had been written. The next day, with Mr. Yamakawa accompanying me, I left for Miyajima. It was 2 September.

I looked at the town of Hiroshima while I proceeded from Yokogawa to Koi. It was a field of charred ruins. The city street car, which just began to run between Koami-cho and Koi, had numerous flies on the ceiling. It was a strange sight. We took a boat from

Miyajima-guchi. I saw the old big torii (Shinto shrine archway) and the beautiful Itsukushima Shrine, but they just looked like a faded landscape painting to me. I wanted to go to the reception center and see the face of my mother as soon as possible. I was so eager to see her that I felt the boat was extremely slow. Soon we arrived at the center, a big building to the north of the shrine. When I stood at the entrance, I felt some kind of anxiety, an emotion difficult to express.

Attending Mother

I looked for Mother with my teacher. It was a big room with tens of tatami mats, and the spaces between A-bomb survivors lying on futons (bed-clothes) produced a forlorn atmosphere. We took one round but couldn't find her. While I took the second round, looking into the face of each person, I was astonished to find Mother, lying on her face and exhausted. She was a small person, but she looked even much smaller. Suppressing the tremor in my voice, I called her quietly. There was no answer. I called her again. Then, she noticed and slightly raised her head. She saw the teacher behind me and took out some bills to give to him. He refused to receive them, and left there after a short while saying that he had business at the school.

When Mother told me about my father's death, I was not so surprised. I might have been somewhat ready to hear the news. Deprived of a flush of hope, I imagined my father burned by fire in death agony. My heart was wrung. We didn't know if my elder brother, who had gone abroad to war, was dead or alive. I naturally had a dark outlook for our future, but I resolved firmly to continue to live with my mother no matter how poor we would be. Mother told me to take the cloth off her back, which I found covered with brown burns so that she couldn't lie on her back. Why does my mother, as innocent as a person could be, have to be tortured like this? I could not suppress the anger I felt. I took care of her two nights and three days. However, the only medicine provided was Mercurochrome. We were even short of creosol. When Mother arrived at the center, she was fine and even washed other people's clothes, but when I got there, she couldn't even move.

She was engaged in building demolition work near the Tsurumi Bridge when she was exposed to the flash. She couldn't do anything for Mrs.

Takai, who was immediately burned to death in front of her, and she climbed Hijiyama Hill in a hurry with her back burned. From the hill, she looked at the city, which was a hell on earth. With other people, she was first accommodated in the reception center in Ninoshima and later moved to Miyajima. The terrible gas that entered into the depths of her body gradually damaged her bones and organs. She completely lost her appetite.

Remorse

No one had disposed of my mother's urine, so her lower body gave out a stench. Her stool was not like that of a human being. Its color and smell were like those of internal organs that had been melted and had become sticky liquid. I felt that the only way to give back her humanness was to clean the chamber pot often. Though I was eager to care for her, I became negligent once. On the second night at the center, I heard Mother's small voice calling me, but I was so sleepy that I pretended I didn't hear her. She called me twice but didn't say anything more. Whenever I remember this, there is a sharp pain in my heart.

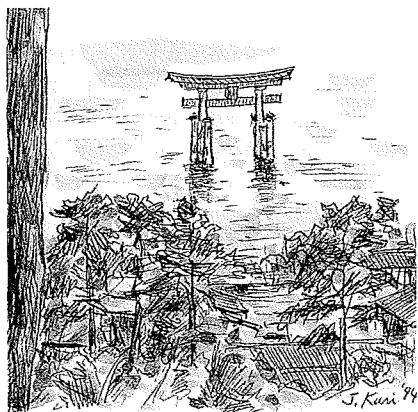
At the camp, simple food, such as salty soup with a dumpling, was served three times. No boiled rice was served. We were allowed to drink as many cups of soup as we liked, and I had three or four more cups of soup. My mother smiled wryly. At that time, she was too weak to speak. I saw the front of a big torii, gateway to a Shinto shrine, from the window of the lavatory. Looking at the B-29 bomber that sometimes came flying over, I shouted to myself, "Idiot!" It was all the resistance I, as a boy, could offer, and I sometimes cried secretly in the lavatory.

Mother's Death

At lunch time on 4 September, the third day, Mother started to writhe in pain. Her unusual action completely upset me. All I could do was to absent-mindedly look at her suffering. After agonizing for 30 minutes, she regained her calmness. However, it was the last calmness, the sign of the end of life. I continued calling her name, clinging to her body. Tears welled up in the eyes of my speechless mother and rolled down her cheek. I wondered if the tears were from the sorrow of eternal parting between mother and child or from anxiety about my future. I shall never forget Mother's tears on that day.

I continued crying even after a

Continued on next page



Many A-bomb survivors were taken to Miyajima.
(Illustration by author.)

Continued from previous page

white cloth was placed over her face. Some irritated people reproached me, telling me to "Be quiet!" Shouldn't I feel sorry for the death of my most precious mother? My tears seemed to forget to stop until evening.

Return to Tsutsuga Village

A middle-aged man happened to come to the camp as an attendant, and he was kind enough to offer to take charge of me, probably pitying me, left an orphan. I answered I would decide after consulting with my teacher at the Saihoji Temple where I had been evacuated. He decided to take me there. Wrapping my mother's personal belongings, I had a rice ball made for lunch. The man and I left Miyajima Island, leaving what had to be done, including my mother's burial, to the camp officials.

Arriving at the Miyajima-guchi station of a private railway, I found a streetcar already pulled up and about to leave the station. I already had a return ticket but the man did not, and he bought his own ticket. He hurried to the platform after he had his ticket punched. I tried to follow him, but a man at the wicket told me that the ticket I had was for a train and not for a streetcar. He showed me the way to the national railway station, and I started walking toward the station at once, never thinking of anything. There is no way of knowing if the man left for Hiroshima by streetcar or returned to Miyajima. The fact that the one ticket I had served as the turning point of my fate still makes me think of the mystery of fate.

The train I boarded took me closer to Tsutsuga Village, from Miyajima-guchi to Yokogawa and from Yokogawa to Kabe to Aki-imuro. I felt relieved when a truck driver picked me up and took me from Aki-imuro to Kake. An old man who shared the ride had a water bottle and gave me some water. The water tasted so good that it was the very experience of water coursing down through my bowels. I found that the old man was returning to Tsutsuga Village and asked him to take me there.

It was very far from Kake to Tsutsuga. The road, which ran along a river, seemed endless. Late at night and half asleep, I tottered after several persons. When I reached Tsutsuga Village, I noticed there was no one but the old man who had given me water. We walked for another 40 minutes and finally reached the front of the Saihoji

Temple at dawn. I felt indescribably happy. I expressed my thanks and said farewell to the old man and entered the main hall of the temple. I thought I had to report to my teacher that I had returned, but I decided to do so in the morning because I did not want to wake him up. Carrying my bedclothes, I stole into a mosquito net, under which some children were sleeping, and I lay down. In the morning, my teacher was very surprised to learn that I had returned. I had never experienced such a long trip.

Left Alone

I resumed life at the temple. An increasing number of children were leaving the temple with a parent or sibling or other relative who came to take them home. However, traffic was completely paralyzed due to a heavy flood and washed-out roads caused by an unprecedented typhoon in the prefecture. So, there was no choice but to walk all the way to Hiroshima.

Children who had homes to return to were happy. Most of the children had lost either a parent or another family member. Only I had lost both my parents and had no relatives. I had nowhere to go except an orphanage where I was taken care of. In spite of my sheer unhappiness, as a child, I did not think so seriously of my situation.

In the end, only three children, including myself, remained behind at the temple, which was too big for the three of us. I heard that the relatives of Yoshihiro Inoue and Yoko Minematsu would come to the temple later for some reason. Then, it was decided that children, including those living in neighboring villages who had

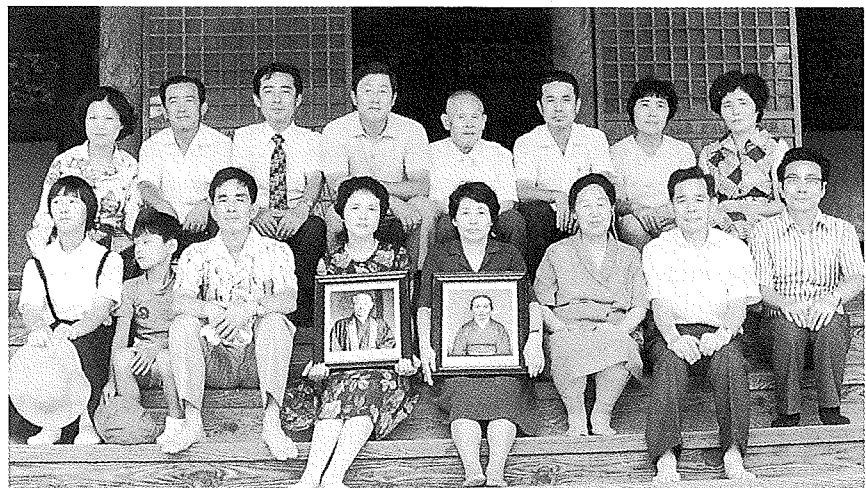
no home to which to return, would be accommodated in a temple at Togouchi, adjacent to Tsutsuga.

When it began to get dark on 3 October, I alone was hurriedly crossing a mountain pass. There was no one to be seen, and everything was ominously still and silent. An 11-year-old boy, I only thought of running out of the weird miscellaneous trees, not fearing a future life that would bring me loneliness and starvation. Frequently frightened at the sound of my own footsteps, I kept running, only wishing I could reach the village as soon as possible.

Lapse of 21 Years

It is impossible to find scars left by the war on the faces of A-bomb survivors after 21 years. However, I believe that they secretly have unforgettable memories of those dark days.

I was on my way home from Tsutsuga Village, where I visited for the first time in 21 years. The Saihoji Temple stood silently. Its splendid copper roof had weathered, showing the lapse of 21 years. The school that had boasted a shining corridor was no longer there; a modern three-storeyed school building of reinforced concrete stood in its place. The precincts of the Tsutsuga Shrine, where I had looked up at the atomic cloud, and the landscape of the village spreading to the south reminded me of how it had been when I saw it 21 years before. I am over 30 years old now, but I can never forget my various experiences in this village as a memory of stamped wheat plants. Is this nothing but my sentimentality?



This picture was taken in August 1975, when the author visited Saihoji Temple with the others who also lived there 30 years before. Mr. Kuribayashi is at the right end in the front row. The photographs show the late head priest and his wife, who looked after the children as if they were their own. (They happen to be the grandparents of Mr. Yutaka Ogasawara of [the Secretariat].) (Photograph courtesy of author.)

Nagasaki and Hiroshima Local Liaison Councils Discuss Issues Surrounding Proposed F₁ Study; Hiroshima Meeting First in 15 Years

In its efforts to become more accessible to the community and more sensitive to community concerns, in the last two years, RERF has undertaken the re-establishment of local liaison councils in Nagasaki and Hiroshima. After a ten-year hiatus, the Nagasaki Local Liaison Council was reformed in November 1997. (See RERF Update 9[1]: 14.) A second meeting was held last October, and the Hiroshima Local Liaison Council was reconstituted in November after 15 years. The councils provide a forum for discussion between RERF representatives and community representatives, including members of the local and prefectural governments, various academic, medical, and research organizations, and bombing survivors.

Nagasaki Local Liaison Council

On 1 October 1998, RERF's Nagasaki Local Liaison Council met for the second time since its re-establishment. Among the council's agenda items were the conduct of the proposed F₁ (second-generation atomic-bomb survivors) study and RERF Nagasaki laboratory's upcoming 50th anniversary events in addition to reports on RERF's research activities and collaborative efforts and the recommendations of the Scientific Council and the Multinational External Peer Review of the Department of Radiobiology.

