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RERF

**Radiation Effects
Research Foundation**

**A Cooperative
Japan-US
Research Organization**

Annual Report

1 April 1999–31 March 2000

Radiation Effects Research Foundation

A Cooperative Japan-US Research Organization

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Organization of RERF

RERF Directors, Supervisors, and Scientific Councilors

1 April 1999–31 March 2000

Permanent Directors

Shigenobu Nagataki, chairman

former dean, Nagasaki University School of Medicine

Sheldon Wolff, vice chairman and chief of research

professor emeritus of cytogenetics, Department of Radiology, and director emeritus, Laboratory of Radiobiology and Environmental Health, School of Medicine, University of California, San Francisco

William J Schull, permanent director

director emeritus and Ashbel Smith professor of academic medicine, Center for Demographic and Population Genetics, Graduate School of Biomedical Sciences; professor of human genetics, School of Public Health, University of Texas Health Science Center

Senjun Taira, permanent director

former director, Tohoku Regional Medical Affairs Office, Japanese Ministry of Health and Welfare

Directors

Kazuaki Arichi, councilor, Japan Institute of International Affairs

Masumi Oike, chairman, Japan Anti-Tuberculosis Association

Toshiyuki Kumatori, consultant, Radiation Effects Association

Jonathan M Samet, professor and chairman, Department of Epidemiology, Johns Hopkins University School of Hygiene and Public Health

Patricia A Buffler, dean and professor of epidemiology, Division of Public Health Biology and Epidemiology, School of Public Health, University of California, Berkeley

Richard B Setlow, senior biophysicist, Biology Department, Brookhaven National Laboratory, adjunct professor of Biochemistry and Cell Biology Department, State University of New York at Stony Brook

Supervisors

Shudo Yamazaki, former director-general, National Institute of Infectious Disease

David Williams, senior financial advisor, US National Academy of Sciences

Scientific Councilors

Tomio Hirohata, professor emeritus, Kyushu University Faculty of Medicine

Hiromichi Matsudaira, chairman, Radiation Effects Association

Yusuke Nakamura, director, Human Genome Center, Institute of Medical Science, University of Tokyo

Masao Sasaki, professor, Radiation Biology Center, Kyoto University

Shinichiro Ushigome, professor, Department of Pathology, Jikei University School of Medicine

Theodore L Phillips, Wun-Kon Fu distinguished professor and associate director, University of California San Francisco Cancer Center

Maurice S Fox, Lester Wolfe professor of molecular biology, Massachusetts Institute of Technology

Susan Preston-Martin, professor, Preventive Medicine, University of Southern California Norris Comprehensive Cancer Center

J Martin Brown, professor and chairman, Division of Radiation Biology, Department of Radiation Oncology, Stanford University School of Medicine

Joe W Gray, professor of Laboratory Medicine and Radiation Oncology, University of California, San Francisco

Introduction

Message from the Chairman

Shigenobu Nagataki, M.D.

In publishing this FY1999 annual report, I would like to express my sincere appreciation to the A-bomb survivors, and many other people interested in our work, for their support and cooperation.

Nowadays, we often hear news about the consolidation and bankruptcy of enterprises, and that a large number of people have lost their jobs because of restructuring for the purpose of a more streamlined management. RERF cannot stand as an outsider of the befalling harsh events. A sense of continuing financial crisis, due to the strong yen and a reduced US budget, has led to the curtailment of employees of RERF, and has become a major obstacle in the improvement of morale. In addition, as mentioned in the previous annual report, the present US financial commitment will expire in 2001, and no guarantee of financial support thereafter has been offered as of March 2000. This financial issue, one of our most important problems, was included in the agenda at the Japan-US meeting held in October 1999 in Hawaii, where both governments exchanged their opinions. However, this issue is still pending, and a further discussion will take place sometime in 2000. While we would continuously ask for support from the governments of the US and Japan, we must seriously think about what we should do by ourselves.

Taking into account its days as the Atomic Bomb Casualty Commission (ABCC), RERF has been conducting its research for over half a century. The achievements accumulated through the years have greatly contributed to the welfare and health not only of A-bomb survivors but also of those exposed to radiation in the world. We should spare no effort to have our research recognized as being essential now and in the future, and supported by local communities, as well as organizations and institutes concerned in and out of the country. At RERF, measures have been actively taken for recruiting research scientists for the purpose of strengthening the research system. From April 1999 until the present, a total of nine new research scientists were appointed (four to the Department of Clinical Studies, two to the Department of Epidemiology, one to the Department of Radiobiology, one to the Department of Genetics, and one to the Department of Statistics). Other appointments included one young employee to the Department of Information Technology and three more to the

Secretariat. In addition, the supplementary budget provided for economic recovery allowed us to repair the deteriorated facilities to some extent.

On a more cheerful note, I would like to point out that good progress was made in our research. Concerning the health effects study on A-bomb survivors' children planned by RERF, RERF and *Niseikyo* (the All Japan Second Generation A-bomb Victims Liaison Council) had repeatedly held discussions for nearly two years. On May 19, 1999, both parties managed to reach an agreement for the conduct of the said study, and signed a letter of confirmation. The future plan of this F₁ health effects study was discussed at the 26th meeting of the Scientific Council held in April, one month prior to the signing, and a report was made at the 33rd Board of Directors meeting held in June regarding the history of the signing and the context of the letter of confirmation. An explanation was also given for our decision to establish a scientific committee and an ethics committee, each of which would be composed of individuals from other institutions and organizations, at the earliest. With this, the first meeting of the Scientific Committee was held in December of that year, and active discussions were exchanged. In January of the following year, the first meeting of the Ethics Committee was held, and a plan for a pilot mail survey was reviewed then. The pilot mail survey will be conducted in May in order to see whether the questions asked and the method used are appropriate.

At the Japan-US meeting mentioned previously, opinions were exchanged regarding the 1986 Dosimetry System (DS86) as well as financial matters, and the discussion gave direction to the creation of a Japan-US joint committee. As a result, a US-Japan Joint Dosimetry Workshop was held in March 2000 in Hiroshima, and discussions were actively held by the specialists from Japan and abroad. It was decided that the views obtained would be reflected in the final report to be published in September 2000 by the National Academy of Sciences (NAS) Dosimetry Committee.

Over half a century since the atomic bombing, many A-bomb survivors have passed away. I would like to close my message by expressing my sincere condolence and pray for the peaceful repose of their souls.

Report from the Vice Chairman and Chief of Research to the 2000 Board of Directors Meeting

Sheldon Wolff, Ph.D.

This past year, like other years, has seen significant changes in the office of chief of research. Dr. Clark Heath, whom I had reported had replaced Dr. Seymour Abrahamson as associate chief of research and was scheduled to succeed me as vice chairman and chief of research, decided to return to the United States in the middle of December, leaving the office vacant for the last six months.

I also want to inform you of other significant changes in our scientific personnel that have occurred since we last met. We have lost some key people, made some new appointments, and are heavily involved in trying to fill our vacant positions.

Dr. Kiyohiko Mabuchi, who for many years was head of the Department of Epidemiology, left us to take a position with the epidemiology branch of the National Cancer Institute of the US National Institutes of Health. Dr. Yukiko Shimizu, the assistant chief of the department, has taken on Dr. Mabuchi's responsibilities during the period in which we are carrying out an international search for a new head of the department. In this department we have also hired Dr. Catherine Sauvaget, who has an M.D. from France as well as a Ph.D. in epidemiology from Tohoku University in Japan.

For chief of Nagasaki Department of Epidemiology, we have been able to recruit Dr. Akihiko Suyama to replace Dr. Yoshisada Shibata, who assumed a professorship at Nagasaki University.

Further, to succeed Dr. Kazunori Kodama, who had resigned as chief of the Department of Clinical Studies in Hiroshima to take up a chair in Hiroshima University, we have been able to recruit Dr. Gen Suzuki from the National Institute of Radiological Sciences in Chiba. He assumed the duties of department chief as of the first of the year.

In October Dr. Harry Cullings, who has a strong health physics and statistics background, joined the Department of Statistics where he has mainly been involved in DS86 matters.

In August the Department of Genetics was augmented by the arrival of Dr. Inaho Danjo, who had been trained at the National Institute of Genetics and in Germany. She brings her extensive molecular biological skills to

the department.

This year also saw the arrival of Dr. Donald MacPhee from Australia as the new chief of the Department of Radiobiology. He came to us as a result of an international search. This department now is below maximum strength because of the departure of Dr. Keisuke Iwamoto to join the Department of Radiation Oncology at UCLA School of Medicine. Dr. Terumi Mizuno has also left. Several candidates have responded to the advertisements we, in conjunction with the National Academy of Sciences, have put out internationally seeking molecular radiobiologists to fill these two positions.

In Nagasaki we have also added the position of senior consultant by attracting Dr. Renjyu Maeda, a longtime member of the Nagasaki medical community. Furthermore, we have employed Dr. Toshiro Usa as a research scientist.

This year we carried out one notable workshop, which dealt with DS86 issues. As you know, DS86, the dosimetry system we utilize at RERF and which is basic to establishing risk estimates per unit dose of radiation worldwide, has some imperfections. For instance there are discrepancies between the numbers of neutrons predicted by DS86 to have been present at certain distances from the hypocenter and new sophisticated measurements of the amount of neutrons found there. Because of the publicity attendant on the discrepancies, some courts in Japan, mistakenly thinking that DS86 thus has no value at all, have handed down unscientific decisions regarding the damaging health effects that people might have suffered from exposure to radiation from the bombs. So there is intense interest in determining how much modification DS86 will require to fit the data even more adequately than it does at present. In the US, the National Academy of Sciences has a committee on dosimetry for RERF that is studying the problem, and in Japan there is a large dosimetry working group also so involved. The workshop brought the two groups together to exchange data, concepts, and hypotheses on the matter, and then to formulate suggestions as to how to proceed to resolve the issues in a timely fashion.

Our long awaited F₁ study has finally begun after

agreement was reached with the representatives of the *Niseikyo*, the All-Japan Second Generation A-bomb Victims Liaison Council. The initial stage consists of the mailing of a pilot questionnaire to some 300 people to enable us to refine the questions before sending out a final form to between 15,000–18,000 people. The plans are then to follow the questionnaire with clinical examinations of participants to study the appearance of possible late onset genetic diseases.

Two new collaborative interdepartmental programs have been proposed. One of these deals with data bases, data management, and informatics, which are becoming more and more important in this computerized era in which we accumulate and store huge amounts of information that has to be accessed and analyzed.

The second deals with our finally beginning to utilize our frozen sera, which for many years were stored away, awaiting the time when appropriate techniques would become available to enable us to exploit the sera for valuable biomedical information. We have already asked the Scientific Council for advice on these programs and, because the amount of serum from any one person is limited, will most likely involve other experts before settling on a final experimental design.

As in the past, to inform you in more detail about the current scientific programs and our progress in the past year, I have asked the department chiefs to prepare updates on the work carried out under the various research protocols (RPs) and to list their 1999 publications.

Chronology of Events

Chronology of Events

1 April 1999–31 March 2000

April 1999

- 7–9 The 26th Scientific Council meeting was held in Hiroshima. (See Appendix One for meeting report.)
- 13 Twenty employees were commended for long service (Hiroshima).
- 14 A meeting was held with the All Japan Second Generation A-bomb Victims Liaison Council (*Niseikyo*) at RERF's Nagasaki laboratory.
- 15 Four employees were commended for long service (Nagasaki).
- 15 Dr. Mohamed El Baradei, director-general of the International Atomic Energy Agency (IAEA), visited RERF.
- 29 Dr. Seymour Abrahamson, former RERF vice chairman, was decorated with the Third Order of the Sacred Treasure at its spring conferment. On May 12 he was presented with a letter of commendation and a medal by the Japanese Minister of Health and Welfare at their headquarters, and was later received by the Emperor in the Imperial Palace. Dr. Abrahamson was recognized for his leading role in the field of genetics in Japan since 1968, and also for his contributions, through the Japan Radiation Research Society, to developments in the studies of radiation effects on humans in Japan. On four occasions, intermittently for more than six years since 1988, Dr. Abrahamson has served, as vice chairman and chief of research at RERF, giving guidance particularly concerning the health effects study, the life span study, and the genetic study for A-bomb survivors.

April 7–9 26th Scientific Council Meeting

Pictured from left to right, front to back: Row one: Dr. S. Ushigome, Dr. M. Sasaki, Dr. J. W. Gray, Dr. J. M. Brown, Dr. M. S. Fox, Dr. T. Hirohata, Dr. S. Preston-Martin, Dr. H. Matsudaira, Dr. S. Yamazaki, Mr. D. Williams; Row two: Dr. S. Fujita, Mr. K. Kunitoshi, Mr. R. D. Sperry, Dr. D. L. Preston, