Newly Formed Scientific Council Meets in Hiroshima

by Seymour Abrahamson
Associate Chief of Research

The 25th meeting of RERF's Scientific Council was held in Hiroshima 18-20 March 1998. It was a new council with a new plan of operation, which is delineated below from the council's own report.

Excerpted from the council's final report: *This was the first regular meeting in Hiroshima of the newly constituted Science Council, as mandated by the Blue Ribbon Committee. In the past, the council has met and heard scientific presentations from all RERF departments at each annual meeting, formulating as a result specific recommendations concerning research activities and directions. The new council will operate differently. Annually, an in-depth critical peer review of the science in one department / program will be carried out by a multinational panel of outside experts in the particular field. Each department will be reviewed every five years on a rotating basis. The Science Council, at its annual meeting, will discuss and formulate recommendations based on the most recent peer review, monitoring at subsequent meetings the progress of each department in achieving the changes recommended at peer*

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放影研 RERF update

Volume 9, Issue 2, Autumn 1998

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

Peer Review and Science Council Recommendations on Board Agenda

by Seymour Abrahamson, Associate Chief of Research

The 32nd meeting of the board of directors was held in Hiroshima 17 and 18 June 1998.

RERF Chairman Dr. Shigenobu Nagataki opened the meeting and presented an extensive overview of RERF's accomplishments, critical issues that must be addressed for the future success of the program, and his role in improving RERF's relationship with the public.

Status reports on a variety of issues were presented for the board's information. Also for their information, four scientific presentations were made: F_1 studies by Dr. Nori Nakamura; Noncancer mortality in the Adult Health Study by Dr. Kazunori Kodama; Noncancer mortality in the Life Span Study by Dr. Don Pierce; and Status of DS86 dosimetry deliberations by Dr. Warren Sinclair.

Dr. Sheldon Wolff presented the recommendations of the multinational peer review of the Department of Radiobiology. (*See Radiobiology Peer Review Provides Foundation for Change, page 3.*) The review panel's recommendations and RERF's responses were approved by the board following extensive discussion.

Councilor Dr. Matsudaira presented the detailed recommendations of the 25th meeting of the Science Council in March. (*See Newly Formed Science Council Meets in Hiroshima, page 1.*) After deliberations, these recommendations were also approved together with the research activities plan for fiscal year 1998. The audit report of research activities for fiscal year 1997 and research activities during that year were also described and approved.

An extensive discussion concerning RERF's research mission and whether other funding sources should be sought in pursuit of basic research mechanisms beyond the mission will require further discussion.

Secretariat Chief Kazumasa Kunitoshi presented the fiscal year 1998 working budget and the fiscal year 1999 budget request, both of which were approved, and changes to

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Pictured from left to right, front to back: Row one: Dr. S. Taira, Dr. J. Samet, Mr. K. Arichi, Dr. P. A. Buffler, Dr. S. Nagataki, Dr. S. Wolff, Dr. T. Kumatori, Dr. W. K. Sinclair, Dr. M. Oike. ***Row two:*** Dr. S. Abrahamson, Ms. K. Ono (chief, Publication and Documentation Center), Mr. R. D. Sperry, Ms. C. S. Berkley, Mr. D. Williams, Dr. I. Shigematsu, Dr. F. Hawkins, Dr. P. Gilman, Mr. M. Eaton, Dr. T. Sato, Mr. H. Kuroki, Dr. S. Fujita (assistant chief, Department of Statistics). ***Row three:*** Mr. T. Imada (acting chief, Information Technology Department), Dr. K. Mabuchi (chief, Department of Epidemiology), Mr. H. Tominaga, Dr. K. Kodama (chief, Department of Clinical Studies), Mr. K. Kunitoshi, Dr. A. A. Awa, Dr. E. Douple, Dr. J. Weiss. (*Photo by Junso Takayama.*)

In Memoriam

Hiroshi Maki, RERF Consultant Emeritus, 1904-1998

Dr. Hiroshi Maki, RERF consultant emeritus, passed away early in the morning of 23 October at 94. Dr. Maki served as ABCC associate director from his arrival in 1948 until ABCC's reorganization into RERF in 1975. He was also director of the JNIH Hiroshima Branch Laboratory (currently the National Institute of Infectious Diseases). A memorial ceremony was held at the Alliance Christian Church in Saeki-ku, Hiroshima 24 October.

NIH Branch Lab Chief Maki 10 September 1951, three years after his arrival at ABCC. *(ABCC file photo)*

This photograph have been removed because it is protected by copyright.

Associate Director Maki and Business Administrator Michael Rappaport fold the ABCC banner at ABCC's closing ceremonies, November 1975. Director LeRoy Allen watches. *(Chugoku Shimbun, 28 January 1988)*

Dr. Maki sharing a relaxed moment with Director George B. Darling, 17 June 1970. *(ABCC file photo, taken by Max Defors)*

Dr. and Mrs. Maki at home in July 1998, when they were visited by RERF alpinists. *(courtesy of Naohiro Hayakawa)*

A native of Tokyo, Dr. Maki came to Hiroshima at a time of harsh economic conditions immediately after World War II, when the city, completely destroyed by the atomic bomb, had just started reconstruction. In Hiroshima, he endeavored to initiate studies on the effects of the atomic bombing on humans.

As an administrator, Dr. Maki served simultaneously as director of the JNIH Hiroshima Branch Laboratory of the Japanese National Institute of Health of the Ministry of Health and Welfare, representing the Japanese side, and as ABCC associate director. Dr. Maki represented Japan for 27 years at ABCC, until it was reorganized into RERF. After retiring, he continued on as a consultant for three years, before assuming emeritus consultant status.

It is not hard to imagine that Dr. Maki's most difficult task was serving as liaison between the US and Japan and between ABCC, the A-bomb survivors, and concerned parties in the local community. He endeavored to resolve these difficult tasks with superhuman perseverance and magnanimity. Dr. Maki, inconspicuously but sincerely, contributed to setting the foundation stone for the study projects of ABCC/RERF that are highly evaluated the world over today.

The September *RERF Newsletter* reported that Dr. Maki and his wife welcomed members of RERF's Alpine Club to their home July 18. Club members visited Dr. Maki, the club's first president, for an interview on the occasion of the 35th anniversary of the club. Dr. Maki served as the club's president for three years. He and his brothers were known widely as Japanese mountaineers.

Dr. Maki's always smiling kindly face will be missed. RERF extends its deepest condolences to the Maki family. May he rest in peace.❑

RERF Staff News

Dr. Nagataki First Siebold Award Recipient RERF Chairman **Shigenobu Nagataki** received the first Siebold Award at Würzburg University in Germany on 24 July. The award, named after German physician Philipp Franz von Siebold, who came to Japan during the later Edo period as an attachment to the Dutch East Indies trading firm, was instituted two years ago, on the occasion of Siebold's bicentennial, to recognize outstanding achievement in the field of medicine at Würzburg and Munich Universities in Germany, Leiden University in the Netherlands, and Nagasaki University in Japan. The presentation of the award to Dr. Nagataki follows his establishment two years ago of an international symposium for scientific exchange between these four universities with which Siebold is connected. At that time, Dr. Nagataki was dean of the Nagasaki University School of Medicine.

Dr. Kodama Becomes Royal Fellow At its annual meeting in Torquay 23 to 26 June, The Faculty of Public Health Medicine of the Royal College of Physicians of the United Kingdom honored **Kazunori Kodama** with fellowship in the college. Dr. Kodama, chief, Department of Clinical Studies, Hiroshima, became only the fourth Japanese recipient of this tribute, which recognizes outstanding achievement in the fields of public health and preventive medicine. Since 1994, Dr. Kodama has been involved in the British Council's *British Epidemiology and Public Health Course,"* intended to introduce British-style practical epidemiology to the world.

Former RERF Director Kono Decorated **Mr. Tomoyuki Kono**, former RERF permanent director and chief of Secretariat, was decorated with the Third Order of the Rising Sun at its spring conferment. Mr. Kono received the award from Prime Minister Hashimoto at the

*See **Staff News** on page 15*

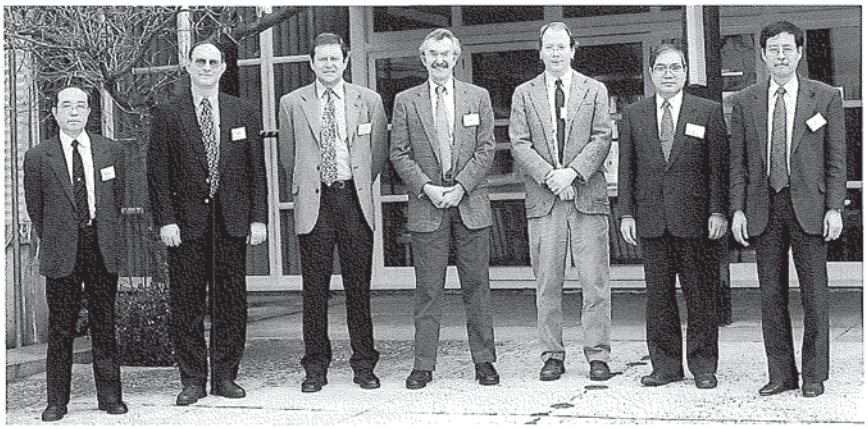
Radiobiology Peer Review Provides Foundation for Change

by Seymour Abrahamson, Associate Chief of Research

As reported in the last *Update,* RERF initiated its program of multinational peer review of individual departments with evaluation of the radiobiology department 13 to 15 January 1998. A seven-member panel of specialists in radiobiological research convened in Hiroshima to review the program and address areas for improvement. Their tasks included the scientific review and evaluation of ongoing and future work; evaluation of staff and their research activities; and analysis of program operation, including staff interaction, collaborations, and scientific management. They were also asked to comment on general and specific staffing levels and program needs and suitability of physical facilities and research equipment to the program. The panel's recommendations provide an in-depth analysis of existing research projects and will assist in planning research in light of existing limitations in personnel and biological resources.

The review agenda included an initial overview of the department by Dr. Toshio Seyama, acting Radiobiology chief, individual researchers' presentations of their molecular oncology, molecular epidemiology, and immunology work, a question session for reviewers, and inspection of RERF's research facilities and discussions with individual researchers.

Radiobiology researchers and their presentations were: Dr. Sadayuki Ban: *Genetic alterations responsible for primary breast cancer of A-bomb survivors;* Dr. Kiyohiro Hamatani: *Activation of* RET *oncogene in thyroid cancer among survivors;* Dr. Keisuke S. Iwamoto: *The search for the molecular events responsible for A-bomb-radiation-induced liver carcinogenesis;* Dr. Terumi Mizuno: *Possible molecular radiation fingerprints in A-bomb-survivor skin cancer;* Dr. Seishi Kyoizumi: *Molecular epidemiology/ immunology overview;* Dr. Yoichiro Kusunoki: *Long-term impairment of the hematolymphoid system and its relation to disease in A-bomb survivors;* Dr. Yuko Hirai: *Detection of AT heterozygotes by ATM protein expression;* Dr. Tomonori Hayashi: *Immunologic background in A-bomb survivors: Possible population bias and susceptibility to diseases;* Dr. Seishi Kyoizumi: *Blood cell bank for molecular epidemiology;* and Dr. Yuko Hirai: *Collection of tumor-tissue samples: Current status and future plans.*



Pictured from left to right: Drs. M. Sasaki, J. W. Gray, R. Cox, J.M. Brown, K. T. Kelsey, K. Takatsu, O. Niwa. (*Photo by Junso Takayama.*)

Panel Recommendations

The panel presented detailed comments on each of the staff presentations. Following is a brief summary of their suggestions.

The molecular study on breast cancer was listed as a major project to pursue because of the high relative risk from radiation and the availability of early onset cases that may be associated with inheritance of breast cancer susceptibility genes. In addition to making specialized technical comments, they pointed out for this and other similar programs the need to pay special attention to ethical issues concerning knowledge gained on inherited susceptibility genes. In the same vein, the panel endorsed studies on the molecular mechanisms of thyroid cancer. Work on molecular studies of liver cancer and skin cancer was received less enthusiastically with the suggestion that work within RERF be phased out over the next year except where collaborative efforts with outside scientists interested in these areas can be established. Thus, RERF staff would be able to provide assistance to the favored projects.

Continuing work in the immunology program was recommended to develop better understanding of infection pathogenesis and possibly cancer development. It was emphasized that collaborative efforts with the clinical department take place to relate the laboratory studies to the development of cardiovascular diseases and other forms of morbidity recognized in the Adult Health program.

In addition to the above-mentioned research projects, two other studies, one on detection of ataxia telangiectasia (AT) heterozygote in relation to breast cancer susceptibility and a second on HLA subtypes, were discussed. The panel recommended restricting efforts in these areas because of limited testing power.

With respect to the maintenance of biological resources, cell bank and tumor tissue samples, the panel enthusiastically supported the maintenance and safeguarding of this unique resource and offered specific suggestions for database management and sample retrieval

In summary, the panel considered the mission-oriented work in molecular oncology, i.e., molecular epidemiology, and immunology important to RERF's role. They offered further suggestions regarding intra- and interdepartmental collaborations and interactions and the need to provide greater research incentives to junior staff including more representation at international meetings. They also favored efforts to establish fellowships to fund visiting scientists and postdoctoral workers. This, in substance, covers most of their recommendations. In 1999, RERF is planning a workshop on advances in immunology, which should help focus its studies on immunology and clinical disorders

Review panel members included:

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review. In addition, the council will review the overall direction and future plans for research being carried out in the individual programs and RERF as a whole and respond to specific problems raised by RERF investigators, directors, or the peer-review team.

At the present meeting, the council asked each department chief to review current departmental research and present their plans for the next several years to inform the new council of the breadth of RERF research activities. Later, individual council members met with investigators from each department for two hours to learn more about specific projects, research in progress, and new findings. The stimulating atmosphere in many of the laboratories was noted. On the second day, the council met with Dr. Seyama, who discussed in detail his response to the recent peer review of his department. Special sessions were held to discuss the studies of children of exposed individuals (F_1 studies) and questions related to data analysis and to hear a description of the interdepartmental program on liver cancer.

The council felt that the peer review of the radiobiology department had been thorough and constructive. It shared the views of the review committee and generally agreed with its recommendations. Dr. Seyama made a detailed and constructive response to all these recommendations at the council meeting.

The council raised the issue of the need for specific consideration of the ethical problems developing concerning informed consent and the collection and use of biological samples, especially DNA. The importance of this issue was emphasized by the peer-review committee. The council communicated their concern to the directors and recommended they develop a comprehensive policy as soon as possible.

Overall, the council was pleased with the progress of RERF research. The scientists should continue to seek improved interaction and collaborations within the programs at RERF and outside, establishing wherever possible university contacts and collaborative research projects with scientists at other institutions. They should be encouraged to make more presentations at international meetings. Mechanisms for internal critical appraisal should be developed and open seminars that cross departmental boundaries encouraged.

Pictured from left to right, front to back: Row one: Dr. M. Fox, Dr. J.W. Gray, Dr. S. Okada, Dr. J.B. Little, Dr. H. Matsudaira, Dr. S. Preston-Martin, Dr. T. Hirohata. ***Row two:*** Mr. D. Williams, Dr. S. Ushigome, Dr. E. Douple, Dr. S. Abrahamson, Dr. S. Taira, Dr. S. Nagataki, Dr. S. Wolff, Dr. J. Weiss, Mr. K. Kunitoshi, Mr. R. D. Sperry, Dr. M. Sasaki. ***Row three:*** Dr. T. Seyama, Dr. A. A. Awa, Dr. K. Kodama, Dr. N. Nakamura, Dr. K. Mabuchi, Dr. Y. Shibata, Dr. D. L. Preston, Dr. Akahoshi. *(Photo by Junso Takayama.)*

Finally, RERF should be continually evaluating its research mission and orientation as the program matures, the number of survivors declines, and the research will likely take a more mechanistic approach. More attention will need to be given to the general problem of the effects of radiation exposure. This should include work utilizing model systems to examine radiation effects in cellular systems and perhaps whole animals. As this change occurs, RERF and its individual investigators should consider making a more concerted effort to seek funding for their research from outside sources. Such external funding is likely to become necessary as RERF broadens its scientific base.

With respect to the council's specific recommendations for each department, it was clear that they were favorably impressed with the progress made by each program. General issues of concern will be described.

In Epidemiology, the council pointed out that the professional staffing level is inadequate and encouraged additional recruitment and more interaction with Japanese and international institutions. The critical role played by the Department of Statistics in all major RERF projects and departments was singled out. The council emphasized the need for "vigorous communication in both directions" prior to beginning new investigations, noting that "continuing contact with the collaborating statistician will help maintain confidence in the robustness of results and suggest additional or alternative approaches."

The Department of Clinical Studies' in-depth studies of the participants in the Adult Health Study program provide the advantage of detecting radiation-related changes in morbidity incidence. (Such findings as those on skin and thyroid cancers, benign tumors, and cardiovascular disorders, are a critical adjunct to the noncancer mortality studies.)

High priority was given to the Department of Genetics' new collaborative study with Clinical Studies on genetic regulatory mechanisms of hypertension as well as ongoing studies in cytogenetics and biochemical DNA mutagenesis studies.

The council also heard from four departments on an interdepartmental study of chronic liver disease and hepatocellular carcinoma. After lengthy discussions with the staff, the council recommended a thorough evaluation of the study population size and the power of testing a modest relative risk that complicates this multifactorial study. They also encouraged seeking funding from outside sources for investigation of nonradiation-related aspects of the study.

RERF owes a special debt of gratitude to the Science Council members, whose independent and sound scientific advice has helped shape our research programs. Councilors make considerable personal effort to understand our programs, and their deliberations on each of the separate research projects provide critical feedback to researchers and the board of directors. Therefore, it is both fitting and proper that Drs. Shigefumi Okada

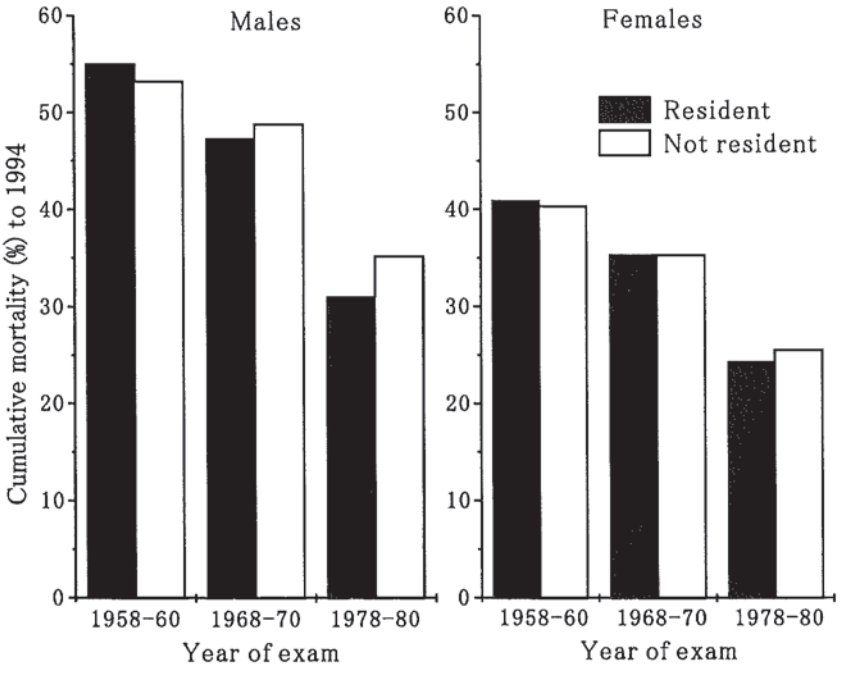
*See **Council** at bottom of next page*

Mortality Comparison between Migrants from and Residents of the Catchment Area in the Adult Health Study

by Fumiyoshi Kasagi, Associate Senior Scientist, Department of Statistics

The Adult Health Study (AHS) was initiated in 1958 to monitor physiological and biochemical changes and disease morbidity and examine radiation health effects in atomic-bomb survivors through biennial clinical examinations. The AHS population consists of four city-sex-age-matched groups, including a core group of those with acute radiation symptoms exposed to radiation within two kilometers of the hypocenter.

Health monitoring of the AHS is conducted for those resident within the program's catchment area; migrants from the area are not contacted for participation in clinical examination unless they return to live in the catchment area. Thus, migration from the catchment area is a possible source of bias in the risk assessment of health effects conducted through the AHS examinations.



The figure shows age-dose-adjusted cumulative mortality through 1994 for those AHS cohort members alive at the time of the first cycle (1958-60), sixth cycle (1968-70), and eleventh cycle (1978-80). Residents of the catchment area are compared to migrants from the area. For both sexes, cumulative mortality among migrants is somewhat lower for those surviving until the first cycle but somewhat higher for those surviving through the 1978-80 cycle. A similar pattern is seen for cumulative mortality during the first ten years of follow-up for each of these three groups.❑

Council *continued from previous page*

and John B. Little, who are retiring from the council after 13 and six years, respectively, received commemorative awards for faithful and devoted service from Chairman Nagataki.

The meeting was cochaired by Drs. John B. Little, *James Stevens Simmons professor of radiobiology, Harvard University School of Public Health*, and Hiromichi Matsudaira, *consultant, Japan Science and Technology Corporation*. In addition to the two cochairs, other Scientific Council members attending the meeting were: Drs. Shigefumi Okada, *professor emeritus, The University of Tokyo*; Tomio Hirohata, *professor emeritus, Kyushu University*; Shinichiro Ushigome, professor, *Department of Pathology, Jikei University School of Medicine*; Masao Sasaki, *professor, Radiation Biology Center, Kyoto University*; Susan Preston-Martin, *professor, Department of Preventive Medicine, University of Southern California/Norris Comprehensive Cancer Center*; Maurice S. Fox, *Lester Wolfe professor of molecular biology, Massachusetts Institute of Technology*; and Joe W. Gray, *professor of laboratory medicine, University of California, San Francisco*. Scientific Councilor Theodore L. Phillips, *professor and chairman, Radiation Oncology, University of California, San Francisco*, did not attend the meeting. Meeting observers were: Mr. Masayuki Kimura, *director*, and Dr. Toshinobu Satoh, *assistant director, Planning Division, Health Service Bureau, Japanese Ministry of Health and Welfare*; Mr. Frank C. Hawkins, director, Office of International Health Studies, and Dr. Joe Weiss, *program manager, Postdoctoral Fellowship Program, and Japan Project Team coordinator, US Department of Energy*; and Dr. Evan Douple, *director, Board of Radiation Effects Research, Commission on Life Sciences, National Research Council, US National Academy of Sciences (NAS)*. Also attending the meeting were Mr. David Williams, *senior financial officer, NAS*; and *RERF representatives*: Dr. Shigenobu Nagataki, *chair*; Dr. Sheldon Wolff, *vice chairman and chief of research*; Dr. Senjun Taira, *permanent director*; Dr. Seymour Abrahamson, *associate chief of research*; Dr. Akio Awa, *associate chief of research*; Mr. Kazumasa Kunitoshi, *chief, Secretariat*; and Mr. Richard D. Sperry, *administrative advisor*.

The 26th meeting of the Scientific Council will be held 7-9 April 1999.❑

Photo Credit In the previous issue of *RERF Update* (Volume 9, Issue 1, Spring 1998), the picture accompanying the story on the meeting of the 24th Scientific Council (p.10) was printed with the permission of David Braun of David Braun Photography, San Francisco, California.❑

Search for germinal mutation by two-dimensional electrophoresis of DNA fragments

by Jun-ichi Asakawa
Senior Scientist, Department of Genetics

More efficient and more specific approaches for the rapid and accurate identification of spontaneous and induced germinal mutations by ionizing radiation have been desired. Recently, I developed a highly reproducible two-dimensional electrophoresis (2-DE) system of DNA fragments as a mutation-screening method. This 2-DE approach permits visualization of thousands of end-labeled *Not*I fragments (spots) from a genomic DNA digest without using any probes. Computer programs developed by Rork Kuick, a computer scientist studying with James V. Neel at the University of Michigan, have been used to analyze the complex 2-DE patterns. The computer-based image analysis detects the presence or absence and any changes in intensity of each spot. The spot intensity represents the copy number of the visualized spot DNA; thus, we can detect insertion/deletion/rearrangement (I/D/R) throughout the genome simultaneously. Previously, we implemented a computer-assisted 2-DE analysis of human DNA fragments from six mother/father/child trios to explore the potential usefulness of this approach. The results and preciseness of the technique were described in *RERF Update* [7 (1): 3-5, 1995]. In this communication, I will describe the present status of a feasibility study for the detectability of germ-cell mutations in mice using 2-DE DNA analysis.

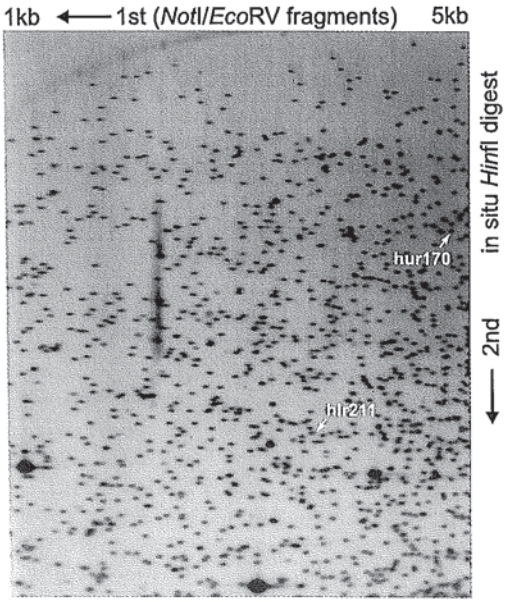
Materials and Methods

We obtained 79 F_1 mice (BALB/c) from the spermatogonial cells of eight males irradiated with 5 Gy of X rays and 54 control F_1s born to the same males before irradiation. The F_1 mice were killed at 10 weeks after birth and DNAs were prepared from the spleens. A genomic DNA was digested with restriction enzymes *Not*I and *Eco*RV. The protruding ends produced by *Not*I were filled with ^{32}P-labeled deoxynucleotides by T7 polymerase. About 1 microgram of DNA sample was electrophoresed on an agarose noodle gel cast in Teflon tubing, with an inner diameter of 2.4 mm and length of 60 cm. We prepared two types of gels for each mouse, one for 1~5 kb- and the other for 5~9 kb-first-dimensional DNA fragments. The separated DNAs were in-gel digested with *Hin*fI (1-5 kb fractions) or with *Pvu*II (5-9 kb fractions) and further separated by the second dimension electrophoresis. The gels were dried and autoradiographed.

Results and Discussion

The specific isotope labeling of the *Not*I sites is the key distinction of the 2-DE approach and results in specific visualization of DNA fragments containing the *Not*I site at one or both ends. The *Not*I sites are frequent in the unmethylated "CpG islands," common at the 5' end of genes. Thus, *Not*I fragments represent a high proportion of the active genes. A typical digital image of the autoradiogram is shown in Figure 1. Approximately 1100 DNA spots were visualized on each 2-DE preparation. The spots were detected and each spot intensity (area size × density) was measured by the BioImage (BioImage, Ann Arbor, Michigan USA) image analysis system before automatic spot matching by Rork Kuick's computer programs. The F_1s are inbred mice, so the intensity of any spot appearing on the gel is usually expected to be determined by two homologous DNA fragments. In principle, this system will detect genomic alteration I/D/R events. Some I/D/R events could eliminate a second fragment from the gel leaving one DNA fragment at the usual position, and the autoradiographic intensity of this spot should decrease by one-half. To detect I/D/R mutations associated with a 50% decrease in spot intensity, the coefficient of variation of spot intensity should be less than 0.12, and 510 and 580 spots on the two gel types (1-5 kb and 5-9 kb), respectively, meet this criterion.

By now, we have analyzed 132 gels and surveyed 74,028 spots from the exposed and 92 gels and 50,018



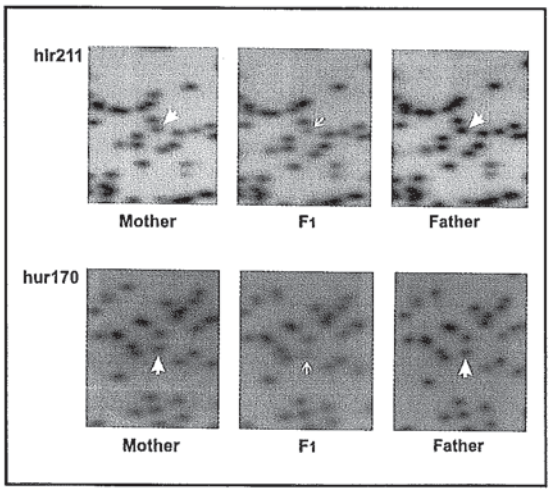


Figure 1. *A digitized 2-DE image of BALB/c mouse DNA. The enzyme combination is* NotI/EcoRV-HinfI. *The two white arrows indicate spots in which mutations were detected.* **Figure 2.** *Close-ups of examples of the mutations.*

spots from the control group. In the exposed group, eight mutant spots with half normal spot intensity were detected in eight F_1s. Two siblings from one male parent contained the same mutation (a cluster of two); three siblings from a different male parent had the identical mutation (a cluster of three); and each of three F_1s carried an independent mutation. Thus, a total of five independent mutations were detected. In the control group, there were two independent mutations, but one was part of a cluster found in two sibling F_1s. Thus, two mutations were detected in 50,018 spots from the control and five mutations in 74,028 spots from the exposed group. (See Figure 2 on the previous page for examples of the mutations.)

Molecular analysis has been carried out to understand the characteristics of the mutational event. A *NotI/Eco*RV DNA library, which contains all of the DNA fragments visualized on the 2-DE gels, was constructed for direct cloning of spot DNAs. The DNAs prepared from the library were digested with *Not*I. A 2-DE gel was prepared from a mixture of the isotope-labeled *Not*I digests (1/10) and unlabeled digests (9/10). DNAs were extracted from the gel portion of each spot on the dried gel and cloned into a vector having a *NotI/Hin*fI or a *NotI/Pvu*II cloning site.

Among the five from the exposed group, one mutation was an insertion-type mutation, an insertion of approximately 550-bp sequence of 3' end of the L1 transposable element. Two were deletion-type mutations, a 3-bp (CTT) deletion in a (CTT)n repetitive sequence and a 4-bp (CTCT) deletion in a (CT)n repeat sequence. Judging from the 2-DE patterns, the remaining two mutations seem to have resulted from deletions; they are under study. The two mutations found in the controls are deletion-type mutations. One contained a deletion bigger than 25-kb involving at least two *Not*I sites.

For more than 40 years, the scientific basis for estimating the genetic risks of the radiation exposure has been the data obtained from mega-mouse experiments performed at the Oak Ridge National Laboratory. The induced mutation rates from the "7-locus" system of Russell varied quite extensively depending on the gene examined (Searle, AG: *Advanced Radiation Biology*, 1974 [4]: 131-207). We are curious to know if the average mutation rate of the seven loci represent the average sensitivity of the whole genome. In addition to the 5-Gy series, we have conducted a 3-Gy series mouse experiment. We obtained about 200 treated F_1s from irradiated spermatogonial cells and about 80 control F_1s. The 2-DE approach will allow the detection of mutations, mainly deletions, and provide a well-averaged genomic radio sensitivity in mammalian mutagenesis because thousands of the *Not*I fragments (again, mostly functional genes but not junk DNAs) will be examined.

Using the DNA 2-DE method, it is now possible to detect deletion- and insertion-mutation accurately, and we have established methods for cloning and characterization of the normal and/or mutated DNA fragments. We believe that this approach will be the most powerful and useful technique currently available in the germinal mutation study of A-bomb survivors.

This research has been a collaboration between RERF staff Mieko Kodaira, Masahiro Itoh, Nori Nakamura (Department of Genetics), Hiro Katayama (Information TechnologyDepartment), Sachiyo Funamoto, Sachiko Tomita, and Dale Preston (Department of Statistics).❑

Board Meeting *continued from page 1*

RERF rules and regulations, which were also approved.

Dr. Richard B. Setlow, senior biophysicist and member of the U.S. National Academy of Sciences, was elected to the board, replacing Dr. Warren Sinclair. Dr. Sinclair's 15-year service was subsequently noted with great appreciation and a commemorative gift.

Dr. Yusuke Nakamura, director of the University of Tokyo's Human Genome Center, and Stanford University oncology professor, Dr. J. Martin Brown, were elected to five-year terms as councilors, replacing Drs. Shigefumi Okada and John B. Little, who were to retire 30 June.

Mr. Yasutaka Ogushi of the Nagasaki Secretariat was appointed to the operating committee, replacing Mr. Takaaki Hashiguchi, who also retired at the end of June.

Dr. Nagataki announced that the second multinational peer review will occur in November and focus on the epidemiology department.

Attending the meeting were RERF directors: Drs. Shigenobu Nagataki, *RERF chairman*; Sheldon Wolff, *RERF vice chairman and chief of research*; Senjun Taira, *RERF permanent director*; Toshiyuki Kumatori, *vice president, Radiation Effects Association*; Masumi Oike, *vice chairman, National Social Insurance Societies Association*; Warren K. Sinclair, *president emeritus, National Council on Radiation Protection and Measurements*; Patricia A. Buffler, *dean and professor of epidemiology, School of Public Health, University of California, Berkeley*; and Jonathan M. Samet, *chairman, Department of Epidemiology, The Johns Hopkins University School of Hygiene and Public Health*; and Mr. Kazuaki Arichi, *permanent director, Japan Institute of International Affairs*. Dr. William J. Schull did not attend the meeting.

Also in attendance were RERF Supervisor Mr. David Williams, *senior financial officer, National Academy of Sciences*, and Science Councilor Dr. Hiromichi Matsudaira, *chairman, Radiation Effects Association*.

Observers included Dr. Toshinobu Sato, *assistant director*, and Mr. Hiromasa Kuroki, *chief, Medical Care Activities Unit, both of the Planning Division, Health Service Bureau, Japanese Ministry of Health and Welfare*; Mr. Frank C. Hawkins, *director*, and Dr. Joseph Weiss, *Japan Project Team, both of the Office of International Health Studies, U.S. Department of Energy (DOE)*; Mr. Milton Eaton, *DOE representative, U.S. Embassy, Tokyo*; Mr. Paul Gilman, *executive director*, Dr. Evan Douple, *director, Board of Radiation Effects Research*, and Ms. Catherine Berkley, *administrative associate, all representing the Commission on Life Sciences, National Research Council, U.S. National Academy of Sciences*; and Drs. Itsuzo Shigematsu, *consultant emeritus*, Seymour Abrahamson, *associate chief of research*, and Akio Awa, *associate chief of research*, and Mr. Kazumasa Kunitoshi, *chief of Secretariat*, and Mr. Richard D. Sperry, *advisor, Secretariat, all representing RERF*.

The next scheduled board meeting will be 23 June 1999 in Nagasaki.

The meeting was closed at 4:10 on 18 June 1998 by Dr. Nagataki.❑

Clonal Chromosome Aberrations in Atomic-bomb Survivors: Deletion 5q and Inversion 14, Characteristics of Leukemia-Related Changes

by Kazuo Ohtaki, Research Scientist, Cytogenetics Laboratory, Department of Genetics

Over the past 10 years, chromosome aberrations using specific G-banding staining technique were analyzed in about 54,000 lymphocytes from 168 atomic-bomb (A-bomb) survivors, 25 distally and 143 proximally exposed, with average DS86 doses of 0 Gy and 2.05 Gy, respectively. Analyses are in progress, and two issues, both related to clonal proliferation of cells, are reported.

Cluster of deletions at long arm of chromosome 5

We were interested in examining distribution of deletions in lymphocytes from A-bomb survivors to see if any chromosomal regions over- or underrepresent the deletions.

Although we have collected 921 interstitial deletions, several chromosomes, including small chromosomes 19 to 22, failed to record interstitial deletions. This is probably due to their relatively small sizes, small number of bands, and large G-negative bands at chromosomal ends rather than the presence of haploid-sensitive genes (causing cell lethality) because apparent terminal deletions were observed in these chromosomes. Although our collection of interstitial deletions may not be large enough for saturation, we found a large cluster of interstitial deletions in the long arm of chromosome 5 (5q) in addition to smaller clusters at chromosomes 2q, 3p, 6q, 7p, 11q, and 13q. This 5q deletion (5q–) comprised nearly 30% of all the interstitial deletions. The results do not mean, however, that genes or DNA segments located at 5q are disposable. Rather, the cells bearing such deletions undergo positive selection because 5q– deletions in lymphocytes from the same survivors tended to be identical, i.e., of clonal origin, although the size and position of 5q– deletions varied among different survivors (data not shown). We do not know if these clonal events occurred in bone marrow stem cells or in mature T lymphocytes, but the following information suggests the former to be more likely.

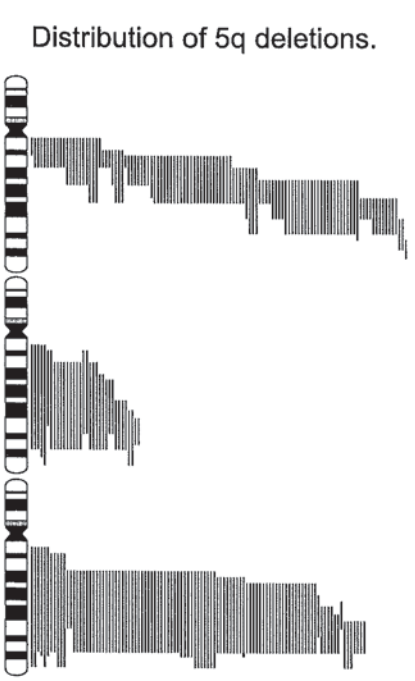


Figure 1. *Detailed map of interstitial deletions in chromosome 5 long arm. Each line represents a deleted part. The top panel shows distribution of the deletions among lymphocytes from A-bomb survivors. The middle and lower panels (modified after Le Beau et al. 1993), represent distributions of 5q deletions associated with myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) patients either therapy-related (middle) or de novo (lower).*

Figure 1 shows the detailed map of 5q– deletions observed in lymphocytes from survivors (top) and cells from myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) patients (middle and bottom). Some 50% or more of therapy-related MDS or AML patients (middle) are reported to carry chromosome 5 deletion. Among de novo, i.e., not related to previous therapy, MDS and AML patients, the frequency of patients carrying 5q– is lower, 10 to 15%. Compared with the deletion sizes observed in these patients, the deletions observed in lymphocytes from the survivors are distinctly smaller.

We compared the frequency of 5q– cells with hematologic data of the survivors. In the 143 proximally exposed survivors, six carried 5q– cells at frequencies of 2% or higher, but none showed abnormalities in hematologic data. Therefore, there seems to be no direct association between the frequency of 5q– cells and clinical manifestations of the diseases.

In summary, several tumor suppressor genes are suggested to be present in the long arm of chromosome 5, and deletion of more than one such tumor suppressor gene seems to play an important role in the development of AML and MDS. However, it is difficult to imagine that 5q deletions are the sole cause for the development of the diseases because large deletions are occasionally observed in lymphocytes from apparently healthy survivors. It seems likely, therefore, that 5q deletion, probably in bone marrow stem cells, facilitates the cells' undergoing clonal proliferation, but additional events are required for disease onset.

Cluster of inversion 14

It is well established that the risk of leukemia, including chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL), and acute myelogenous leukemia (AML), is elevated in exposed A-bomb survivors in a dose-related manner. However, there has been no evidence for increased risk of lymphoma or T-cell leukemia. T-cell leukemias are known to carry specific chromosomal translocations or inversions that result in activating cellular oncogenes, such as TCL1 (14q32), by placing a powerful promoter of T-cell antigen receptor (TCR) β gene (7q35) or TCR α/β gene (14q11) next to the oncogenes. This has led us to examine the G-banding data for any aberrations resembling those associated with T-cell acute lymphocytic leukemia (T-ALL) and T-cell chronic lymphocytic leukemia (T-CLL).

Thirty translocations and 118 inversions corresponding to those re-

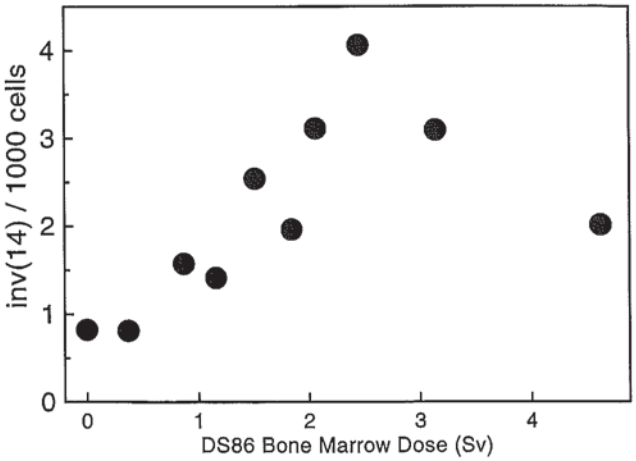


Figure 2. *Frequency of inversion14(q11q32) versus the mean DS86 dose (Sv) assuming neutron RBE of 10. Each point represents about 5,000 cells examined by G-banding.*

ported in T-cell leukemias were observed. It is especially noteworthy that as many as ~80% of these were inversions of chromosome 14 with breakpoints at 14q11 and 14q32, i.e., inv(14) (q11q32).

Figure 2 shows the dose response for the frequency of inv(14) (q11q32). Each point represents about 5,000 cells examined. Again, we were surprised to find a clear dose-related increase in frequency. Furthermore, it is worth mentioning that among the high-dose-exposed survivors, two or more cells with inv(14) (q11q32) were frequently observed in the same donors, either in single blood samples or in blood samples taken on different occasions. Thus, it seems probable that these are clonal derivatives.

Although the frequency of inv(14) (q11q32) increased with dose, it is too high to be explained by random breakage and rejoining of chromosomes after exposure to A-bomb radiation unless we assume an extremely strong positive selection in these cells. Specifically, among the aberrations unrelated to T-cell leukemia, there were only ten additional inversions of chromosome 14, and none had breakpoints at either 14q11 or 14q32. Further, translocations between the two homologs of chromosome 14 [t(14;14) (q11;q32)] are also known to be associated with T-cell leukemias, but none of the 12 t(14;14) translocations observed among all 14,440 translocations was t(14;14) (q11;q32).

In general, one expects radiation-induced chromosome breakage to be randomly distributed along chromosome arms in direct relationship to chromosome size. Clearly, the remarkably high frequency of inversions (14) (q11q32) suggests some other mechanism is involved. We suggest, therefore, that radiation exposure did not directly induce the inversions. Instead, we believe that the genetic disease ataxia telengectasia (AT) may provide some insight to our observations. AT patients frequently develop the same inversion we have found in T cells. In some patients, over 50% of the peripheral T lymphocytes are of the t(14:14) aberrant type, but they showed no clinical signs of leukemia. It is also the case that AT patients have an undeveloped thymus. Finally, AT patients are at an increased risk of T-cell leukemia. Thus, translocations or inversions at q11q32 involving 14q11 and 14q32 may be a preleukemic but not sufficient condition for T-cell leukemia. In our situation, it is well known that high-dose exposed survivors suffered severe thymocyte loss soon after exposure. We suggest that this was followed by migration of bone marrow stem cells into the temporarily "damaged" thymus to undergo cellular repopulation. During this transient period, the developing thymocyte population was exposed to conditions similar to those in the AT patient thymus, which leads to the specific inversion type and their clonal descendants persist. It is a mystery, however, why more than 100 inv14 (q11q32) inversions were found in the survivors whereas no t(14;14) (q11;q32) translocations were found. In AT patients, cellular defect in DNA repair of double strand breaks is known in addition to underdeveloped thymus whereas A-bomb survivors are proficient in the DNA repair. Since the DNA repair is expected to leave the broken ends of DNA unrejoined for a longer period, more illegitimate rejoinings are expected to take place in the thymus of AT patients. Such a genetic difference might be the cause of a sharp difference in the generation of inversion 14s only in the survivors and inversion 14s and translocation 14s in AT patients.

Reference

Le Beau MM, Espinosa R, Neuman WL, Stock W, Roulston D, Larson RA, Keinanen M, and Westbrook CA, Cytogenetic and molecular delineation of the smallest commonly deleted region of chromosome 5 in malignant myeloid diseases. Proceedings of the National Academy of Sciences USA 1993; 90: 5484-88.❑

563 International Reprint Requests

During fiscal year 1997, RERF received 563 reprint requests from 32 countries on four continents. Of those, 43% (243) were from the U.S., 25% (142) were from India, and 15% (86) were from Japan.

RERF journal article reprints are available upon request by contacting the Publication and Documentation Center at 5-2 Hijiyama Park; Minamiku; Hiroshima 732-0815 Japan or by e-mail: pub-info@rerf.or.jp.❑

***Peer Review** continued from page 3*

(panel chairman) Dr. Roger Cox, *head, Radiation Effects Department of the National Radiological Board, UK*; Dr. Joe W. Gray, *professor, Laboratory Medicine and Radiation Oncology, Cancer Center, University of California, San Francisco School of Medicine, USA;* Dr. Masao Sasaki, *professor, Radiation Biology Center, Kyoto University, Japan;* Dr. J. Martin Brown, *professor and director, Division of Radiation Biology, Department of Radiation Oncology, Stanford University School of Medicine, USA;* Dr. Karl T. Kelsey, *associate professor, Occupational Medicine and Radiobiology, Harvard University School of Public Health, USA;* Dr. Ohtsura Niwa, *professor, Radiation Biology Center, Kyoto University, Japan;* and Dr. Kiyoshi Takatsu, *professor and chair, Immunology Department, The Institute of Medical Science, The University of Tokyo, Japan.* Drs. Gray and Sasaki are RERF scientific councilors.

Dr. Evan Douple, *director, Board on Radiation Effects Research, Commission on Life Sciences, National Academy of Sciences, US,* also attended the proceedings as an observer.❑

Immunity Polarization in Atomic-Bomb Survivors: From the Viewpoint of the Th1/Th2 Paradigm

by Yoichiro Kusunoki, Associate Senior Research Scientist,
Tomonori Hayashi, Research Scientist, and
Seishi Kyoizumi, Laboratory Chief
Immunology Laboratory, Department of Radiobiology

Th1/Th2 paradigm

The immune system consists of heterogeneous cell populations that have diverse functions, and cells in the system interact with each other to protect individuals from infections and malignancies. Due to the constitutional complexity of the immune system, definitive evaluation of each immunological parameter in individuals has not been possible with regard to disease manifestation and protection. However, recently, it has become possible to classify immune responses into roughly two types, Th1 and Th2, according to profiles of cytokines (intercellular protein mediators) produced by helper T-cell subsets.[1] Polarization of immune responses to either Th1 or Th2 is now believed to play a role in the development of many diseases (Figure 1). Cytokines that mediate Th1 immunity and enhance cellular immunity, such as cytotoxic T lymphocyte (CTL) responses, are IFN- γ, IL-2, and IL-12. Cytokines that mediate Th2 immunity and enhance humoral immune responses by prompting antibody production from B lymphocytes are IL-4, IL-5, IL-6, and IL-10. Th1 and Th2 regulate each other, and their balance is important to facilitate quick and effective elimination of pathogens. However, once response to a pathogen is polarized to either Th1 or Th2, it is hard to restore equilibrium because the cytokines overproduced by either Th1 or Th2 further enhance the response, resulting in disease manifestation. For example, Th2-polarized responses in the respiratory system cause allergies, such as asthma. Overall immunity in AIDS patients is polarized to Th2 and cannot prevent opportunistic infections by viruses, bacteria, and other agents. On the other hand, Th1 responses to the body's own antigens seem to cause development of many autoimmune diseases. Further, Th1 is believed to act more effectively against tumor development (Figure 1).

Immunological findings at RERF

Major findings obtained from RERF's immunology program on the Adult Health Study atomic-bomb participants, which started in 1981, are: 1) dose-related impairment of T-cell immunity, especially decreases of CD4 helper T cells [2] and IL-2 production;[3] 2) increase of $CD4^-CD8^-$ αβT cells [4] that primarily produce Th2 cytokines; 3) increases of B cells[2] and immunoglobulin production;[5] and 4) impairment of viral immunity in A-bomb survivors.[6] The fact that these effects are evident even 50 years after the A-bombings suggests that radiation exposure acted as a trigger, polarizing the survivors' immunity toward Th2.

Possible mechanisms of radiation-induced immunity polarization

The hypothetical mechanisms by which the immune systems of A-bomb survivors have long been polarized to Th2 are suggested as follows. First, production of IL-1, IL-6, and IL-10 might have been induced by A-bomb radiation, as suggested by animal studies.[7-10] These cytokines might have induced differentiation of helper T-cell precursors into Th2 cells and/or suppressed Th1 cells. Second, extrathymic differentiation of T cells was enhanced by radiation as shown in mouse experiments.[11] $CD4^-CD8^-$ αβT cells derived from this alternative T-cell differentiation pathway are thought to primarily produce Th2 cytokines such as IL-4 and IL-5.[12] Third, Th2 polarization might induce reactivation of Epstein-Barr virus that encodes viral IL-10, which shows functional similarity to human IL-10.[13] Fourth, Th2 polarization cannot control infections by intracellular bacteria,[14] reactivation and infections of the bacteria might repeatedly occur. Such infections might further polarize subsequent immune responses to Th2. Thus, immune system imbalance induced 50 years ago may still persist today in A-bomb survivors.

Involvement of immunity polarization in disease development

Several clinical observations in A-bomb survivors can be interpreted from the viewpoint of immunity polarization. The mortality rate[15] from cardiovascular diseases and incidence[16] of the diseases in these survivors are significantly increased with radiation dose. In this regard, it is interesting that chronic inflammation by *Chlamydia pneumoniae* infection was found to develop atherosclerosis-causing circulatory diseases in a different population.[17] Since immune responses polarized to Th2 could not efficiently clear *Chlamydia pneumoniae* that reside within macrophages, endothelial and muscle cells, recurrent infection, and reactivation of the microbe might have frequently occurred in A-bomb survivors (Figure 2). A preliminary study showed that the proportion of CD4 helper T cells in peripheral blood lymphocytes are significantly decreased in A-bomb survivors who have histories of myocardial infarction (Kusunoki, et al., manuscript in preparation), suggesting that abnormality in helper T-cell immunity may be related to disease onset. Similarly, liver diseases in A-bomb survivors might partly be caused by decreased Th1 responses to hepatitis viruses. Further, since decreased Th1 immunity cannot effectively stimulate tumor-specific cytotoxic T-lymphocyte (CTL) cancer killing cells, cancer cells might have easily escaped from the immune surveillance in A-bomb survivors.

The immunological study unique to RERF is a longitudinal analysis of a large group of A-bomb survivors. Prospective and retrospective studies would make it clear whether radiation-induced polarization of helper T-cell immunity is involved in development of cancers and noncancer diseases in the survivors.

References

1. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. Nature 1996; 383: 787-93.
2. Kusunoki Y, Kyoizumi S, Hirai Y, Suzuki T, Nakashima

See Immunity Polarization References on page 15

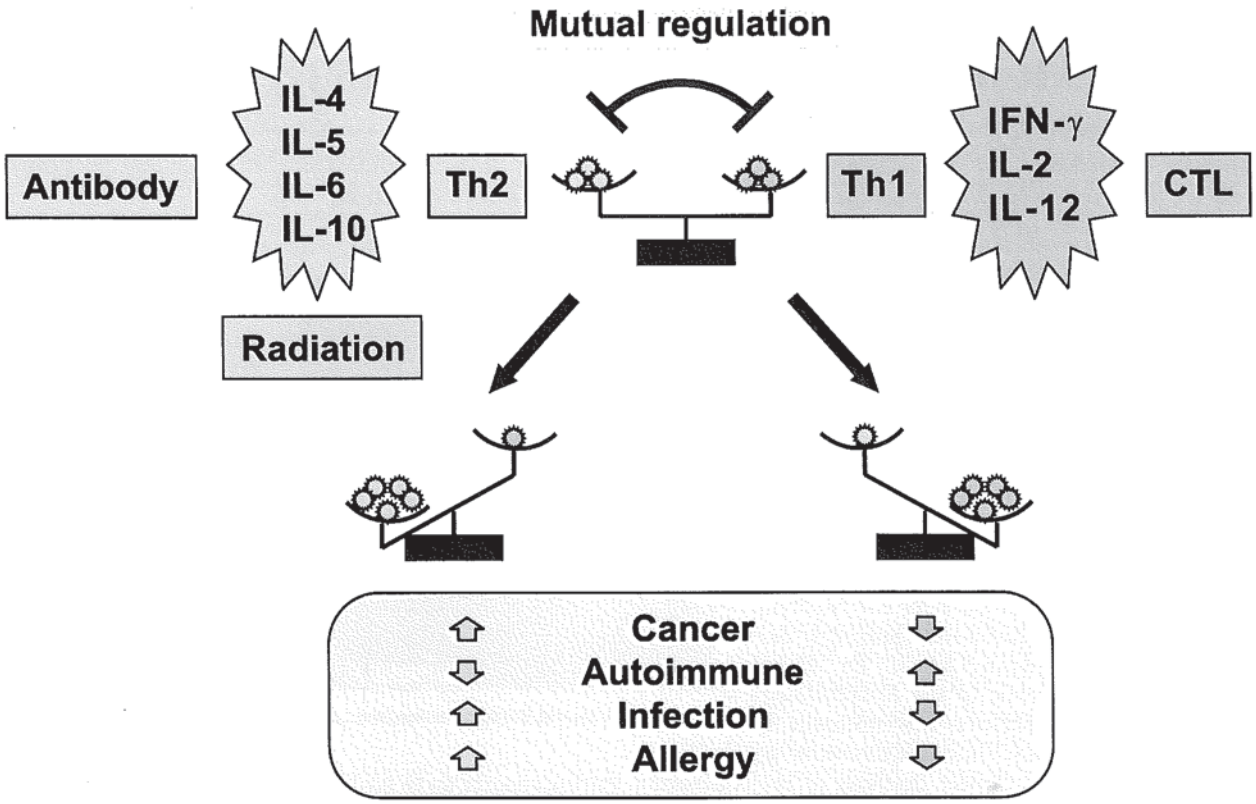


Figure 1. *Immunity polarization (Th1 versus Th2) relating to disease development. A-bomb radiation might have acted as a trigger for polarization of the survivors' immunity toward Th2.*

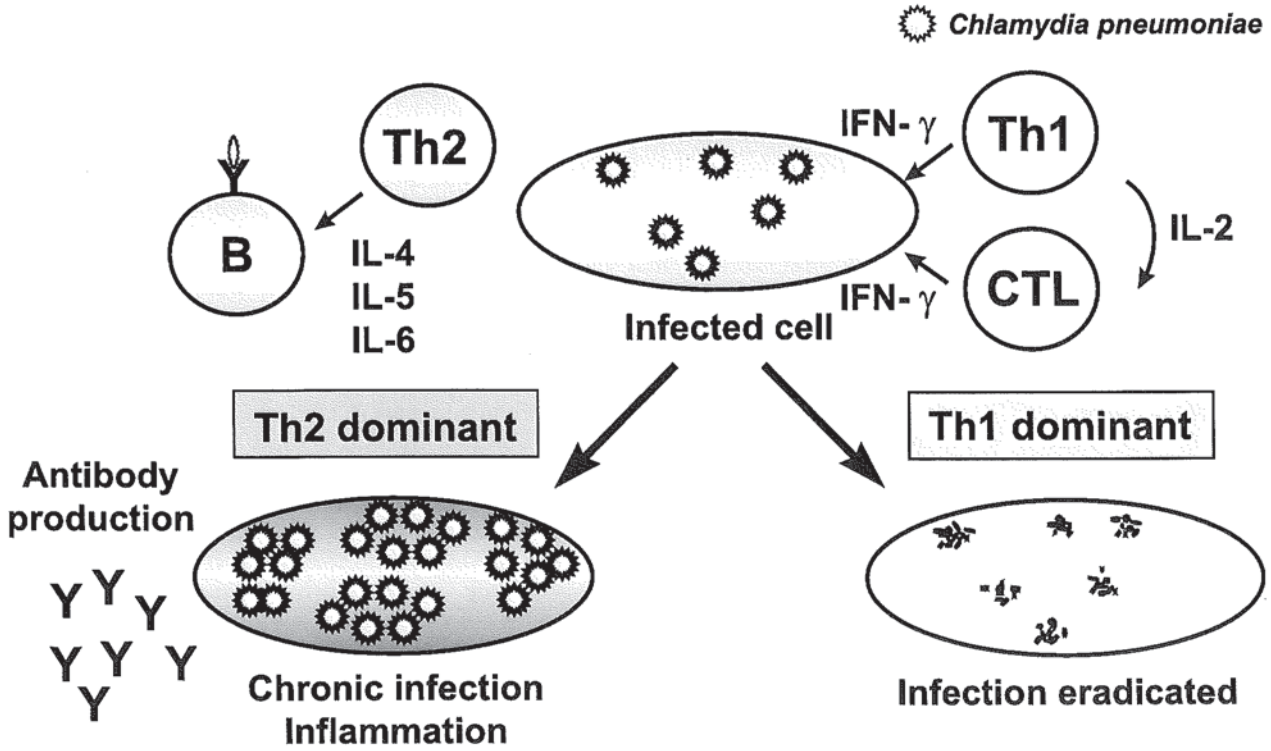


Figure 2. *Immune responses to intracellular microbes such as* Chlamydia pneumoniae *are effective to eradicate the microbes when Th1 responses are dominant to produce IFN-γ, which activates infected cells to lyse the microbes, whereas the microbes can survive inside the cells despite the presence of antibodies to them when Th2 responses are dominant. The latter immunological condition allows persistence and reactivation of the infection.*

Looking Back

Miller's Memories of ABCC-RERF, 1953-1990: Part 4

Leaving ABCC: The View from Washington

by Robert W. Miller
Scientist Emeritus, Genetic Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, U.S.A.

Editor's Note: Dr. Miller contributed a series of three articles to Update *in the winter, spring, and summer of 1994 (Volume 5, Issue 4, and Volume 6, Issues 1 and 2). In those pages, Dr. Miller reminisced about his days at ABCC, where he served first as chief of Pediatrics for the Hiroshima and Nagasaki laboratories from 1953 to 1955 and later as chief pediatrician for ABCC's Child Health Survey from 1958 to 1960. In the following article, Dr. Miller relates some of his experiences after his first departure from ABCC, when he moved to Washington and began work for the National Research Council of the National Academy of Sciences (NAS). After leaving ABCC, Dr. Miller moved on to serve as chief of the Epidemiology Branch, director of the Office of International Affairs, and chief of the Clinical Epidemiology Branch of the National Cancer Institute of the National Institutes of Health in Bethesda. His pursuits, which included membership on the Board of Radiation Effects of National Research Council and of RERF's Scientific Council, have kept him in touch with Japan and ABCC/RERF for more than four decades.*

NIH File Photo

RERF Update, Volume 6, Number 1

The author and his wife, Holly, September 1998, and leaving Hiroshima in 1955 as newlyweds.

February 21, 1955, my wife and I were married in Kobe. We left ABCC May 18 and arrived in Rochester, New York about two weeks later, unemployed. As a pediatrician with postgraduate training in radiation effects on the human, I had gone to ABCC for experience in the two fields combined, and I served as chief of pediatrics in Hiroshima for 18 months. In choosing a fellowship in radiation biology, I sought to avoid narrowing my interest to one organ system or a subspecialty, such as hematology or neonatology. In looking for a position after working at ABCC, I found I was too narrow; no one needed a pediatrician with knowledge of radiation effects. As I made the rounds, I was repeatedly advised to become a pediatric radiologist, which would require another three years of residency training.

After four months, word came that **Frank (Tax) Connell, Ph.D.**, the professional associate in the ABCC office at the National Academy of Sciences (NAS), was leaving immediately. Here was a position on a month-to-month basis for which I was qualified and from which I could look without haste for an academic position.

We arrived in Washington early in October. **R. Keith Cannan, Ph.D.**, the recently appointed chairman of NAS's Division of Medical Sciences, was responsible for ABCC, among many other activities. He was a biochemist and an outstanding administrator. Much of the time, he oversaw a substantial number of committees that developed reports on questions of national medical importance. Dr. Cannan attended parts of the meetings, and if one was not going well, he put it on track. He was an Englishman who was gifted in speech and writing, and his editing brought committee reports up to his high standard. By observing him, I gained insight into how to enhance committee productivity.

Because Dr. Cannan was not a physician, I helped him with daily ABCC-related medical matters and recruiting. He seldom changed my writing on medicine, but thank-you letters were a different story. He could make each one heartfelt and add a special touch specific for the recipient.

Years later, the position I occupied became much more influential when the Division of Medical Sciences, directed by a full-time top level scientist, was replaced by the Commission on Life Sciences, directed by a committee of scientists who met at intervals.

Soon after Dr. Cannan arrived at NAS, he realized that ABCC was in trouble scientifically and administratively. Advice on its program had been given by leaders of clinical specialties through consultative visits to the clinics in Japan and the periodic meetings of the Committee on Atomic Casualties in Washington. Dr. Cannan, a basic scientist, was the key person in bringing out the importance of epidemiology in the scientific design of the studies in Japan. Clinicians at that time, if they thought of epidemiology at all, considered it only in connection with infectious diseases. Chronic-disease epidemiology was just beginning to emerge, as at NAS's Medical Follow-Up Agency (MFUA), where World War II veterans were studied regarding the relationship of military experience to subsequent disease. The program, still active, was initiated in 1946 by a surgeon, **Michael E. DeBakey**, and a statistician, **Gilbert W. Beebe**. Although the MFUA, directed by Dr. Beebe, was part of NAS, it had no regular connection with ABCC until 1955.

Having been a recent staff member of ABCC in Hiroshima, I understood well both the research and interpersonal problems that existed there. As an example, while ABCC clinicians collected data from medical examinations of survivors, the biostatistics department estimated ra-

diation exposures as distance from the hypocenter, information which, to reduce observer bias, was not recorded on medical charts. When the clinicians then analyzed their data, they had difficulty getting crucial exposure estimates because the biostatisticians felt the data was theirs alone.

The foibles of the ABCC staff members were magnified by their isolation in a small overseas community. The director had the difficult task of unifying the staff and maintaining a good working atmosphere while relating effectively to Japanese officials, scientists, survivors, news media, and the ABCC workers' union. Staff morale and scientific design, except for the genetics program, were major problems in 1955, when Dr. Cannan convened the Francis Committee. The committee's chairman, **Thomas Francis, Jr.**, had just completed the massive Salk polio vaccine trial. As a physician-virologist, he was an expert on infectious-disease epidemiology. Other committee members were **Seymour Jablon**, an MFUA statistician, and **Felix E. Moore**, chief of statistics at the National Heart Institute, who had served in military intelligence related to Japan during World War II. The group left for Hiroshima just as we arrived in Washington. On the basis of my experience with American consultants to ABCC, I expected they would succumb as usual to VIP treatment and the enchantment of being in Japan and, thus, produce a bland report.

However, the Committee was at ABCC for three weeks, where they fanned out and learned from staff members and their wives of virtually all the problems in research design and morale. The Francis Report, dated November 6, 1955, summarized this information and provided a future plan, which is still in effect today. It called for a unified central program, the components of which were a fixed population base, epidemiologic detection or continuing morbidity survey, clinical detection, postmortem detection, death certificate study, and staff requirements. Details for each of these areas were itemized, and the importance of basing the population in the *honseki* (permanent address) was stressed. (Changes of address and vital events are reported to the office in custody of the records, the records themselves termed *koseki*. No matter where in Japan a person is, vital events are reported to the office of the individual's permanent address and entered into the *koseki*, a system which greatly simplifies follow-up.) These recommendations led to the establishment of the Life Span Study of about 120,000 people, which was based on death certificate study, and the Adult Health Study of about 20,000 people, which was based on clinical examinations. The Francis Report is something of a landmark in epidemiology.

A curious note: In the Washington file on ABCC was a letter written by a well known science administrator before membership in the committee was finalized. The letter said that Dr. Francis was not likely to succeed—a prediction from a clouded crystal ball. About a year later, another acute-disease epidemiologist was sent alone as a consultant to see if he could add to the recommendations. He had trouble adapting his approach through acute-disease epidemiology and was unable to add anything.

Dr. Cannan then turned his attention to recruitment. As director, **George B. Darling, Dr.P.H.** was suggested. He had trained in epidemiology at MIT and Yale, was professor in Yale's epidemiology department, and had had extensive experience in academic administration. He and his wife came to NAS for an interview, and while Dr. Cannan described the science and administration to Dr. Darling, my wife and I described life in Japan to Mrs. Darling. They agreed to go for two years and stayed for 15, until his retirement in 1972.

Next, continuity had to be established in the Departments of Medicine, Pathology, and Statistics. Dr. Cannan arranged with Yale, UCLA , and the MFUA to provide the first chiefs for the respective departments, and those chiefs were: **James W. Hollingsworth, M.D.** (Yale, Medicine), **Sidney C. Madden, M.D.** (UCLA, Pathology), and **Dr. Beebe** (MFUA, Statistics). When their terms ran out, they were replaced by the departments from which they had come. This continued for several replacements until each department exhausted its supply of available people. The University of Washington in Seattle replaced MFUA as a source of biostatisticians.

For the medical staff, Dr. Cannan turned for help to his friend, **James Shannon, M.D.**, director of the National Institutes of Health (NIH). The military draft of physicians at the time required all eligible men to serve for two years, usually at the end of internship or residency. An alternative to the army or navy was the public health service (PHS), where the two years could be spent in research at NIH. Dr. Shannon arranged for the men we selected (and his staff approved) to enter the public health service to be assigned to NIH and detailed to ABCC. He also arranged for me to work with one of his administrators on the details of assignment, which at first suffered the complication of no pay checks for several months. Part of my job was to interview candidates and accompany them to meet Dr. Cannan. Some senior people were also interviewed apart from the PHS program. In an effort to make a favorable impression, they usually opened with a long, diffuse statement, something Dr. Cannan could not tolerate. In a single sentence, he would sum up what had been said, and the visitor, realizing he was out of his league,

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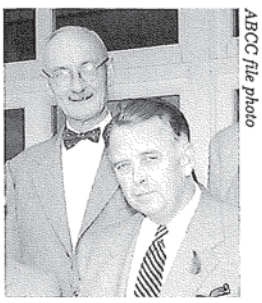
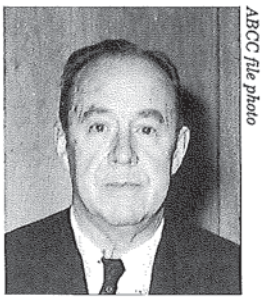
left to right: Drs. Cannan and Darling; Dr. Beebe; and the Francis Committee, Drs. Francis, Jablon, and Moore.



ABCC file photo

courtesy of author



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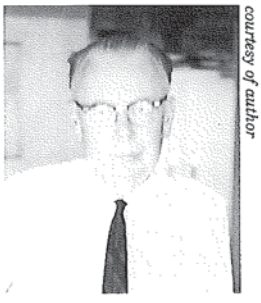

courtesy of author

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remained silent thereafter. When he left, Dr. Cannan would comment, "He didn't have much to say, did he?"

The air force assignment of **Howard B. Hamilton, M.D.** came to our attention in 1955. He was a laboratory scientist who was to be given routine clinical duties at an air base, and **Louis Hempelmann, M.D.**, for whom he worked, wrote to ask if Dr. Cannan could intervene to get Howard assigned to ABCC. Howard was assigned to the air force base in Nagoya, and a few weeks later, he was detailed to ABCC, where he served as chief of the laboratories until his retirement 29 years later.

At interviews for the ABCC staff, I tried to develop a question that would predict whether the candidate would enjoy Japan. The question that seemed best correlated was, " Do you like *The New Yorker* magazine?" With rare exception, the people who liked *The New Yorker* loved Japan. My explanation is that in each issue a variety of observations can be made from the magazine's diverse features, which include vignettes about life in New York, cartoons, news breaks, such as "Block that Metaphor," reviews, profiles, fiction, and poetry. Living in Japan is full of things to discover too.

While at NAS, I heard that a woman had telephoned and told the operator she would like to speak to someone about leaving her body to science when she died. The operator said, "Just a moment. I'll connect you with personnel." I sent the anecdote to *The New Yorker*, which published it three weeks later in "The Talk of the Town" and sent me a check for $25.

While I was at NAS, the report of its Committee on the Biologic Effects of Atomic Radiation was being prepared. This was the first use of ABCC data for radiation protection. Among its conclusions: The greatest exposure of the general population was from radiology, especially fluoroscopy for diagnoses that could be made as well or better at much lower exposure by x-ray film studies. A similar report was being prepared by **William Court Brown** and **Richard Doll** for the (UK) Medical Research Council. For that report, **Sir Harold Himsworth** visited Dr. Cannan to seek unpublished ABCC data. Dr. Cannan asked me for whatever we had. Without sufficient thought, I gave him a copy of the newest leukemia data, which Court and Doll analyzed and published, ahead of **Niel Wald** and his hematology group at ABCC.

The Committee on Atomic Casualties, which advised on ABCC research, was convened whenever Dr. Cannan accumulated a full agenda for it. The Committee's influence is reflected in the lack of reference to it in ABCC histories, except for a failed attempt by **John Z. Bowers, M.D.**, who, as I recall, based much of what he wrote on the minutes of the Committee's meetings. I remember only one meeting during my time at NAS. The chairman was **Lee Farr, M.D.**, a pediatric nephrologist in full-time research at Brookhaven National Laboratory. I helped plan the meeting, at which I spoke briefly on our new findings in children ten years after exposure to the bomb. As I told of small head size and mental retardation after in utero exposure and the excess leukemia after childhood exposure, I could hear stage whispers of ridicule by **Drs. Eugene Pendergrass** and **Richard Chamberlain**, chairman of Radiology and his successor at my alma mater. In those years, radiologists were hostile to reports of adverse radiation effects in the human. When I finished, Dr. Farr joined them by thanking me for my "recitation."

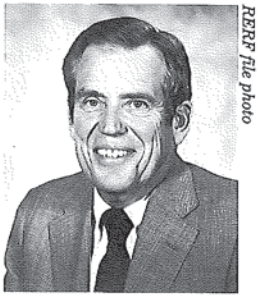
I was involved not only in recruitment but also in recommending replacement of professional staff. **Lowell A. Woodbury, Ph.D.**, a neurophysiologist, was chief of Biostatistics at ABCC. I expressed concern to Dr. Cannan about his future as his contract came up for another renewal. He was not trained in statistics, and the longer he stayed in Japan, the fewer opportunities he would have for a position in the U.S. when he finally returned. However, soon after returning to the U.S., he found a position with WHO to improve vital statistics in Thailand, where he spent the rest of his career.

Arthur W. Pryde, M.D., chief of Radiology, had spent eight years at ABCC and was getting increasingly far from new radiological procedures. Same worry as with Woodbury. Pryde had had his residency training at the University of Pennsylvania. After marrying in Japan, he decided it was time to get re-established in the U.S.. He took a six-month refresher course at the university and quickly found a position in California, where he remained for the rest of his career.

We wondered where we would find his replacement from the high-salary field of radiology when along came **Paul M. St. Aubin, M.D.**, who had trained at Massachusetts General Hospital. He spent two years at ABCC before returning to Boston, and later, he was radiology chairman at the University of Nebraska from 1963 to 1965.

While at NAS, I realized my main interest was in disease etiology as studied epidemiologically. **James V. Neel, M.D., Ph.D.** visited Dr. Cannan from time to time to discuss a study of the effects of inbreeding as evaluated in the unexposed children who were in the ABCC Genetics Study of 1948 to 1954. Jim needed a pediatrician to supervise the clinical examinations of about 7500 children in Hiroshima and Nagasaki. At that time, about 5% of marriages were between first cousins and another 2% were between 1-1/2 or second cousins. By spending a year with Jim at the University of Michigan, I could help prepare the study and obtain an M.P.H. in the School of Public

*See **Looking Back** on page 24*



RERF file photo

courtesy of author

NAS file photo

courtesy of author

left to right:
Drs. Hollingsworth, Hamilton, Woodbury, *and* Pryde

Staff News continued from page 2

Imperial Palace in Tokyo in the presence of the emperor and empress. Mr. Kono was recognized for his long government service, including his contribution to the improvement of the Japanese social insurance system. Mr. Kono served at RERF from July 1986 to June 1994.

Shigematsu Receives Nakatomi Award Former RERF Chairman **Itsuzo Shigematsu** received the eighth Nakatomi Health Science Promotion Award March 19 in Tokyo. The award was established by the Nakatomi Health Science Foundation to support studies in the fields of medicine, pharmacology, and sports science as well as overseas study and international research exchange programs that contribute to the improvement of health.

Administration In the spring issue of *Update*, we failed to report that **Kazumasa Kunitoshi** assumed the position of chief of Secretariat effective 2 July 1997, replacing Yasukiyo Hirano. Mr. Kunitoshi came to RERF from the Chugoku Regional Finance Bureau under the Japanese Ministry of Finance, where he served as chief of the Department of Property Management.

Department of Clinical Studies **Michiko Yamada**, associate senior scientist, Division of Clinical Medicine, was promoted to senior scientist effective 1 June.

Department of Epidemiology Hiroshima Department Chief **Kiyohiko Mabuchi** is on a six-month sabbatical from 1 September, working with the U.S. National Cancer Institute Radiation Epidemiology Branch to develop a collaborative skin cancer project utilizing information from atomic-bomb survivors and cancer mortality studies in Russia's southern Ural Mountains. Yoshisada Shibata, Nagasaki department chief, is filling in for Dr. Mabuchi.

Department of Genetics **Janine Katanic**, a Purdue University School of Health Sciences doctoral student, was at RERF as a visiting scientist from 12 May to 11 August to receive instruction in the preparation of tooth enamel samples, the conduct of pilot studies to understand ultraviolet-related electron spin resonance signals in tooth enamel, and the measurement of teeth from atomic-bomb survivors. Her visit was supported by the U.S. Department of Energy Health Physics Faculty Research Award Program administered by Oak Ridge-associated universities.

Department of Radiobiology Department Chief **Toshio Seyama** resigned 30 June after more than eight years with RERF. Dr. Seyama joined the staff as a research scientist and had been assistant department chief until January of this year, when he became acting department chief with a concurrent assignment as chief of the cell biology laboratory. He was promoted to department chief effective 22 June. Dr. Seyama is now teaching at Yasuda University in Hiroshima. **Keisuke S. Iwamoto,** research scientist in the cell biology laboratory, was promoted to senior research scientist effective 1 April.

Department of Statistics **John B. Cologne**, associate senior scientist, was promoted to senior scientist 1 June.❑

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Recent Scientific Publications

The following 88 manuscripts were reported published by RERF staff members since the Spring 1998 Update. *Publications are arranged by study program and in reverse order by research protocol (RP) numbers from which the work reported emanates. Publications not directly related to a given RP are listed separately after these as collaborative and institutional publications, and a separate section 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. The following codes are used to identify RERF departments in publications and the section on meeting participation and oral presentations (See page 22.): Clinical Studies, Hiroshima (CH); Clinical Studies, Nagasaki (CN); Epidemiology, Hiroshima (EH); Epidemiology, Nagasaki (EN); Genetics (G); Radiobiology (R); Statistics (S); Information Technology (IT); and RERF Director (D).

***(Japanese)** indicates original article is in Japanese; **(J)** after an entry with an RERF Report number indicates 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.*

Publications Arranged by Study Program and Research Protocol

Life Span Study

RP 14-78 Collaborative Group on Hormonal Factors in Breast Cancer (RERF authors: Mabuchi K (EH), Preston DL (S)). *Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer.* Lancet 1997 (October); 350(9084): 1047-59.

RP 1-75 Mabuchi K (EH), Ron E (National Cancer Institute, Bethesda, Maryland, USA), Preston DL (S). *Cancer incidence among Japanese atomic-bomb survivors.* In: Boice JD, Jr, ed. Implications of New Data on Radiation Cancer Risk. Bethesda, Maryland, USA: National Council on Radiation Protection and Measurements; 1997 (March 1), pp 41-9. (Proceedings of the Thirty-Second Annual Meeting of the National Council on Radiation Protection and Measurements, Arlington, Virginia, 3-4 April 1996).

Pierce DA (S). *Statistical aspects of RERF cancer epidemiology.* In: Peterson LE (Baylor College of Medicine, Houston, Texas, USA), Abrahamson S (D), eds. Effects of Ionizing Radiation: Atomic-Bomb Survivors and their Children (1945-1995). Washington, DC, USA: Joseph Henry Press; 1998 (April), pp 91-9.

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Shimizu Y (E). *Life span and cancer risk in atomic-bomb survivors exposed to low-level radiation doses.* FY-1997 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association) 1998 (March), pp 41-2. **(Japanese)**

Adult Health Study

RP 2-75 Kasagi F (S), Kodama K (CH), Fujiwara S (CH), Yamada M (CH). *Study of association between low-dose radiation exposure and disease prevalence.* FY-1997 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association) 1998 (March); 43-4. **(Japanese)**

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Soda M (EN), Akahoshi M (CN). *Effect of ABCC-RERF Adult Health Study on life span.* FY-1997 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association) 1998 (March); 36-7. **(Japanese)**

Immunology Studies

RP 1-93 Kusunoki Y (R), Yamaoka M (R), Maki M (R), Saito C (R), Suzuki T (R), Hirai Y (R), Kyoizumi S (R), Seyama T (R), Kodama K (CH). *Effects of atomic-bomb radiation on human immune responses. (13) Study on repertoire of T lymphocyte antigen receptors.* Hiroshima Igaku (Journal of the Hiroshima Medical Association) 1998 (March); 51(3): 364-8. (Proceedings of the 38th Late A-bomb Effects Research Meeting, 1997). **(Japanese)**

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RP 9-92 Fujiwara S (CH), Cologne JB (S), Akahoshi M (CN), Kodama K (CH), Kusumi S (Institute of Radiation Epidemiology, Radiation Effects Association, Tokyo), Yoshizawa H (Hiroshima University School of Medicine), Nagataki S (D). *Prevalence of hepatitis C virus infection among atomic-bomb survivors.* Hiroshima Igaku (Journal of the Hiroshima Medical Association) 1998 (March); 51(3):344-5. (Proceedings of the 38th Late A-bomb Effects Research Meeting, 1997). **(Japanese)**

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RP 18-59 Watanabe T (Secretariat), Yamashita T (EN), Fujita S (S). *Collection of materials exposed to atomic-bomb radiation in Hiroshima and Nagasaki (FY 1997).* FY-1997 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association) 1998 (March), pp 78-9. **(Japanese)**

Special Cancer Studies

RP 1-91 Mabuchi K (EH), Tokuoka S (EH). *Radiation, salivary gland tumors and characterization of histologic features.* Igaku no Ayumi (Journal of Clinical and Experimental Medicine) 1997 (November); 183(7): 468-9. **(Japanese)**

Tumor, Tissue, and Leukemia Registries

RP 18-61 Mabuchi K (EH). *Tumor registries and cancer incidence studies.* In: Peterson LE (Baylor College of Medicine, Houston, Texas, USA), Abrahamson S (D), eds. Effects of Ionizing Radiation: Atomic-Bomb Survivors and their Children (1945-1995). Washington, DC, USA: Joseph Henry Press; 1998 (April), pp 117-29.

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Chen W (Department of Medicine [DM], University of Washington [UW], Seattle, Washington, USA), Chatta GS (DM/UW), Rubin WD (DM/UW), Clark JG (Fred Hutchinson Cancer Research Center [FHCRC], USA), Hackman RC (Department of Pathology/UW; FHCRC), Madtes DK (FHCRC), Ligitt DH (Department of Comparative Medicine/UW), Kusunoki Y (R), Martin PJ (DM/UW), Cheever MA (DM/UW). *T cells specific for a polymorphic segment of CD45 induce graft-versus-host disease with predominant pulmonary vasculitis.* Journal of Immunology 1998 (July 15); 161(2): 909-18. **(Japanese)**

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endometrium during the menstrual cycle and early pregnancy. Human Reproduction 1998 (April); 13(4): 1036-43.

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Shigematsu I (D). *Radiation and health—Lessons from atomic-bomb survivors.* Journal of Cardiovascular Surgery (Torino) 1998 (April); 39(Suppl. 1 to No.2): 193-8.

Takino H (Nagasaki University School of Medicine [NUSM]), Yamasaki H (NUSM), Ozaki M (NUSM), Abe T (NUSM), Sera Y (NUSM), Kondo H (NUSM), Sakamaki H (NUSM), Akazawa S (NUSM), Eguchi K (NUSM), Nagataki S (D), Yamaguchi Y (NUSM). *The nation-wide prevention study of Type 1 NIDDM in Japan.* Diabetes 1998 (May); 47 (Supplement 1):A225. (Abstract Book for the 58th Scientific Sessions, Chicago, Illinois, USA, 13-16 June 1998).

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Disease Institute [ABDI]/NUSM), Namba H (ABDI/NUSM), Hoshi M (Research Institute for Radiation Biology and Medicine, Hiroshima University), Yokoyama N (NUSM), Izumi M (NUSM), Nagataki S (D). *Prevalence of goiter and urinary iodine excretion levels in children around Chernobyl.* Journal of Clinical Endocrinology and Metabolism 1997 (October); 82(10):3430-3.

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Ito M (Atomic Bomb Disease Institute [ABDI]/Nagasaki University School of Medicine [NUSM]), Sekine I (ABDI), Ashizawa K (NUSM), Nishikawa T (NUSM), Nagataki S (D), Yamashita S (ABDI/NUSM), Kotova L (Gomel Specialized Medical Dispensary [GSMD], Belarus), Penasyuk GD (GSMD). *Cytologic characteristics of pediatric thyroid carcinoma around Chernobyl, Republic of Belarus.* Acta Cytologica 1997 (September); 41(5): 1642-4.

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Meeting Participation

RERF researchers reported attending 21 international meetings at which they made 11 presentations and 23 Japanese meetings at which they made 27 presentations from 1 April to 30 September. If oral presentations were given, the titles of the presentations appear in italics after the associated research protocol number. "No RP" precedes oral presentations not associated with specific protocols. Department codes are the same as for publications. (*See page 16.*)

International Meetings (outside Japan or of an international group)

Cancer Registry Training Program, 30 March - 10 April 1998, San Francisco, California, USA
Koyama K (EH)

US-Japan Symposium on Cardiovascular Research, 2-4 April 1998, Nara, Japan
Kodama K (CH), Takahashi N (G)

The First International Workshop on Advanced Genomics, 27-28 April 1998, Tokyo, Japan Kodaira M (G), Tsuyama N (R), Takahashi N (G)

The 13th International Congress of Cytology, 10-14 May 1998, Tokyo, Japan
Matsushima R (EN), Mizuno M (EH)

The International Workshop on China-Japan Cooperative Epidemiological Studies for High Background Radiation Area and Medical Research Workers, 19-20 May 1998, Tokyo, Japan Shimizu Y (EH)

Seminar on Research of Long-Term Radiation Effects in Japan, 23-24 May 1998, Taipei, Taiwan, Republic of China Kodama K (CH)

The 2nd International Conference on Long-Term Health Consequences of the Chernobyl Disaster, 1-6 June 1998, Kiev, Ukraine
Kodama K (CH); Taira (D), moderator, Epidemiology Research

The 17th Scientific Meeting of the International Society of Hypertension, 7-11 June 1998, Amsterdam, The Netherlands
Kodama K (CH)

RP 2-75 Akahoshi M (CN), Soda M (EN), Tominaga T (CN), Nakashima E (S), Seto S (Nagasaki University School of Medicine [NUSM]), Yano K (NUSM). *Trends of blood pressure and body mass index, and metabolic aberration(s) in chronic hypotensive subjects.*

RP 2-75 Akahoshi M (CN), Soda M (EN), Tominaga T (CN), Nakashima E (S), Seto S (Nagasaki University School of Medicine), Yano K (NUSM). *Close correlation between fatty liver and coronary risk factors: A population study of men and women in Nagasaki, Japan.*

The 18th Annual New England Epidemiology Seminar—Logistic Regression Modeling, 22-26 June 1998, Boston, Massachusetts, USA
Koyama K (EH)

Annual Scientific Meeting of the Faculty of Public Health Medicine of the Royal College of Physicians of the United Kingdom, 23-26 June 1998, Torquay, United Kingdom
Kodama K (CH), inducted as a fellow

The 6th International Conference on Alzheimer's Disease and Related Disorders, 18-23 July 1998, Amsterdam, The Netherlands

RP 5-92 Mimori Y (Hiroshima University School of Medicine), Yamada M (CH), Sasaki H (CH), Kasagi F (S), Ikeda J (HUSM), Kodama K (CH), Nakamura S (HUSM), Nagataki S (D). *Cognitive decline in the elderly Japanese population.*

First International Seminar on Radiation and Thyroid Cancer, 20-23 July 1998, St. John's College, Cambridge University, United Kingdom

No RP Nagataki S (D). *Thyroid cancer in atomic-bomb survivors* and *Atomic-bomb survivors population and the Marshall Islands.*

The First Siebold Lecture at Wurzberg University, 24 July 1998, Wurzberg, Germany

No RP Nagataki S (D). *Lessons from Hiroshima, Nagasaki, and Chernobyl: Radiation and the thyroid.*

The 32nd Annual Meeting of the International Association of Cancer Registries, 17-19 August 1998, Atlanta, Georgia, USA

RP 18-61 Soda M (EN), Akahoshi M (CN), Ichimaru S (CN). *Colon cancer incidence among the cohorts of atomic-bomb survivors in Nagasaki, Japan.*

The 3rd International Heart Health Conference, 29 August - 2 September 1998, Singapore

RPs 2-75, 4-85 Kodama K (CH). *Dietary and other lifestyle changes and CVD: 26-year follow-up of the NIHON-SAN study.*

Diagnosis and Treatment of Radiation Injury, 31 August - 3 September 1998, Rotterdam, The Netherlands

RP 1-75 Pierce DA (S). *Cancer and noncancer risks in atomic-bomb survivors.*

The 3rd European Federation of Immunological Societies (EFIS) Immunology Conference— Molecular Determinants of T-cell Immunity, 6-9 September 1998, Tatra Mountains, Slovakia

RP 1-93 Kyoizumi S (R), Umeki S (R), Kusunoki Y (R), Cologne JB (S), Iwamoto KS (R), Hirai Y (R), Seyama T (R), Ohama K (Hiroshima University School of Medicine). *Life span of human memory T-cells in the absence of T-cell receptor expression.*

The 2nd International Conference on Health of Radiation, Ecology, and Health, 16-19 September 1998, Semipalatinsk, Kazakstan
Taira S (D)

International Conference on Programmed Cell Death, 17-18 September 1998, Fribourg, Switzerland

RP 1-93 Hayashi T (R), Kyoizumi S (R), Kusunoki Y (R), Seyama T (R). *Mechanisms of suppression of radiation-induced apoptosis in a bcl-2-transfected human T-cell leukemia line.*

The 71st Annual Meeting of the American Thyroid Association, 18 September 1998, Portland, Oregon, USA Nagataki S (D)

The 12th International Mouse Genome Conference, 30 September - 3 October 1998, Bavaria, Germany

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). *Study on spontaneous and X-ray induced germ cell mutations in mice detected by computer-assisted two-dimensional DNA gel analysis.*

Meetings in Japan

The 54th Meeting of the Japanese Society of Radiological Technology, 8-11 April 1998, Kobe Sakamoto I (CN)

The 95th Annual Meeting of Japanese Society of Internal Medicine, 9-11 April 1998, Fukuoka Tominaga T (CN)

No RP Nagataki S (D). *Environment and health: Quantitative analysis and countermeasures against radiation hazard.*

The 87th Annual Meeting of the Japanese Society of Pathology, 14-16 April 1998, Hiroshima Mizuno M (EH), Tasaki H (EN)

RP 6-91 Hayashi Y (Hiroshima City Asa Hospital), Tsuda N (Nagasaki University School of Medicine), Tokunaga M (EH), Tokuoka S (EH), Preston DL (S), Mabuchi K (EH). *Study of the thyroid gland tumors among A-bomb survivors, 1950-1990.*

RP 1-75 Mabuchi K (EH). *Radiation epidemiology: Recent findings and future.*

The 5th Annual Meeting on Hypertensive Heart Research, 18 April 1998, Tokyo

RP 2-75 Seto S (Nagasaki University School of Medicine), Akahoshi M (CN), Yano K (NUSM). *A study on the occurrence of ECG left ventricular hypertrophy and the progress of blood pressure by a 26-year longitudinal follow-up.*

The 47th Annual Meeting of the Japanese Association of Medical Technologists, 7-8 May 1998, Osaka Kai N (CN), Mishima S (G)

FY1998 Joint Annual Meeting of the Biometric Society of Japan and the Japanese Society of Applied Statistics, 12-13 May 1998, Tokyo

RP 36-63 Izumi S (S), Fujisawa H (Tokyo Institute of Technology). *Estimating the probabilities of false positive and false negative errors in the blood group data.*

The 71st Annual Meeting of the Japan Endocrine Society, 4-6 June 1998, Fukuoka
Tominaga T (CN)

No RP Nagataki S (D). *Lessons from the Chernobyl nuclear power plant accident.*

The 21st Meeting of the Japanese Society of Cancer Epidemiology, 5-7 June 1998, Niigata
Koyama K (EH)

The 39th Late A-bomb Effects Research Meeting, 7 June 1998, Nagasaki

RP 2-94 Iwamoto KS (R), Mizuno T (R), Tokuoka S (EH), Mabuchi K (EH), Seyama T (R). *Development of radiation-induced cancers in humans: molecular lessons from the atomic-bomb survivors.*

RP 1-93 Kusunoki Y (R), Kyoizumi S (R), Yamaoka M (R), Maki M (R), Hirai Y (R), Kasagi F (S), Kodama K (CH), Seyama T (R). *Effects of atomic-bomb radiation on human immune responses. (14) Relationship between decrease in the ratio of peripheral CD4 T cells and the development of myocardial infarction.*

RP 8-93 Ohtaki K (G), Nakamura N (G), Awa AA (G). *Chromosome aberration: INV(14)(Q11Q32) in lymphocytes from Hiroshima A-bomb survivors.*

RP 18-59 Preston DL (S), Mabuchi K (EH), Kodama K (CH), Fujita S (S). *Relationship of epilation and subcutaneous hemorrhage to distance from hypocenter.*

RP 5-92 Yamada M (CH), Mimori Y (Hiroshima University School of Medicine), Sasaki H (CH), Kasagi F (S), Ikeda J (HUSM), Nakamura S (HUSM), Kodama K (CH). *Study of cognitive function disorder among A-bomb survivors.*

The 67th Annual Meeting on Radiation Council, 10 June 1998, Tokyo Mabuchi K (EH)

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

RP 11-81 Hayashi T (R). *Characterization of human breast epithelial stem cells and induction of carcinogenic mutations by ionizing radiation.*

RP 11-81 Kyoizumi S (R). *A SCID-hum mouse model for studying human stem cells.*

Meeting on the Research Group for Population-Based Cancer Registration in Japan, 17-18 June 1998, Osaka

RP 18-61 Mabuchi K (EH), Koyama K (EH), Dote M (EH). *Area-specific cancer registration in Hiroshima Prefecture.*

18th Conference of the Japanese Society of Bone Morphometry, 25-27 June 1998, Okayama
Fujiwara S (CH)

4th Familial Tumor Research Symposium, 27 June 1998, Tokyo
Hirai Y (R)

33rd General Meeting of the Japanese Association for Cerebrocardiovascular Disease Control, 9-10 July 1998, Tokyo
Kodama K (CH), Shimizu M (CH)

The 15th National Institute of Radiological Sciences-Radiation Effects Research Foundation-Research Institute for Radiation Biology and Medicine, Hiroshima University (NIRS - RERF - RIRBM) Research Exchange Seminar, 17 July 1998, Hiroshima

RP 4-86 Fujita S (S), Sasaki H (CH), Kasagi F (S). *Physiological aging indices and prognosis.*

RP 7-85 Kodaira M (G), Katayama H (IT), Funamoto S (S), Preston DL (S), Nakamura N (G), Asakawa J (G). *Molecular analysis of radiation-induced mutations in mouse germ cells by two-dimensional electrophoresis of DNA.*

RP 2-91 Koyama K (EH), Mabuchi K (EH), Tokuoka S (EH). *An epidemiologic study of skin cancer among atomic-bomb survivors.*

23rd Chugoku Area Radiation Effects Research Meeting, 24 July

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1998, Okayama Nakamura N (G), Chair, Session on Cellular Radiosensitivity

No RP 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.*

No RP Kyoizumi S (R), Hayashi T (R), Seyama T (R). *Analysis of radiosensitivity of the epithelium of the human small intestine using SCID-hu mice.*

The 66th Annual Meeting of the Japan Statistical Society, 27-30 July 1998, Tokyo

No RP Nakashima E (S), Tsuji S (Hiroshima Citizen Hospital), Ohtaki M (Hiroshima University Research Institute of Radiation Biology and Medicine). *The regression analysis of the ordered categorical response data — Analysis of arteriosclerosis obliterans (ASO) data.*

The 16th General Meeting of Japanese Society of Bone Metabolism, 5-8 August 1998, Tokyo

RP 2-75 Fujiwara S (CH), Kasagi F (S), Kodama K (CH), Nagataki S (D). *Mortality after spine and hip fractures from long-term cohort study.*

The 2nd Meeting of the Japanese Association for Medical Management of Radiation Accidents and Forum of Experts for Medical Care of the Exposed, 8 August 1998, Tokyo Taira S (D)

No RP Nagataki S (D). *Medical problems of iodine administration for medical care of the exposed.*

The 7th Annual Meeting on Japanese Associations of Cancer Registries, 3-4 September 1998, Nagoya Hayama S (EN), Koyama K (EH), Hamamatsu M (EN), Mikami S (EH), Shinozuka N (EH), Soda M (EN)

The 21st Annual Scientific Meeting of the Japanese Society of Hypertension, 24-26 September 1998, Hiroshima Akahoshi M (CN), Takahashi N (G)

The 57th Annual Meeting of the Japanese Cancer Association, 30 September - 2 October 1998, Yokohama Nagamura H (R)

RP 7-92 Ban S (R), Mizuno T (R), Hayashi T (R), Iwamoto KS (R), Hamatani K (R), Seyama T (R). *Feasibility of whole genome amplification to immortalize DNA obtained from archival tissues.*

RP 1-93 Hayashi T (R), Kyoizumi S (R), Kusunoki Y (R), Seyama T (R), Suzuki F (Hiroshima University Research Institute for Radiation Biology and Medicine), Trosko JE (Michigan State University School of Medicine). *Radiation-induced apoptosis in hematopoietic stem cells.*

RP 4-94 Iwamoto KS (R), Mizuno T (R), Tokuoka S (EH), Mabuchi K (EH), Seyama T (R). *A dose-dependent increase in the frequency of p53 mutations in hepatocellular carcinomas of the atomic-bomb survivors.*

RP 18-81 Kyoizumi S (R), Hayashi T (R), Seyama T (R). *Analysis of apoptosis in human small intestine using SCID-hu mice.*

RP 2-94 Yano M (Hiroshima University School of Medicine), Asahara T(HUSM), Dohi K (HUSM), Iwamoto KS (R), Seyama T (R). *Analysis of p53 and hMSH2 mutations in the progression of hepatocellular carcinoma.*❑

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Health. I would then spend one year with the team in Hiroshima and another in Nagasaki and return to Ann Arbor for a final year at the School of Public Health on a dissertation using study data for a doctorate in public health (epidemiology). Dr. Francis, professor of epidemiology, accepted me for training in the school beginning in September 1957.

Early in our Washington stay, Mrs. Cannan telephoned my wife, whose English was not yet fluent, and invited us to dinner at the Cosmos Club. I asked my wife where we were to meet the Cannans, and she said, "The ladies' room." It turned out to be the ladies' entrance to the club, which was sex-specific in those days. After two years in Washington, as the time for our departure for Ann Arbor neared, I said to my wife that Dr. Cannan may not realize how much I helped him. However, he and Mrs. Cannan again invited us to the Cosmos Club—this time for a farewell luncheon, which proved to be a surprise party attended by division staff.

Soon after Dr. Cannan's retirement in 1967, he was elected a member of NAS, an honor he truly deserved.❑

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