Sixteen of the council's 22 members and three coordinators attended the meeting. Tetsuo Yokoyama, then-president of the Nagasaki University, is the council's president and chaired the meeting; the university's medical school dean at that time, Takayoshi Ikeda, is council vice president. Councilors include members of the prefectural and city governments; the university and its medical school, hospital, and Atomic Disease Institute; local hospitals and medical associations; and various nonprofit and survivors' foundations. RERF representatives included Chairman Shigenobu Nagasaki, Vice Chairman and Chief of Research Sheldon Wolff, Permanent Director Senjun Taira, Hiroshima and Nagasaki Secretariat Chief Kazumasa

Kunitoshi and Nagasaki Assistant Secretariat Chief Hiroyuki Tominaga, Nagasaki Epidemiology Chief Yoshisada Shibata, Nagasaki Clinical Studies Chief Masazumi Akahoshi, and Nagasaki Secretariat Assistant Chief Yasutaka Ogushi.

Dr. Nagasaki indicated the desire that RERF be more open to the public, and he noted the need for external review to maintain high scientific standards and for more international collaborations.

Drs. Taira and Shibata responded to questions concerning F₁ issues. Representatives of the F₁ survivors (*Niseikyo*) had taken issue with RERF's acquisition of information from public *koseki* (family registration) records for a proposed mail survey planned as a preliminary step in the study, alleging that their privacy had been invaded. Ongoing discussions with the F₁ groups are seeking to address their concerns, and explanation of the planned procedures is being offered. (*Editor's note:* At the time of this *Update*, those meetings seem to be nearing their conclusion.) The liaison council recommended that RERF proceed with diligence in considering the ethical issues involved in such study.

At a press conference following the meeting, RERF Chairman Shigenobu Nagasaki repeated his intentions that RERF be an open institution and that more international exchanges and collaborations be sought in the future, and he called for the continuation of present studies, with emphasis on epidemiology.

Hiroshima Local Liaison Council

On 10 December, the Hiroshima laboratory's local liaison council convened after a 15-year hiatus arising over the question of RERF's relocation in 1983. (Prior to that, the council met biennially.) Fourteen members of the local community, including representatives for the prefectural and city governments, were in attendance, and Hiroshima University President Yasuo Harada was elected council president and Hiroshima University Medical School Dean Yuichiro Matsuura was elected vice president. RERF presented a

summary of its last 15 years of activities and concerns, and as in the Nagasaki meeting, the Hiroshima council discussed issues surrounding the planned F₁ study. Dr. Nagasaki also advised council members regarding the November peer review of RERF's Department of Epidemiology.

With regard to the F₁ study, the council recommended the establishment of two committees—a scientific advisory committee and an ethics advisory committee—to investigate how the study should be conducted and what problems might surface in the process. The scientific committee's membership would include epidemiologists, clinical geneticists, and radiologists; and the ethical advisory committee would comprise legal and public relations experts as well as F₁ representatives. Liaison council members agreed to meet with the Second Generation A-bomb Victims Liaison Council to discuss the proposed plan.

The Hiroshima council's members represent local peace organizations, medical associations and hospitals, universities and medical schools, and A-bomb and H-bomb survivors groups in addition to the local governments.

A board of secretaries was also established during the meeting, and plans were made to conduct subsequent meetings annually.

New Software, continued from page 9 offers online help, supports English and Japanese, and allows users to view, copy, rename, and delete tables within the application.

A newer version of Easy Click is being developed that will be much more flexible and allow access to any RERF variable (as opposed to the current, predefined list). Support for Adult Health Study clinical information (longitudinal data format) is also planned, along with more robust import and export features.

The combination of a more extensible data base and a flexible, easy-to-use program for accessing research data is making RERF data more accessible than ever before.

For further information regarding Easy Click, please contact the author: Eric Grant (egrant@rerf.or.jp).

Clinical Studies Chief Kodama Co-Chairs Third British Epidemiology and Public Health Course

Hiroshima Department of Clinical Studies Chief Kazunori Kodama and Dr. Walter W. Holland, head of the Department of Public Health Medicine of the United Medical and Dental Schools of Guy's and St. Thomas's Hospitals, London, co-chaired the Third British Epidemiology and Public Health Course 29 November through 5 December in Hiroshima. Sponsored jointly by the British Council, the Cooperative Foundation against Environmental Pollution, and the Daiwa Anglo-Japanese Foundation, the course was the third of a series intended to introduce young Asian epidemiology and public health students to the British practice of epidemiology. The 29 participants came from Bangladesh, China, and South Korea as well as Japan. This more advanced course was developed in response to requests from participants in the two earlier courses.

Morning lectures were followed by student presentations and discussions in the afternoons and evening sessions

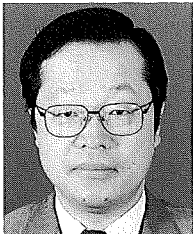
that required participants to develop cooperative research protocols. Some of the topics covered in lectures included the role of epidemiologic study in tobacco control and smoking; asthma; elderly health care, including home and institutional care and dementia and functional disabilities; genetic concerns related to pregnancy-induced and essential hypertension and to osteoporosis; cardiovascular diseases; dietary- and alcohol-related studies; air pollution and pneumoconiosis; insulin-dependent diabetes; and hostility and health-related behavior.

Dr. Saeko Fujiwara, assistant chief, Department of Clinical Studies, spoke about the epidemiologic study on osteoporosis conducted in RERF's Adult Health Study cohort. RERF Chairman Emeritus Itsuzo Shigematsu, who served as chairman emeritus of the course's operating committee, presented a lecture on the history and future of epidemiology in Japan as one of three lectures on the last day of the course.

Dr. Kazunori Kodama Resigns to Join Academia

by Saeko Fujiwara, Assistant Chief, Clinical Studies, Hiroshima

Hiroshima's Clinical Studies Chief Kazunori Kodama resigned from RERF effective 31 March, to join the faculty of Hiroshima University as professor of health science in the Section of Health of the Department of Medical Science.



Dr. Kodama has almost a quarter-century association with ABCC-RERF. He started his career in ABCC's Department of Medicine shortly after completing his internship at Hiroshima University Hospital, and he stayed through the Foundation's 1975 reorganization, until his departure for five years of further training in the United States. Upon his return from the U.S., Dr. Kodama came back to RERF for two years but again left temporarily to acquire experience in emergency care in the Intensive Care Unit of Hiroshima University Hospital. In 1987, he resumed his epidemiological research at RERF as chief of the Division of Medicine. He later

became department assistant chief and, in 1989, department head, his position until his March departure.

Dr. Kodama has held the Department of Clinical Studies together through the years with his outstanding leadership. He is thoughtful and attentive, and with his strong drive, he has pushed forward many projects while maintaining good relations with other departments and the local community. Dr. Kodama's contributions to RERF are praiseworthy, and his achievements in the fields of epidemiology and public health are impressive inside and outside Japan. Dr. Kodama has authored and coauthored more than 200 publications. Last year, he was honored with fellowship in England's Royal College of Physicians, and he is expected to serve as Secretariat chief for the 2001 International Conference on Preventive Cardiology to be held in Japan.

We regret his departure, and he will be deeply missed. Nevertheless, we wish him further success in his new challenges and look forward to his continued support and guidance.

Abrahamson, continued from page 2

another workshop—one on clinical genetics. His presentation introduced the central topic of concern for the workshop, the issues surrounding the proposed F₁ health study, a subject that was also on the on the Blue Ribbon Panel agenda.

In his earlier terms, Dr. Abrahamson had watched RERF suffer through financial crises that resulted in a depletion of staff, and he verbalized his ongoing concern with these issues as he retired in December. His support of the organization and individual staff members was, indeed, a hallmark in his tenure at RERF. He was perhaps most proud of his continuing efforts in maintaining close contact with department chiefs and research staff to receive their input on the direction of research and to advise them in their individual research interests. His fairness in dealing with the concerns of each department and not showing partiality toward his own area of expertise (genetics) is particularly noteworthy. Seymour's overall support for the Foundation's mission and for those who carry out that mission is well regarded by staff, and his warmhearted, outgoing personality and quick sense of humor have endeared him to many. His is always a welcome face.

It is hoped that Dr. Abrahamson's thoughtful contributions to RERF's scientific work will continue for many more years and that his many friends in Japan will be able to see him from time to time, as they did at his March return, when he participated in the clinical genetics workshop.

In his farewell remarks to staff in RERF's *Japanese Newsletter*, Seymour concluded, "Again, it is time to say 'Goodbye.' I know that I shall return at every opportunity to short meetings, but it is unlikely that I can return for extended periods. Moreover, RERF needs younger administrators. I thank all of you for making RERF a world-class institution; each in your own way has contributed to our prominence. It has been a great privilege and honor for me to share this effort with you. I will continue to provide my support whenever I can. I can only say with great sincerity that my time here was the most important part of my scientific career."

We offer our thanks to Seymour as well and an open door.

Farewell to Dr. Akio A. Awa: Former Genetics Chief Leaves RERF after 32 Years
by Nori Nakamura, Chief, and Yoshiaki Kodama, Cytogenetics Laboratory Chief, Department of Genetics

Dr. Akio A. Awa graduated from Hokkaido University in 1956 and completed his doctoral work there in 1963 in the world-famous cytogenetics laboratory headed by Professor Sajiro Makino. In 1965, after two years as a research fellow, Dr. Awa became a research assistant at Hokkaido University. In 1967, he joined RERF, where for nearly 30 years, he conducted both biodosimetric and genetic studies. He is the founder of RERF's current cytogenetics laboratory and served as genetics department chief from 1985 until his official retirement in 1995. Since his retirement, he has continued at RERF as a consultant from 1995 to 1997 and then as assistant chief of research from 1997 until March 31, 1999. April 1, he began a more relaxed retirement as part-time consultant.

Dr. Awa's most valuable contribution to science is the development of the use of conventional Giemsa staining to score stable-type aberrations, a technique not generally considered achievable until recently. Past studies involving the G-banding technique applied on the same metaphases demonstrated a scoring efficiency of about 70% or more. Unfortunately, Dr. Awa's foresight proved him to be ahead of his time, and his results were not widely appreciated. This is why we say he has "high-tech eyes," and we believe his good eyes to be mutually related to his talents as a cartoonist.



tional Giemsa estimations of translocation frequencies, the latter rate about 70% of the former, as expected. It should be mentioned that the conventional method detects not only translocations but also deletions and inversions not detectable by FISH. If we include these additional types of aberrations, Dr. Awa's detection rate of all stable-type aberrations is almost the same as that by FISH. Compared with monochromatic Giemsa-stained metaphases, FISH-stained cells are colorful and fantastic, showing 40 red chromosomes and six yellow chromosomes. But, the conventional method is one-tenth the cost of FISH. In this context, we may say that it is the "poor-man's FISH," provided that trained "high-tech eyes" are available for chromosome analysis.

Dr. Awa's cytogenetic data have been known to show quite a large variation in aberration frequency among survivors bearing similar physical radiation doses estimated by either the T65D or the current DS86 system, a phenomenon termed "statistical overdispersion." Because of this large variation, as a criticism of Dr. Awa's results, cytogenetic data were not seen to be valuable as individual biological dosimeters.

Several years ago, when Nori Nakamura moved from the radiobiology department to the cytogenetics laboratory, he carried out a new biodosimetric study using teeth extracted for medical reasons and donated from A-bomb survivors. The technique, called electron spin resonance (ESR), measures radiation-induced stable radicals (CO_2^-) maintained in the crystalline structure of tooth enamel. Since the total number of radicals induced by radiation is linearly related to dose, ESR signal intensity can be used for dose estimation. After the first study of 100 teeth, we found that ESR-estimated dose and cytogenetically estimated doses of the same survivors fit very closely. Some survivors with physical doses greater than 1 Gy demonstrated aberration frequencies in the control range, and ESR data of such survivors did not show any evidence for radiation exposures! Thus, the combined ESR and cytogenetic data strongly suggested that the "statistical overdispersion" is primarily due to problems in physical dose estimation

and not technical problems in cytogenetics or individual variation in radiation responses. Because computer calculation of individual dose is based on interview records taken more than ten years after the bombings and individual memory is not always correct, such a reporting bias cannot be avoided.

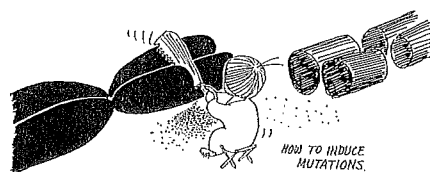
Thanks to Dr. Awa's devotion to RERF and his foresight, we are now in a very unique position to conduct biodosimetric studies using both cytogenetic and ESR techniques. No other single laboratory in the world can conduct these two totally different fields of research. As descendants of Dr. Awa's laboratory, we are proud. All he achieved was right but could be repeated by only a few cytogeneticists because "unfortunately," Dr. Awa could see too clearly. Because scientific findings must be reproducible by other researchers, Dr. Awa's achievement could not be widely recognized. We can conclude with pity that he was born too early. It is our task now to publicize his results with more supportive information.

Because of space limitations, we cannot touch on his effort in conducting the cytogenetic study in children of bombing survivors (F_1), but we hope to have a future opportunity to do so.

Dr. Awa will continue with RERF as a part-time consultant, and we still have work to do. Among other samples, cytogenetic slides of nearly 100 survivors exposed in factories to the Nagasaki bomb, whose physical doses are well recognized as overestimated, are waiting for his scrutiny.

Editor's Note: Before leaving, Dr. Awa wanted to express his appreciation to all of those people who have helped him through the years, particularly those technical staff, whose "superb" work supported his own.

He wrote to staff of his mixed feelings at his departure after 32 years, ending with, "I wish to express my sincere thanks to all of you whose continued support and help have encouraged me a great deal. I hope that your future research activities at RERF will be bright and promising."

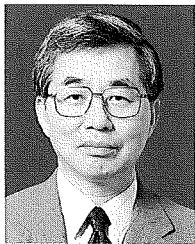


Recent innovations in DNA technology allow us to use chromosome-specific DNA probes to paint any chromosomes. This method, known as fluorescence *in situ* hybridization, or FISH, is now widely accepted as an objective method to detect stable-type chromosome aberrations, particularly reciprocal translocations. The recent summary of our data clearly confirmed a close fit between FISH and conven-



Thank You, Dr. Shibata!

By Koji Nakamura, Assistant Chief,
Department of Epidemiology, Nagasaki



Editor's Note: Dr. Yoshisada Shibata, department chief of RERF Nagasaki Laboratory's Department of Epidemiology, resigned effective 30 November 1998, after more than a dozen years of service to RERF. He received his doctorate in engineering from Tokyo University, where he served as a research associate and lecturer in the

university's Faculty of Engineering prior to graduation. After receiving his degree, he headed the Field Survey Laboratory of the Department of Epidemiology of the National Institute for Minamata Disease until he came to RERF. At RERF, he served variously as acting chief and then chief of the Department of Epidemiology and Biometrics prior to assuming leadership of the Department of Epidemiology after the Departments of Epidemiology and Biometrics and Epidemiological Pathology were reorganized into a single department in July 1995.

Dr. Shibata has published numerous papers and chapters, particularly in relation to radiation-related thyroid disease, and in 1997, he coedited with Dr. Shunichi Yamashita the book, Chernobyl: A decade (Elsevier). In 1994, he coauthored with Dr. Shigenobu Nagataki and other Nagasaki RERF and Nagasaki University researchers an article for the Journal of the American Medical Association, which received international recognition: Thyroid diseases among atomic bomb survivors in Nagasaki (JAMA 272: 364-70). His primary research interests are radiation and thyroid diseases, in utero exposure to radiation, and statistical methods based on fiduciary probability. Dr. Shibata has been actively involved in the Chernobyl Sasakawa Health and Medical Cooperation Project.

RERF Nagasaki is located near the western end of Japan, which has placed the Foundation at a disadvantage in more than one way. One disadvantage has been that the Nagasaki staff, both professional and general, has been relatively small. One day in 1986, Mr. M, my senior, told me, "The assistant chief-elect of the Department of Epidemiology and Biometrics seems to be tough." I thought, "Who is this 'tough' person? Will he or she put us through the wringer? Never mind, he/she belongs to a different department."

After Dr. Shibata assumed his new position, I watched how he operated and understood the meaning of "tough." He was strict and blunt.

Dr. Shibata immediately became involved in creating the master file and tumor registry data bases, and he engaged in a joint study with Nagasaki University's First Department of Internal Medicine to examine the thyroid in the residents in the Nishiyama district. Soon after, he left for the United States to study. Upon his return, Dr. Shibata visited Russia, Belarus, and Ukraine to conduct studies on the Chernobyl Nuclear Power Plant accident. He also took part in the planning and conduct of a mail survey of the Life Span Study participants.

I was deeply impressed by his quick judgment and ability to report calmly after his shocking experience, while staying at his parents' home, of the great January 1995 Hanshin-Awaji earthquake. He reminisced, "That was the

biggest tremor I had ever experienced. Looking at the situation around us, I concluded that there was nothing to gain by staying there. As soon as I decided to head for Nagasaki, we got in a car and drove away."

Dr. Shibata is an engineering graduate, which may have influenced his taking the initiative in automating and rationalizing the Department of Epidemiology's activities. We often discussed our work, and though communication between the boss and subordinates often tends to be a one-way channel, in which the orders of the former are merely conveyed to the latter, Dr. Shibata patiently talked with us until we could understand his point of view. Never has he missed a slip up in our writing, and he has made corrections mercilessly. But, working closely with him, I have found him of a much warmer nature than I had imagined. I have had the good fortune of being thoroughly taught by him. Dr. Shibata has always given me the impression that he is a scholar. Now, he is going to be a university professor, a real scholar.

Dr. Shibata's departure is a loss to RERF, but it is a blessing for him to become a medical school professor. Here are my words of farewell to Dr. Shibata: "Please send out to the world's physicians who can understand the sufferings of the patients, and don't forget to give RERF support from Nagasaki University."

Thank you very much for guiding us so well for 12 years and three months.

Administration

Clark W. Heath, Jr. was appointed associate chief of research effective 7 January 1998, replacing **Seymour Abrahamson**, who retired 31 December. (See stories and pictures, page 2.)

31 December, both Secretariat assistant chiefs retired. **Torao Sasaki** (pictured on next page) had been with ABCC-RERF for more than 38 years, having joined ABCC in the pathology contacting section and assisted in contacting services for 22 years. In 1973, Mr. Sasaki moved into the accounting section of the Secretariat, where he was assistant chief and then chief of accounting before his promotion to assistant Secretariat chief in January 1997. Mr. Sasaki returned to RERF as a part-time advisor in the Secretariat effective 1 January 1999.

Hiroyuki Tominaga (pictured on next page) was with ABCC and then RERF just over 37 years. He began in ABCC's clinical contacting section and moved on to the Department of Statistics before he transferred to the personnel section of the Secretariat in 1984. After becoming chief of that section, Mr. Tominaga was promoted to assistant chief of the Secretariat in January 1997. Mr. Tominaga was re-employed as a full-time advisor in the Secretariat effective 1 January 1999.

Akio A. Awa, RERF consultant and associate chief of research, resigned effective 31 March 1999. (See story and picture, page 23.)

Hiroshima

Department of Clinical Studies

Dr. Kazunori Kodama, RERF Hiroshima's Department of Clinical Studies chief, resigned 31 March to begin as professor of health science at Hiroshima Medical School on 1 April. (See story and picture, page 22.)

Dr. Masaki Shimizu, research scientist in the Division of Medicine, who joined RERF 1 April 1997, resigned effective 31 March 1999. He will work for the Ministry of Health and Welfare in Tokyo.

Department of Epidemiology

Department Chief **Kiyohiko Mabuchi** returned 20 March from a six-month sabbatical, during which he worked with the U. S. National Cancer Institute Radiation Epidemiology Branch developing a collaborative project using information from A-bomb survivor studies and Ural Mountains cancer mortality studies. During his absence, **Yoshisada Shibata**, Nagasaki epidemiology chief, filled in for him. Following Dr. Shibata's resignation (*below and previous page*), Hiroshima Assistant Chief **Yukiko Shimizu** acted in Dr. Mabuchi's place.

Eric J. Grant, who had been serving as a research assistant in the department through a grant from the National Cancer Institute since 1 December 1997, was employed as an RERF research scientist effective 1 November 1998. Mr. Grant was a research programmer in the Division of Medicine at the University of Michigan Medical Center before coming to RERF.

Department of Genetics

Mimako Nakano, research scientist in the cytogenetics laboratory, was promoted to associate senior scientist effective 1 April 1999.

Department of Radiobiology

Kazumi Tanabe (*pictured this page*), chief of technicians, retired from RERF effective 31 December 1998 after 37 years with ABCC-RERF.

Department of Statistics

Harry Cullings, a postdoctoral student in the University of Pittsburgh-Department of Energy training program in radiation sciences, visited RERF from 7 October to 17 December 1998. Dr. Cullings is also working as a consultant to the National Academy of Science's newly established dosimetry committee, reviewing the quality of DS86-related physical measurements with Drs. Wayne Lowder and Takeshi Maruyama.

Dr. Cullings' initial activity at RERF involved improving and extending the DS86 physical sample and measurement data base created at RERF in the spring of 1998 by checking the entered neutron activation measurement, adding gamma-related measurement data, and compiling a complete bibliography of measurement-related papers and other documents. Dr. Cullings also worked with **Eric Grant**, of the Department of Epidemiology, in developing a data entry program that was set to the investigators responsible for sample collection, measurement, and DS86-estimate computation. (*See software story, page 9.*)

During his last weeks at RERF, Dr. Cullings and Drs. Lowder and Maruyama met with researchers at Hiroshima University, Kanazawa University, and the National Institute for Radiological Sciences in Chiba to review and discuss aspects of the measurements carried out at these institutions. Dr. Cullings is expected to return to RERF this spring to continue his work on DS86 physical measurement data.

Publication and Documentation Center (PDC)

Department Chief **Kimiko Ono** (*See picture this page.*) retired 31 December, following almost 39 years of service to ABCC and RERF. After receiving her B.A. degree in English from Jogakuin College, Ms. Ono was employed in March 1960 as a clerk-typist in the editorial office newly organized by Dr. Yasuyoshi Nishimaru. Ms. Ono's command of English and her meticulous editing abilities in both English and Japanese as well as her artistic interests and skills lent themselves to the successful editing, design, and layout of ABCC-RERF's many publications. In recent years, Ms. Ono served as chief of the department's administration and support section and assistant department chief prior to assuming the chair 1 July 1997. As editorial coordinator of RERF's home page, Ms. Ono was instrumental in the Foundation's successful initiation into yet another publication medium.

Because of her almost four decades' involvement with ABCC-RERF and its publications and information data bases, Ms. Ono's knowledge of the organization's history was quite extensive, and her presence as an information source will be sorely missed. However, we are happy that she now has more time to dedicate to her family and other interests.

At Ms. Ono's departure, **Reiko Sasaki**, chief of PDC's editorial and publications section, was promoted to a concurrent assignment as assistant department chief and chief of the department's administration and support section, effective 1 January.

Nagasaki

Department of Epidemiology

Yoshisada Shibata, department chief, resigned effective 30 November 1998 to assume the position of professor and chair of the Department of Radiation Epidemiology of the Radiation Effects Research Unit of the Atomic Bomb Disease Institute at Nagasaki University School of Medicine. (*See story, previous page.*)

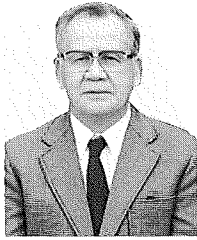
Until he is replaced, **Midori Soda**, assistant department chief, is serving as acting chief (effective 10 December 1998).



Five December Retirees Log More than 150 Years of Service to ABCC-RERF
From left to right: Mr. Kazumi Tanabe, chief of technicians, Department of Radiobiology; Ms. Kimiko Ono, department chief, Publication and Documentation Center; Dr. Seymour Abrahamson, associate chief of research; Mr. Torao Sasaki, assistant chief, Secretariat; and Mr. Hiroyuki Tominaga, assistant chief, Secretariat.

Dr. Eizo Tajima, Japanese Chair of the U.S. and Japan RERF Dosimetry Committee

Dr. Eizo Tajima, professor emeritus of the science department at St. Paul's (Rikkyo) University and Japanese chairperson of the U.S. and Japan RERF Dosimetry Committee, passed away 10 October 1998 at 85.



Shoichiro Fujita, assistant chief of the Department of Statistics, represented RERF at a farewell gathering organized by the Tajima family in Tokyo on 28 October. Also among the almost 200 mourners were RERF Emeritus Consultant Itsuzo Shigematsu and former RERF Permanent Director Masuo Takabe, Dr. Tajima's middle-school classmate.

As chair of the above-cited dosimetry committee established in 1982, Dr. Tajima, a nuclear physicist, was instrumental in the reassessment of the atomic-bomb dosimetry system. He came to that position having served as vice chairman of the Japanese Nuclear Safety Commission of the Science and Technology Agency, of which he was a member from 1978 until his resignation in 1987. He worked tirelessly to make the dosimetry committee in Japan an advisory council to the Ministry of Health and Welfare, whose liaison at that time was current RERF Permanent Director Senjun Taira, then technical official of the Planning Division of MHW's Health Service Bureau. Dr. Tajima described his involvement with the project and many others in his 1995 autobiography, *The Life of a Nuclear Physicist*. A brief biographical sketch follows from that book.

After graduating from the Tokyo University of Science and Literature in 1938, he entered the Physical and Chemical Research Institute, where he remained until 1953, when he received his doctorate from Tokyo Educational University. During 1949 and 1950, he also worked as a researcher at the Fermi Atomic Nuclear Research Institute at Chicago University in the U.S. In 1953, Dr. Tajima joined the science department faculty of St. Paul's University, from which he retired in 1979. From 1956 to 1987, he served variously as a scientific coun-

cilor for the United Nations Science Committee, a part-time member of the Atomic Energy Committee, and a member of the Nuclear Safety Commission. Following his participation on the dosimetry reassessment committee, Dr. Tajima was appointed as a member of the International Commission on Radiological Protection (ICRP) and later chair of the Nuclear Safety Research Association in 1988.

In an article for *RERF Update* ("The Dawn of Radiation Effects Re-

search," Autumn 1993, 5[3]: 7-9), Dr. Tajima wrote of the "decisive influence on [his] later life" of his involvement in the aftermath of the March 1954 atomic testing in the Bikini atoll. Having watched the events unfold, Dr. Tajima also remarked their influence on the scientific investigation of radiation effects. In a half century of work in that field, Dr. Tajima made a significant contribution to our understanding of the health effects of radiation exposure, and we are grateful.

ABCC Employee Hatsuko Yokoyama, Hiroshima Maiden Mother and Japanese Representative to Welcome House

Former ABCC employee Hatsuko "Helen" Yokoyama died in Hiroshima 22 January 1999. She was 89. Mrs. Yokoyama was born in the U.S.



and was educated in Japan. She graduated from UCLA in psychology in 1933, having been greatly influenced and encouraged by a chance meeting with cultural interpreter Inazo Nitobe, who lectured at UCLA in 1933. Her efforts to understand the Japanese and American cultures placed her in a unique position after the war, and following her employment with ABCC, Mrs. Yokoyama took part in a number of international projects that touched the lives of hundreds of persons throughout her lifetime.

Mrs. Yokoyama worked at ABCC from 1949 until 1955, supporting both Japanese and American staff with her skills as an interpreter and a mediator in times of misunderstanding. She was also called upon to liaise with patients at difficult times. In 1955, when just such skills were needed, Mrs. Yokoyama was invited at the recommendation of ABCC physician Robert Miller to accompany 25 young women to the United States for plastic surgery to help repair injuries suffered in the atomic bombing of Hiroshima, and she volunteered to join the undertaking. Those women came to be known as the "Hiroshima Maidens," and over the one-and-a-half-year period when they underwent hundreds of surgeries at Mount Sinai Hospital in New York, Helen

Yokoyama served as their mother, a role that did not end on their return to Japan. (In his "Looking Back" feature in *RERF Update* [Spring 1994: 6(1)], Dr. Miller describes Mrs. Yokoyama's initial involvement in the "Hiroshima Maidens" project.)

Later, Mrs. Yokoyama represented Japan in establishing "Welcome House," a joint undertaking with Nobel Prize laureate Pearl Buck with the cooperation of Mrs. Miki Sawada of the Elizabeth Sander's Home. Mrs. Buck started the agency to assist in finding homes in the U.S. for Amerasian children, and in that capacity, Mrs. Yokoyama served as liaison in the adoptions of children born to Japanese and American parents.

Hatsuko Yokoyama is survived by her three children. Her daughter, Ai, is RERF's head librarian.

Heath, continued from page 2

reports and recommendations of the several research workshops and departmental peer reviews held in the past year (Clinical Genetics [cover] and Immunology [page 5] Workshops, Radiobiology [*Update*, Vol. 9(2): 3] and Epidemiology [cover] Peer Reviews). As always, staffing needs must be addressed—and those needs this year are accentuated by the departure of critical department heads (in Nagasaki, Dr. Shibata [*See p. 24*] from Epidemiology, and in Hiroshima, Dr. Seyama from Radiobiology and Dr. Kodama [*See p. 22*] from Clinical Studies). The opportunities, however, for productive research using RERF's unique data resources are greater than ever, and the challenges for new interdisciplinary investigations hold great promise for the future.

Dr. William Moloney, ABCC Director of Hematology, 1952-1954

William Curry Moloney, M.D., director of the Atomic Bomb Casualty Commission's (ABCC) hematology division from 1952 to 1954, died in Boston, Massachusetts on 2 November 1998 at age 90. Dr. Moloney was at the forefront in treating leukemia and lymphoma with chemotherapy. He published numerous papers on the relationship between ionizing radiation from the atomic bombings and leukemia, and he served as a hematology consultant for the National Cancer Institute's Radiation Epidemiology Branch and for the U. S. Department of Justice in radiation-related matters, work that in recent years involved his assistance in research related to the Chernobyl accident.

Born in Boston, Dr. Moloney received his medical degree from Tufts Medical School in 1932, and he served on the Tufts faculty from 1934 until his retirement in 1974. He began his work as a family practitioner in Jamaica Plain, in the Boston area. Beginning in 1938, he began consulting work for the Boston City Hospital, where he organized a hematology laboratory in 1948 and served as chief of laboratories from 1954 to 1966. It was during these years that he established the famed Bone Marrow Course, an intensive study of the cellular and tissue changes in the marrow associated with hematopoietic dyscrasias. Through this course passed many of the contemporary leaders in American hematology. Moloney was also one of the first to recognize the need for blood banks and was involved in their establishment throughout the Boston area even before World War II.

Soon after the first evidence began to emerge of an increased incidence of leukemia among the survivors, Grant Taylor, then the Director of ABCC, urged Dr. Moloney to come to Hiroshima. At ABCC, Moloney headed the Department of Medicine, supervised clinic operations, and gathered about him an able staff including Robert Lange, Fred Ownby, and Jack Lewis. In his reminiscences of ABCC (*Song among the Ruins*, Cambridge: Harvard University Press, 1990), Dr. William Schull described Bill Moloney as "perpetually charged with the excitement of science, [one who] never shirked a battle and [who] charmed, provoked, or simply challenged his staff to a pitch of biologic curiosity" (128). While he was with

the Commission, Dr. Moloney not only introduced a program of clinical rounds for the benefit of his American and Japanese colleagues but was instrumental in making available for use in Japan a variety of otherwise unavailable American pharmaceuticals for the treatment of leukemia.

From 1962 to 1963, at the invitation of Drs. Victor Bond, William Conard, and Eugene Cronkite of the Medical Department at Brookhaven National Laboratory, Dr. Moloney helped evaluate the health effects of fallout from Marshall Island hydrogen-bomb testing eight years earlier.

Dr. Moloney recounts his sixty-year career in his autobiography, co-authored with Sharon Johnson, *Pioneering Hematology*, Boston: Francis



Dr. Moloney pictured with members of ABCC's nursing staff. (ABCC file photo)

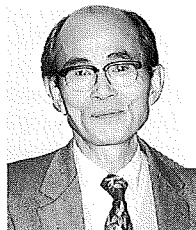
A. Countway Library of Medicine, 1997.

At the time of his death, Dr. Moloney was emeritus professor of medicine at Harvard Medical School and emeritus physician and chief of the hematology division at Peter Bent Brigham Hospital.

Dr. Moloney leaves two sons and a daughter, 24 grandchildren, and seven great grandchildren.

Hitoshi "Gus" Tokai, Nagasaki Interpreter and Translator by Yasutaka Ohgushi, Assistant Chief of the Secretariat, Nagasaki

Mr. Hitoshi Augustine "Gus" Tokai, interpreter and translator in Nagasaki's ABCC-RERF laboratory for more than 40 years, died February 27, 1999, after several months of intermittent health problems. He was 68. He is survived by his wife and three children.



Mr. Tokai was well known to many of the foreign staff and visitors who frequented the Nagasaki facility. He and Brian Burke-Gaffney were thought to be an ideal combination of interpreters. In his book, *Song among the Ruins* (Cambridge: Harvard University Press, 1990), Dr. William Schull called Gus ABCC's "Japanese voice in negotiations with the community" (202).

Mr. Tokai, the father of three children, one autistic, was actively involved in establishing Japan's National Association of Autism to support families with autistic members. He was also president of the Nagasaki

Interpreters' Club.

A sincere man with a wonderful sense of humor, Mr. Tokai was well trusted and well liked by everyone, called upon in his work to engage in a wide variety of social situations. As a teenager, he had been a survivor of the Nagasaki atomic bombing, but his home was only 500 meters from the hypocenter, and he lost his parents and a younger and older sister as well as his older sister's children. He accredited his strong Catholic faith with his consolation at that time. In fact, he studied for the priesthood, spending four years of training studying theology in Montreal, Canada's Grand Seminary. He was not yet ordained when he felt a different vocation.

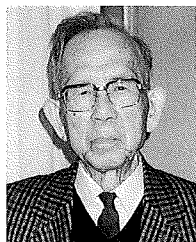
In November 1958, Mr. Tokai began working in the Nagasaki lab's business office, and in October 1985, he became chief of the public relations office. After 34 years, he retired in December 1992, returning to RERF as a part-time translator during 1993 and again in July 1997. He left last June, when he had to be hospitalized, but returned briefly in November and

See *Tokai* on next page

Former RERF Visiting Director and Japanese Diplomat, Tomohiko Hayashi

by Itsuzo Shigematsu, RERF Consultant Emeritus and Former RERF Chairman

Tomohiko Hayashi, who served two terms, from 1975 to 1983, as RERF visiting director, died 23 January 1999, the day after his 93rd birthday. Mr.



Hayashi was one of RERF's first directors following the reorganization of ABCC into RERF; he was recommended by the Ministry of Foreign Affairs. Before arriving at RERF, Mr. Hayashi spent 40 years in the Japanese diplomatic corps.

Mr. Hayashi was born in Hiroshima and graduated from the Hiroshima Higher Normal School (now Hiroshima University), after which he taught English for four years at Tadanoumi Middle School. After completing graduate studies at Utah State University in the U. S., he returned to Japan and joined the Ministry of Foreign Affairs in 1932. In 1937, he took a position at the English

embassy, where it is said he joined the Japanese ambassador to England, Shigeru Yoshida, on his daily horseback rides through Hyde Park. His close relationship with Mr. Yoshida probably motivated Mr. Hayashi to serve for many years on the board of directors of the Shigeru Yoshida International Fund, established after the ambassador's death. He concluded his diplomatic career after serving as consul-general in Winnipeg, Canada. Mr. Hayashi then consulted for Mitsubishi Chemical Industries, Ltd., before coming to RERF in 1975 and joining the other four Japanese directors, Chairman Hisao Yamashita, Permanent Director Masuo Takabe, and Visiting Directors Iwao Yasuda and Raisuke Shirabe.

Mr. Hayashi's sincerity gained him the affection of people wherever he went. He was said to have been treated as an honorary citizen of Winnipeg and invited back to the city even after retirement.

Mr. Hayashi was at RERF dur-

ing my first two years there, and his periodic visits in addition to his semi-annual board meeting visits are still fresh in my mind. He spent his days at his Kita-Karuizawa villa from May to October, and from November through April, he returned to his home in Tokyo. Almost every autumn, in the harvest season, I would receive a big load of his home-grown corn.

On behalf of Chairman Nagataki, I attended Mr. Hayashi's funeral 27 January in Tokyo. Another former RERF staff member, Ms. Katsuko Fukuba, who had been one of many staff he had welcomed to his villa, also came. The service was simple and devoid of pomp, reflecting Mr. Hayashi's unpretentious personality. The chief mourner was his eldest son, Mr. Sadayuki Hayashi, former deputy secretary of the Ministry of Foreign Affairs and now Japan's ambassador to England, a person who has also helped RERF a great deal. I join the whole RERF staff in praying for the repose of Mr. Hayashi's soul.

Dr. Walter J. Russell, ABCC-RERF Radiology Chairman and RERF Advisor, 1959-1989

By Haruma Yoshinaga, former professor, Research Institute for Radiation Biology and Medicine, Hiroshima University and former consultant, RERF Department of Clinical Studies



It was before noon, July 1, 1989, when my wife, grandchild, and I saw Dr. Walter J. Russell and his family off at Hiroshima Station. They were

going back to Seattle, Washington, his hometown, leaving behind Hiroshima, their long-time home. Since that summer day, we had kept up on one another's well-being through Christmas cards and occasional telephone conversations. I had heard recently that he was not well, and on February 23, he died in Seattle. He was 75.

Dr. Russell graduated from St. Louis University in 1952, and in 1959, he became a radiologist. In July of that year, Dr. Russell became radiation department chief at ABCC, and for four years after his July 1985 retirement, he acted as a research consultant, continuing to make a large contribution to RERF research activities. He wrote some 90 technical reports and published numerous

papers in scientific journals.

Immediately after arriving at ABCC, Dr. Russell joined the Nippon Societas Radiologica and other societies. I got to know Dr. Russell when ABCC and Hiroshima University began a joint study on genetic effects and leukemias induced by medical radiation. He strongly encouraged those engaged in the joint study and the young ABCC radiologists to write papers and read them at scientific meetings. Needless to say, he himself wrote and presented many papers. He had a strong belief that "a physician must not forget his/her studies," and in 1971, he earned a doctorate of medical science from Kyushu University. In 1975, he became a fellow of the American College of Radiology and, in 1990, an emeritus fellow.

Dr. Russell also worked very hard so that young Japanese physicians could receive training in the U.S. Physicians and medical scientists all over Japan constantly requested that he edit their papers written in English, and he did, showing no sign of reluctance and sometimes staying up all

night in the process. And, he never received remuneration. How much help Japanese radiologists received from him!

Walter Russell was a kind, considerate, and outstanding physician with a strong sense of justice.

Rest in peace, my friend.

Tokai, continued from previous page

December, when he could be seen every Thursday sitting quietly again at his desk on the fourth floor doing his translating work. He was hospitalized again in January but indicated that he hoped to return to work by March. We were looking forward to his return when we learned that he had died at St. Francisco Hospital.

As Dr. Schull remarked when he spoke of Mr. Tokai's extensive losses in the bombing, "To all of us who live to be old, there comes a time when, among the people we have known, the dead outnumber the living; to Gus and the other survivors, this moment came early" (204). We are saddened that he too is now gone. We will miss him dearly. May his soul rest in peace.

Dr. Isamu Nagai, ABCC Associate Director and Former Director, JNIH Nagasaki Lab

Dr. Isamu Nagai, ABCC-RERF consultant emeritus and former director of the Japanese National Institute of Health (JNIH)'s Nagasaki Branch Laboratory, died in Tokyo 19 March 1999. He was 96. RERF Emeritus Consultant and Former Chairman Itsuzo Shigematsu represented RERF at the funeral.

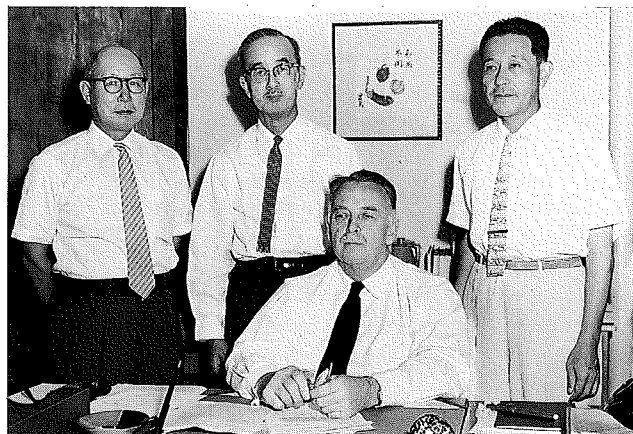
Dr. Nagai received his medical degree from the Keio University Medical School in 1928 and joined the Kitasato Research Institute thereafter. In 1931, he went to the settlement in Shanghai, where he worked for 15 years for the Public Health Service and developed an international sense as well as his English skills. Upon his return to Japan in 1946, Dr. Nagai joined the Ministry of Health and Welfare's (MHW) Prevention Bureau. In August 1947, he transferred to JNIH.

In his roles at JNIH, Dr. Nagai was affiliated with ABCC from its earliest days. In October 1947, he was asked to join the newly established JNIH's director, Rokuzo Kobayashi, and deputy director, Saburo Kojima and the MHW Prevention Bureau director, Kikuo Hamano, in conferring with the United States-Japan Joint Commission on A-bomb Damages. Americans at the meeting included Lt. Col. Carl Tessmer, ABCC's first director, and Drs. Shields Warren and James V. Neel. The Joint Commission called for continued long-term studies of the health effects of radiation from the atomic bombings, and the meeting Dr. Nagai attended resulted in a request by the Americans for JNIH's support. Following that request, MHW sent Dr. Nagai to ABCC in Hiroshima in November 1947 to formulate a plan for their involvement. JNIH then budgeted a small amount for the undertaking and became involved in ABCC's activities.

Dr. Hiroshi Maki (whose October 1998 death was reported in the last issue of Update, (9[2]: 2) was ABCC's only Japanese associate director until 1956, and he was the JNIH director for ABCC's Hiroshima and Nagasaki laboratories during that time. Dr. Maki liaised with Dr. Nagai, who remained in Tokyo, where he supported operations for the JNIH laboratory branches that had been established in Hiroshima and Nagasaki in 1948 and also worked as JNIH's investigation department head and library head.

In 1956, Dr. Masanori Nakaizumi became JNIH's representative at the Nagasaki laboratory prior to Dr. George Darling's 1957 appointment as ABCC chairman. In 1957, under Dr. Darling, a second associate directorship was established for the ABCC Nagasaki laboratory, and Dr. Nagai moved to Nagasaki to serve as associate director of the ABCC Nagasaki laboratory and as director of JNIH's Nagasaki Branch Laboratory, positions he held until his retirement in June 1973, when he began a three-year appointment as special consultant to the ABCC director before assuming emeritus status in 1978.

In ABCC's 1968-9 Annual Report, Dr. Nagai recalled his early years with the Commission, "It is with much joy despite everything that the years following 1957 have seen the establishment of the three major research programs [Life Span Study, Adult Health Study, and F₁ Study], the smooth promotion of a cooperative relationship with JNIH and other central and local organizations concerned, and the very high evaluation of ABCC research results within and outside this country [Japan]." (p. xiv)



ABCC directors, pictured August 23, 1961. From left to right, Drs. Isamu Nagai, Masanori Nakaizumi, George Darling, and Hiroshi Maki. (ABCC file photo)

Dr. Nagai is remembered as a very pleasant man who was very easy to work with and very cooperative. His contributions marked his place in ABCC-RERF history. Together, Drs. Nagai and Maki made great efforts for the development of US-Japanese collaborative studies at ABCC, establishing the foundation for the present RERF.

Our sympathies go out to Kiyoshi Nagai, Dr. Nagai's son, and all those family members and friends who mourn his passing.

Meetings, continued from page 36

Japanese Society of Radiological Technology, 7-8 November 1998, Hiroshima, **Japan**

Thirtieth National Institute of Radiological Sciences (NIRS) Symposium, 19-20 November 1998, Chiba, **Japan**

Forty-first Annual Meeting of the Japan Radiation Research Society, 2-4 December 1998, Nagasaki, **Japan**

Twenty-eighth Annual Meeting of the Japanese Society for Immunology, 2-4 December 1998, Kobe, **Japan**

Thirteenth Annual Congress of the Japan Menopause Society, 5-6 December 1998, Yokohama, **Japan**

International Workshop on Health Effects of Thorotrast, Radium, Radon, and other Alpha Emitters 1999, 19-22 January 1999, Tokyo, **Japan**

Ninth General Meeting of the Japan Epidemiological Association, 21-22 January 1999, Nagoya, **Japan**

Nonlinear Statistical Modeling and Data Analysis, 29-31 January 1999, Toba, **Japan**

Statistics Spring Seminar 1999, 19-21 March 1999, Kawaguchiko-machi, Yamanashi, **Japan**

1999 Spring Meeting of the Atomic Energy Society of Japan, 22 March 1999, Hiroshima, **Japan**

Sixty-third Scientific Meeting of the Japanese Circulation Society, 27-29 March 1999, Tokyo, **Japan**

Scientific Publications

1 October 1998 - 31 March 1999

Following are listings of the 25 manuscripts reported published by RERF staff members between 1 October 1998 and 31 March 1999 and any others not previously reported for the 1998-1999 fiscal year. Publications are arranged in reverse order by research protocol (RP) number by study program. Publications not directly related to a given RP are listed separately after these as collaborative and institutional publications and include RERF director-authored and edited publications. A separate section also follows for Chernobyl-related collaborative research.

Investigators' and authors' names are followed by their affiliations in parentheses. Article, chapter, or book titles appear in italics. Abstracts are included for those articles bound in RERF Report covers. The following codes are used to identify RERF departments in publications and the section on meeting participation and oral presentations (See page 34.):

Clinical Studies, Hiroshima	CH	Clinical Studies, Nagasaki	CN
Epidemiology, Hiroshima	EH	Epidemiology, Nagasaki	EN
Genetics	G	Radiobiology	R
Statistics	S	Information Technology	IT
RERF Director	D		

(**Japanese**) after an entry indicates that the original article is in Japanese; (**J**) after an entry listed with an RERF Report number indicates that a Japanese translation is available.

Those publications designated as RERF Reports have undergone internal review prior to journal submission. Following acceptance and publication by a peer-reviewed journal, reprints are purchased from the publisher and bound with a Japanese summary in RERF Report covers.

Life Span Study**RP 1-75**

Mendelsohn ML (Lawrence Livermore National Laboratory, Livermore, California), Pierce DA (S). *A multimutation model for cancer based on age-time patterns of radiation effects: 2. Biological aspects.* Low Doses of Ionizing Radiation: Biological Effects and Regulatory Control (Invited Papers and Discussions). Vienna, Austria: International Atomic Energy Agency; 1998, p. 123-33.

Pierce DA (S), Mendelsohn ML (Lawrence Livermore National Laboratory, Livermore, California). *A multimutation model for cancer based on age-time patterns of radiation effects: 1. Mathematical and epidemiological aspects.* Low Doses of Ionizing Radiation: Biological Effects and Regulatory Control (Invited Papers and Discussions). Vienna, Austria: International Atomic Energy Agency; 1998, p. 113-22.

Preston DL (S). *Low dose radiation and human health: Risk estimates.* Low Doses of Ionizing Radiation: Biological Effects and Regulatory Control

(Invited Papers and Discussions). Vienna, Austria: International Atomic Energy Agency; 1998, p. 217-29.

Adult Health Study**RP 2-75**

Kasagi F (S). *Facts & figures. Mortality comparison between migrants from and residents of the catchment area in the Adult Health Study.* Hiroshima Igaku [Journal of the Hiroshima Medical Association] 1999 (January); 52(1): 84. (**Japanese**)

Kodama K (CH), Kasagi F (S). *Risk factors of coronary heart disease in the elderly and their trend.* Nihon Junkanki Kanri Kenkyu Kyogikai Zasshi [Journal of the Japanese Association for Cerebro-Cardiovascular Disease Control] 1998 (November); 33(3): 221-9. (**Japanese**)

Immunology Studies**RPs 9-89 and 7-88**

Kyoizumi S (R), Kusunoki Y (R), Seyama T (R), Hatamochi A (Chiba University School of Medicine), Goto M (Tokyo Metropolitan Otsuka Hospital). *In vivo somatic mutations in*

Werner's syndrome. Human Genetics 1998 (October); 103(4): 405-10. (RERF Report 5-98)

Abstract: The frequencies of mutant erythrocytes with loss of heterozygosity at the glycoprotein A (GPA) locus and mutant CD4⁺ T cells lacking surface expression of the T-cell receptor $\alpha\beta$ (TCR)/CD3 complex were measured by flow cytometry for Japanese Werner's syndrome (WRN) patients. The hemizygous and homozygous GPA mutant frequencies (GPA Mfs) and the TCR/CD3-defective mutant frequency (TCR Mf) in WRN patients were found to be significantly higher than those in normal controls in the same age range. However, because these Mfs in the patients are only about twice those in controls, it is difficult to conclude that the WRN gene mutations cause instability of somatic genes. This contrasts markedly with Bloom's syndrome (BLM) patients, whose GPA and TCR Mfs were previously reported to increase about 50- and 15-fold, respectively. The difference in Mfs is one aspect of the large variation in the phenotype observed between WRN and BLM patients, suggesting a different role of the responsible genes, both of which belong to the RecQ DNA helicase gene family, in the control of somatic mutagenesis.

Special Clinical Studies**RP 5-92**

Larson EB (University of Washington School of Medicine [UWSM]), McCurry SM (UWSM), Graves AB (University of South Florida), Bowen JD (UWSM), Rice MM (UWSM), McCormick WC (UWSM), Zee N (UWSM), Homma A (Tokyo Metropolitan Institute of Gerontology), Imai Y (St. Marianna University, Tokyo), White L (National Institute on Aging [NIA], Honolulu, Hawaii), Masaki K (NIA), Petrovitch H (NIA), Ross W (NIA; Honolulu Veterans Affairs), Yamada M (CH), Mimori Y (Hiroshima University School of Medicine [HUSM]), Sasaki H (HUSM). *Standardization of the clinical diagnosis of the dementia syndrome and its subtypes in a cross-national study: The Ni-Hon-Sea experience.* Journal of Gerontology 1998; 53A(4):M313-9.

Yamada M (CH), Sasaki H (CH), Mimori Y (Hiroshima University

School of Medicine [HUSM], Kasagi F (S), Sudo S (HUSM), Ikeda J (HUSM), Hosoda Y (CH), Nakamura S (HUSM), Kodama K (CH). *Prevalence and risks of dementia in the Japanese population: RERF's Adult Health Study Hiroshima subjects*. Journal of the American Geriatrics Society 1999 (February); 47(2): 189-95. (RERF Report 11-97)

Abstract:

Objectives: To study the prevalence rate of dementia and its subtypes in Japan and to investigate the relationship of risk factors, such as demographic features and disease history, to the prevalence of Alzheimer's disease or vascular dementia.

Design: A prevalence study within a longitudinal cohort study.

Setting: The original Adult Health Study (AHS) cohort consisted of atomic-bomb survivors and their controls selected from residents in Hiroshima and Nagasaki using the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. Since 1958, the AHS subjects have been followed through biennial medical examinations.

Participants: Subjects were 637 men and 1585 women aged 60 years or older in the AHS cohort. Forty-eight subjects resided in hospitals and institutions.

Measurements: In addition to the biennial medical examinations ongoing since 1958, a screening test for cognitive impairment (CASI) was conducted by trained nurses between September 1992 and September 1996. The prevalence of dementia and its subtypes was assessed in 343 subjects suspected to have dementia and in 272 subjects with high CASI scores who were selected randomly.

Results: The prevalence of dementia based on DSM III/R criteria, using neurological examination, the IQCODE, and CDR ≥ 1 , was 7.2%. The prevalence of Alzheimer's disease was 2.0% in men and 3.8% in women, and the prevalence of vascular dementia was 2.0% in men and 1.8% in women. The relationship of risk factors to Alzheimer's disease or vascular dementia was investigated by the multivariate logistic linear regression analysis. Odds ratios of Alzheimer's disease for age (in 10-year increments), attained education (in 3-year increments), history of head trauma, and history of cancer are 6.3, 0.6, 7.4, and 0.3, respectively. Odds ratios of vascular dementia for age, history of stroke, and history of hypertension are 2.0, 35.7, and 4.0, respectively. Neither type of dementia showed any significant effects of sex or radiation exposure.

Conclusion: This study is the first study of Japanese dementia rates carried out with a protocol similar enough to that of a US study to allow meaningful comparisons. The prevalence rates demonstrated are more similar to US rates than were found in many previous reports in Japan.

RPs 3-91 and 3-89

Fujiwara S (CH). Concept and epidemiology of *osteoporosis*. Rinsho Kagaku [Journal of Clinical Science] 1998 (15 October); 34(10):1298-304. (Japanese)

Special Clinical Studies and Tissue Registry

RP 2-91

Ron E (National Cancer Institute, Bethesda, Maryland),

Preston DL (S), Kishikawa M (Aichi Human Service Center, Aichi Prefectural Colony), Kobuke T (Welfare Association Onomichi General Hospital, Onomichi, Hiroshima), Iseki M (Institute of Tropical Medicine, Nagasaki University), Tokuoka S (Consultant, RERF), Tokunaga M (Kagoshima University School of Medicine), Mabuchi K (EH). *Skin tumor risk among atomic-bomb survivors in Japan*. Cancer Causes and Control 1998 (August); 9(4): 393-401. (RERF Report 10-97)

Abstract:

Objectives: Elevated risks of skin cancer following high doses of ionizing radiation have long been known. Recent reports on atomic-bomb survivors indicate that nonmelanoma skin cancer can be induced at low to medium doses. We studied atomic-bomb survivors to determine the effects of radiation on specific histologic types of skin cancer and to describe the dose-response relationship.

Methods: Cases of melanoma, nonmelanoma skin cancers, and Bowen's disease were ascertained between 1958 and 1987 for the 80,000 cohort members through the population-based Hiroshima and Nagasaki (Japan) tumor registries augmented by searches of other records.

Results: An excess of basal cell carcinoma ($n = 80$), with some suggestion of a non-linear dose response, was observed. The excess risk decreased markedly as age at exposure increased, and there was no evidence for an interaction between ionizing and ultraviolet radiation. No dose-response was found for squamous cell carcinoma ($n = 69$). The excess relative risk point estimates were large, but statistically nonsignificant for both melanoma ($n = 10$) and Bowen's disease ($n = 26$).

Conclusions: The basal layer of the epidermis appears to be quite sensitive to radiation carcinogenesis, particularly at a young age. The suprabasal layer seems to be more resistant, as shown by the lack of an association for squamous cell carcinomas.

Special Clinical Studies

RPs 5-90 and 2-94 (Cell Biology)

Mizuno T (R), Nagamura H (R), Iwamoto KS (R), Ito T (R), Fukuhara T (EH), Tokunaga M (EH), Tokuoka S (EH), Mabuchi K (EH), Seyama T (R). *RNA from decades-old archival tissue blocks for retrospective studies*. Diagnostic Molecular Pathology 1998 (August); 7(4): 202-8. (RERF Report 8-97)

Abstract: The validity of molecular studies using DNA and RNA extracted from decades-old formalin-fixed and paraffin-embedded tissue blocks has been demonstrated. The quality and usability of DNA and RNA from archival tissues are modified by various factors, such as the fixative, the fixation time, and the postmortem time. However, in contrast to DNA, there are no comprehensive studies quantitatively addressing the feasibility of RNA from old (more than 10 years) archival samples. This study examined the integrity of RNA extracted from 738 autopsy liver and 63 autopsy thyroid cancer tissue blocks procured during a span of nearly four decades, beginning in 1952 and ending in 1989, from the atomic bomb survivors. The integrity of RNA was assessed by amplification of *c-BCR* messenger RNA (mRNA) between two sequential exons with an intervening intron by reverse-transcription poly-

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32 Publications

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merase chain reaction (RT-PCR). The integrity of RNA was influenced by the age of the samples and the postmortem time, but not by the formalin-fixation period. It was possible to amplify more than 60% of the samples. Using these RNAs, the *HCV* genome in liver cancers and the *H4-RET* gene in thyroid cancers were detectable. This study illustrates the possibility of molecular studies using RNA from routinely prepared paraffin blocks stored for long periods and provides the statistics and critical factors to consider in assessing the feasibility of such contemplated studies.

Cell Biology Studies

RP 2-94

Yano M (Hiroshima University School of Medicine [HUSM]; R), Asahara T (HUSM), Dohi K (HUSM), Mizuno T (R), Iwamoto KS (R), Seyama T (R). *Close correlation between a p53 or hMSH2 gene mutation in the tumor and survival of hepatocellular carcinoma patients*. International Journal of Oncology 1999 (March); 14(3): 447-51. (RERF Report 7-98)

Abstract: We analyzed 42 hepatocellular carcinomas (HCC) (38 patients) for mutations in the DNA mismatch repair gene *hMSH2* and the *p53* tumor suppressor gene, a possible upregulator of *hMSH2*. Mutations of the *hMSH2* or *p53* gene were detected in 13 patients (34%). There were no patients who possessed mutations in both genes. There was a significant correlation between mutation of either gene and pathological indicators of malignancy. The survival rate of patients with *hMSH2* or *p53* gene mutation-positive tumors was much poorer than that with *hMSH2* and *p53* gene mutation-negative tumors ($p=0.0012$). Our results suggest that mutations in the *p53* or *hMSH2* gene may closely correlate with the survival of hepatocellular carcinoma patients.

Cytogenetics

RP 8-93

Nakano M (G), Kodama Y (G), Ohtaki K (G), Itoh M (G), Nakamura N (G). *S values are not a signature for a significant contribution of neutrons to the radiation dose received by atomic-bomb survivors*. International Journal of Radiation Biology 1999 (January); 75(1): 47-9. (RERF Report 4-98)

Abstract:

Purpose: It has been proposed previously that the ratio of complete to incomplete translocations as seen by fluorescence *in situ* hybridization (FISH), the S value, can be a cytogenetic fingerprint of exposure to radiation of different qualities. Results from a previous study suggested that the S value is ~ 10 for sparsely ionizing radiations such as X- and gamma-rays, and ~ 2 for densely ionizing radiations. Based on FISH data of atomic-bomb (A-bomb) survivors, which showed an S value of 3.25, a significant neutron component to A-bomb radiation was suggested. To examine the possibility, the present *in vitro* study was conducted using X-rays.

Materials and methods: Human blood lymphocytes were exposed to X-rays and first metaphase were examined with FISH using DNA probes for chromosomes 1, 2 and 4.

Results: The S value was 3.16 for X-rays, which differs from ~ 10 as reported previously, and not larger than the 3.25 obtained from the blood lymphocytes of A-bomb survivors.

Conclusions: S values seem to vary among laboratories even after exposure of cells to sparsely ionizing radiations. Data from this study show that S values are not a signature for a significant contribution of neutrons to the radiation dose received by A-bomb survivors in Hiroshima.

RP 2-66

Cologne JB (S), Pawel DJ (US Environmental Protection Agency, Washington, DC), Preston DL (S). *Statistical issues in biological radiation dosimetry for risk assessment using stable chromosome aberrations*. Health Physics 1998 (November); 75(5):518-29. (RERF Report 4-96)

Abstract: Biological dosimeters are useful for epidemiologic risk assessment in populations exposed to catastrophic nuclear events and as a means of validating physical dosimetry in radiation workers. Application requires knowledge of the magnitude of uncertainty in the biological dose estimates and an understanding of potential statistical pitfalls arising from their use. This paper describes the statistical aspects of biological dosimetry in general and presents a detailed analysis in the specific case of dosimetry for risk assessment using stable chromosome aberration frequency. Biological dose estimates may be obtained from a dose-response curve, but negative estimates can result and adjustment must be made for regression bias due to imprecise estimation when the estimates are used in regression analyses. Posterior-mean estimates, derived as the mean of the distribution of true doses compatible with a given value of the biological endpoint, have several desirable properties: they are nonnegative, less sensitive to extreme skewness in the true dose distribution, and implicitly adjusted to avoid regression bias. The methods necessitate approximating the true-dose distribution in the population in which biological dosimetry is being applied, which calls for careful consideration of this distribution through other information. An important question addressed here is to what extent the methods are robust to misspecification of this distribution, because in many applications of biological dosimetry it cannot be characterized well. The findings suggest that dosimetry based solely on stable chromosome aberration frequency may be useful for population-based risk assessment.

Not Emanating from Specific Protocols

Asakawa J (G). *A genomic scanning—RLGS method*. In: Japanese Electrophoresis Society, ed. Principles and Applications of Electrophoresis. Tokyo: Ishiyaku Publishers, Inc.; 1999 (February 25), p. 95-103. (Japanese)

Asakawa J (G). *Nucleic Acid—DNA cloning*. In: Japanese Electrophoresis Society, ed. Principles and Applications of Electrophoresis. Tokyo: Ishiyaku Publishers, Inc.; 1999 (February 25), p. 250-5. (Japanese)

Collaborative/Institutional/Directors' Publications

Fujiwara S (CH), Fukunaga M (Kawasaki Medical School [KMS], Kurashiki, Okayama), Nakamura T (University of Occupational and Environmental Health, Kitakyushu,

Fukuoka, Chen JT (Cancer Institute Hospital, Tokyo), Shiraki M (Research Institute and Practice for Involution Diseases, Nagano), Hashimoto T (Wakayama Medical College), Yoh K (Hyogo College of Medicine), Nakamura T (Tokyo Metropolitan Geriatric Hospital [TMGH]), Mizunuma H (Gunma University), Tomomitsu T (KMS), Kasagi F (S), Masunari N (CH), Orimo H (TMGH). Rates of change in spinal bone density among Japanese women. *Calcified Tissue International* 1998 (September); 63(3): 202-7.

Ichinose Y, Eguchi K (Nagasaki University School of Medicine [NUSM]), Migita K (NUSM), Kawabe Y, Tsukada T, Koji T (NUSM), Abe K, Aoyagi T, Nakamura H, Nagataki S (D). Apoptosis induction in synovial fibroblasts by ceramide: *in vitro* and *in vivo* effects. *Journal of Laboratory and Clinical Medicine* 1998 (May);131(5): 410-6.

Jia L (Institute of Development, Aging and Cancer, Tohoku University [IDAC/TU], Sendai; China-Japan Friendship Hospital, Beijing), Osada M (IDAC/TU), Ishioka C (IDAC/TU), Gamo M (IDAC/TU), Ikawa S (IDAC/TU), Suzuki T (IDAC/TU), Shimodaira H (IDAC/TU), Niitani T (IDAC/TU), Kudo T (IDAC/TU), Akiyama M (R), Kimura N (Tokyo Metropolitan Institute of Gerontology [TMIG]), Matsuo M (TMIG), Mizusawa H (National Institute of Health Science, Tokyo), Tanaka N (Hadano Research Institute, Food and Drug Safety Center, Hadano, Kanagawa), Koyama H (Kihara Institute for Biological Research, Yokohama City University), Namba M (Institute of Molecular and Cellular Biology, Okayama University Medical School), Kanamaru R (IDAC/TU), Kuroki T (Institute of Molecular Oncology, Showa University, Tokyo). *Screening the p53 status of human cell lines using a yeast functional assay*. *Molecular Carcinogenesis* 1997 (August); 19(4):243-53.

Nakashima T, Sasaki H, Tsuboi M, Kawakami A, Fujiyama K (Nagasaki University School of Medicine [NUSM]), Kiriya T (NUSM), Eguchi K (NUSM), Ichikawa M, Nagataki S (D). Inhibitory effect of glucocorticoid for osteoblast apoptosis induced by activated peripheral blood mononuclear cells. *Endocrinology* 1998 (April);139(4): 2032-40.

RERF. *RERF directors, supervisors, and scientific councilors (as of July 1998)*. Hiroshima Igaku [Journal of the Hiroshima Medical Association] 1998 (September); 51(9): 1165. (Japanese)

Shirahige Y (Nagasaki University School of Medicine [NUSM]), Ito M (NUSM), Ashizawa K (NUSM), Motomura T (NUSM), Yokoyama N (NUSM), Namba H (NUSM), Fukata S, Yokozawa T, Ishikawa N, Mimura T, Yamashita S (NUSM), Sekine I (NUSM), Kuma K, Ito K, Nagataki S (D). Childhood thyroid cancer: Comparison of Japan and Belarus. *Endocrine Journal (Tokyo)* 1998 (April);45(2): 203-9.

Tamura M (Nagasaki University School of Medicine [NUSM]), Yokoyama N (NUSM), Abe Y, Sera N, Tominaga T (CN), Ashizawa K (NUSM), Ejima E, Kiriya T (NUSM), Uetani M, Kuwayama A, Nagataki S (D). Preoperative treatment of growth hormone-producing pituitary

adenoma with continuous subcutaneous infusion of octreotide. *Endocrine Journal (Tokyo)* 1998 (April);45(2): 269-75.

Tamura M (Nagasaki University School of Medicine [NUSM]), Kimura H (NUSM), Koji T (NUSM), Tominaga T (CN), Ashizawa K (NUSM), Kiriya T (NUSM), Yokoyama N (NUSM), Yoshimura T (NUSM), Eguchi K (NUSM), Nakane PK (NUSM), Nagataki S (D). Role of apoptosis of thyrocytes in a rat model of goiter. A possible involvement of Fas system. *Endocrinology* 1998 (August);139(8): 3646-53.

Wolff S (D). *Chromosomes in the assessment of the effects of low levels of genotoxic agents*. *Human and Experimental Toxicology* 1998; 17: 625-32.

Publications of Interest Using RERF Data

Editor's note: Researchers from outside institutions are able to obtain data sets from RERF, and they sometimes incorporate atomic-bomb survivor data into their own studies. Listed in this section is information on such publications that have not been previously reported in Update for 1997 through 1999. Additional entries may be found back to 1987 on the RERF home page (<http://www.rerf.or.jp/eigo/archives/outpub.htm>). Publications are listed alphabetically by author name.

Little MP (National Radiological Protection Board, UK [NRPB]), deVathaire F (Institut Gustave Roussy, France), Charles MW (School of Physics and Space Research, University of Birmingham, UK), Hawkins MM (University of Birmingham School of Medicine, UK), Muirhead CR (NRPB). *Variations with time and age in the risks of solid cancer incidence after radiation exposure in childhood*. *Statistics in Medicine* 1998; 17: 1341-55.

Little MP (National Radiological Protection Board, UK [NRPB]), deVathaire F (Institut Gustave Roussy, France [IGR]), Shamsaldin A (IGR), Oberlin O (IGR), Campbell S (Thames Cancer Registry, UK), Grimaud E (IGR), Chavaudra J (Service de Physique, IGR), Haylock RGE (NRPB), Muirhead CR (NRPB). *Risks of brain tumour following treatment for cancer in childhood: Modification by genetic factors, radiotherapy and chemotherapy*. *International Journal of Cancer* 1998; 78: 269-75.

Little MP (National Radiological Protection Board, UK [NRPB]), Muirhead CR (NRPB). *Curvature in the cancer mortality dose response in Japanese atomic bomb survivors: Absence of evidence of threshold*. *International Journal of Radiation Biology* 1998; 74(4): 471-80.

Little MP (National Radiological Protection Board, UK [NRPB]), Muirhead CR (NRPB), Charles MW (School of Physics and Space Research, University of Birmingham, UK). *Describing time and age variations in the risk of radiation-induced solid tumour incidence in the Japanese atomic bomb survivors using generalized relative and absolute risk models*. *Statistics in Medicine* 1999; 18:17-33.

Continued on next page

34 Publications Using RERF Data, Meeting Participation

Continued from previous page

Stewart A (University of Birmingham School of Medicine, UK). *A-bomb data: Detection of bias in the Life Span Study cohort*. *Environmental Health Perspectives* 1997; 105(Supp 6): 519-21.

RERF Research Presented at Meetings 1 October 1998 - 31 March 1999 (and presentations not previously reported for the fiscal year)

RERF researchers reported attending three meetings outside of Japan at which they made three presentations and 13 meetings in Japan at which they made 26 presentations from 1 October 1998 through 31 March 1999. As with publications, research presentations are listed by research protocol number under the appropriate study program. Meetings are listed chronologically under RP. The same department codes used for publications are used to identify investigators' affiliations.

Life Span Study (LSS)

(RP 1-75)

❖Preston DL (S). **Radiation effects on the atomic-bomb survivors: Recent findings.** *Special Invited Presentations at the Swedish Radiation Protection Institute and the Karolinska Institute, 5 November 1998, Stockholm, Sweden*

❖Preston DL (S). **New findings of long-term radiation effects on cancer and noncancer risks among atomic-bomb survivors and the need for animal experiments.** *Thirtieth National Institute of Radiological Sciences Symposium, 19-20 November 1998, Chiba, Japan*

❖Shimizu Y (EH). **Low-dose- and high-dose-rate atomic-bomb data—Basic data for the evaluation of radiation-induced cancer risk.** *Forty-first Annual Meeting of the Japan Radiation Research Society, 2-4 December 1998, Nagasaki, Japan*

❖Preston DL (S). **Radiation effects on the atomic-bomb survivors: Recent findings.** *South African Council on Nuclear Safety, 11 December 1998, Capetown, South Africa*

❖Shimizu Y (EH). **Cancer risk among atomic-bomb survivors.** *1999 Spring Meeting of the Atomic Energy Society of Japan, 22 March 1999, Hiroshima, Japan*

Adult Health Study (AHS)

(RPs 2-75, 3-89 [Special Clinical Studies])

❖Fujiwara S (CH), Kasagi F (S), Kodama K (CH). **Trend of lifetime risks and mortality after osteoporosis-related fractures.** *Ninth General Meeting of the Japan Epidemiological Association, 21-22 January 1999, Nagoya, Japan*

(RP 2-75)

❖Fujita Y (EH), Kodama K (CH), Kasagi F (S), Fujita S (S), Nose T (Tottori University School of Medicine), Yanagawa H (Jichi Medical School). **Building aging level indices based on ability to perform personal care and household management activities.**

❖Kurusu T (CH), Yamada M (CH), Fujiwara S (CH), Hidaka K (CH), Kodama K (CH). **The contribution of senility to death in the Adult Health Study.**

❖Masunari N (CH), Yamada M (CH), Kasagi F (S), Fujiwara S (CH), Matsuoka K (CH), Ishii K (CH), Kodama K (CH). **Actual state of hypercholesterolemia in the Adult Health Study population: Therapeutic effect of oral medication.**

Fifty-seventh Annual Meeting of Japanese Society of Public Health, 28-30 October 1998, Gifu, Japan

❖Yamane K (CH), Morihara Y (CH), Kurisu T (CH), Yoneyama Y (CH), Kato K (CH; Suzugamine Women's College). **Review of the chest radiography condition using the CR system at the Radiation Effects Research Foundation.** *FY98 Scientific Meeting of Chugoku-Shikoku Branch of Japanese Society of Radiological Technology, 7-8 November 1998, Hiroshima, Japan*

❖Neriishi K (CH), Nakashima E (S), Delongchamp RR (S; National Center for Toxicological Research). **Inflammatory tests in A-bomb survivors without clinical inflammation.** *Forty-first Annual Meeting of the Japan Radiation Research Society, 2-4 December 1998, Nagasaki, Japan*

❖Irita A (Nagasaki University School of Medicine [NUSM]), Akahoshi M (CN), Ashida T (NUSM), Ueyama C (NUSM), Seto S (CN; NUSM), Hayano M (CN; NUSM), Yano K (CN; NUSM). **Effects of atrial fibrillation on cerebral infarction risk factors—Longitudinal study during ten years around the onset of atrial fibrillation.**

❖Matsuo K (CN; NUSM), Akahoshi M (CN), Nakao K (NUSM), Komiya N (NUSM), Hirata T (NUSM), Ueyama C (NUSM), Seto S (CN; NUSM), Hayano M (CN; NUSM), Yano K (CN; NUSM). **Epidemiological study of the association between Brugada syndrome and unexplained sudden death — A longitudinal observation of electrocardiograms in relatively young age population.**

Sixty-third Scientific Meeting of the Japanese Circulation Society, 27-29 March 1999, Tokyo, Japan

Immunology

(RP 1-93)

❖Hayashi T (R), Kyoizumi S (R), Kusunoki Y (R), Seyama T (R). **Suppression of radiation-induced apoptosis of human T-cell leukemia cells by transduction of the *bcl-2* gene.**

❖Kyoizumi S (R), Hayashi T (R), Kusunoki Y (R), Seyama T (R). **Expression of mismatch repair genes in human lymphocytes.**

Twenty-eighth Annual Meeting of the Japanese Society for Immunology, 2-4 December 1998, Kobe, Japan

(RP 11-89)

❖Kusunoki Y (R), Kyoizumi S (R), Honma M (National Institute of Health Sciences), Hamatani K (R), Hayashi T (R), Seyama T (R). **In vivo mechanisms on suppression of generation of cells lacking MHC class I allele expression.** *Twenty-eighth Annual Meeting of the Japanese Society for Immunology, 2-4 December 1998, Kobe, Japan*

(RP 1-85)

❖Arisawa K(EN; Atomic Bomb Disease Institute [ABDI]/Nagasaki University School of Medicine [NUSM]), Soda M (EN), Akahoshi M (CN), Matsuo T (ABDI/NUSM), Nakashima E (S), Tomonaga M (ABDI/NUSM), Saito H (ABDI/NUSM). **Human T-lymphotropic virus type-I infection, antibody titers, and cause-specific mortality among atomic-bomb survivors.**

Ninth General Meeting of Japan Epidemiological Association, 21-22 January 1999, Nagoya, Japan

Special Clinical Studies

(RP 3-89)

❖Fujiwara S (CH), Masunari N (CH), Yamada M (CH), Kasagi F (S), Kodama K (CH), Nagataki S (D). **Dietary habit, its change, and rate of change of bone density.** *Seventh Japanese General Meeting of Osteoporosis, 23-24 October 1998, Niigata, Japan*

❖Moriyama Y (CH), Kurisu T (CH), Yamane K (CH), Yoneyama Y (CH). **Review of cross-calibration of bone mineral density of the lumbar vertebrae and femoral neck by the DXA method using QDR-2000 and QDR-4500.** *FY98 Scientific Meeting of Chugoku-Shikoku Branch of Japanese Society of Radiological Technology, 7-8 November 1998, Hiroshima, Japan*

❖Fujiwara S (CH). **Current status of osteoporotic fracture in Japan.** *Thirteenth Annual Congress of the Japan Menopause Society, 5-6 December 1998, Yokohama, Japan*

Cell Biology

(RP 2-94)

❖Iwamoto KS (R), Mori T (National Institute of Radiological Sciences, Chiba, Japan). **Molecular evidence for cellular selection during radiation carcinogenesis in Thorotrast recipients.** *International Workshop on Health Effects of Thorotrast, Radium, Radon, and other Alpha Emitters 1999, 19-22 January 1999, Tokyo, Japan*

(RP 7-92)

❖Ban S (R). **Direct evidence for the importance of**

the mitochondrial genome in X-ray-induced apoptosis. *1998 Taipei International Conference of Environmental and Occupational Mutagenesis, 26-27 November 1998, Taipei, Taiwan*

❖Ban S (R). **Direct evidence for the importance of the mitochondrial genome in X-ray-induced apoptosis.** *Forty-first Annual Meeting of the Japan Radiation Research Society, 2-4 December 1998, Nagasaki, Japan*

Biochemical Genetics

(RP 7-85)

❖Asakawa J (G), Kodaira M (G), Katayama H (IT), Funamoto S (S), Tomita S (S), Itoh M (G), Preston DL (S), Nakamura N (G). **Detection of spontaneous and X-ray-induced germ cell mutations in mice by computer-assisted two-dimensional DNA gel analysis.**

❖Kodaira M (G), Itoh M (G), Asakawa J (G). **Study on spontaneous and X-ray-induced germ cell mutations in mice detected by computer-assisted two-dimensional DNA gel analysis.**

Forty-first Annual Meeting of the Japan Radiation Research Society, 2-4 December 1998, Nagasaki, Japan

(RPs 7-85, 8-93 [Cytogenetics])

❖Nakamura N (G). **Feasibility of genetic studies in F₁ of atomic-bomb survivors.** *Forty-first Annual Meeting of the Japan Radiation Research Society, 2-4 December 1998, Nagasaki, Japan*

Cytogenetics

(RP 8-93)

❖Kodama Y (G), Nakano M (G), Itoh M (G), Ohtaki K (G), Kusunoki Y (R), Hirai Y (R), Kyoizumi S (R), Nakamura N (G). **Origin of clonal chromosome aberrations in lymphocytes of A-bomb survivors.**

❖Nakano M (G), Kodama Y (G), Ohtaki K (G), Itoh M (G), Nakamura N (G). **S-values are not a signature for a significant contribution of neutrons to the radiation dose received by atomic-bomb survivors.**

❖Ohtaki K (G), Nakamura N (G), Awa AA (G). **Chromosome aberration: inv(14)(q11q32) in lymphocytes from A-bomb survivors.**

Forty-first Annual Meeting of the Japan Radiation Research Society, 2-4 December 1998, Nagasaki, Japan

Presentations from Research Not Associated with an RP

❖Nagataki S (D). **Radiation disorders and iodine.** *Twenty-sixth General Meeting of Japan Emergency Medical Care, 12 November 1998, Takamatsu, Japan*

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❖ Nagataki S (D). **Radiation Emergency Preparedness.** *Study Group of Physicians of Medical Institutes Designated for Treatment of A-bomb Survivors in 1998, Department of Welfare and Health, Nagasaki Prefecture, 20 November 1998, Nagasaki, Japan*

❖ Izumi S (S), Ohtaki M (Research Institute for Radiation Biology and Medicine, Hiroshima University). **Survival data analysis based on the application of the Weibull-gamma model.** *Nonlinear Statistical Modeling and Data Analysis, 29-31 January 1999, Toba, Japan*

❖ Nagataki S (D). **Lessons from the Chernobyl Nuclear Power Plant accident—Publication of the results of scientific studies.** *Thirtieth Seminar for "Safety at nuclear power plants," Nuclear Safety Research Association, 24-26 February 1999, Matsuyama, Japan*

❖ Izumi S (S), Fujisawa H (Tokyo Institute of Technology). **Estimating misclassification probabilities from repeated binary responses.** *Statistics Spring Seminar 1999, 19-21 March 1999, Kawaguchiko-machi, Yamanashi, Japan*

Errata

Each of the following three *Cell Biology Studies* presentations was reported incorrectly in the last RERF Update, the first two as emanating from RP 11-81 and the third as being unrelated to a specific RP. All are based on research from RP 18-81.

(RP 18-81)

❖ Hayashi T (R). **Characterization of human breast epithelial stem cells and induction of carcinogenic mutations by ionizing radiation.**

❖ Kyoizumi S (R). **A SCID-hu mouse model for studying human stem cells.**

Joint Seminar of the Hiroshima Tissue Regeneration Project and the Radiation Effects Research Foundation, 15 June 1998, Higashi-Hiroshima, Japan

❖ Kyoizumi S (R), Hayashi T (R), Seyama T (R). **Analysis of radiosens-**

itivity of the epithelium of the human small intestine using SCID-hu mice. *Twenty-third Chugoku-area Local Radiation Effects Research Meeting, 24 July 1998, Okayama, Japan*

The following Immunology study was reported in the last RERF Update as being unrelated to a given RP.

Meetings Attended
1 October 1998 - 31 March 1999
(and others during the fiscal year not previously reported)

Meetings outside Japan

First International Seminar on Radiation and Thyroid Cancer, 20-23 July 1998, Cambridge, UK
(not previously reported)

First Siebold Lecture, 24 July 1998, Wurzburg, Germany
(not previously reported)

Special Invited Presentations at the Swedish Radiation Protection Institute and the Karolinska Institute, 5 November 1998, Stockholm, Sweden

1998 Taipei International Conference of Environmental and Occupational Mutagenesis, 26-27 November 1998, Taipei, Taiwan

South African Council on Nuclear Safety, 11 December 1998, Capetown, South Africa

Meetings in Japan

Second Meeting of the Japanese Association for Medical Management of Radiation Accidents, 8 August 1998, Tokyo, Japan
(not previously reported)

Seventh Japanese General Meeting of Osteoporosis, 23-24 October 1998, Niigata, Japan

Fifty-seventh Annual Meeting of the Japanese Society of Public Health, 28-30 October 1998, Gifu, Japan

FY98 Scientific Meeting of the Chugoku-Shikoku Branch of the

See Meetings on page 29

(RP 11-89)

❖ Kusunoki Y (R), Kyoizumi S (R), Hayashi T (R), Seyama T (R), Honma M (National Institute of Health Sciences). **Major histocompatibility antigen class I variant cells *in vivo* are eliminated by NK cells.** *Twenty-third Chugoku-area Local Radiation Effects Research Meeting, 24 July 1998, Okayama, Japan*

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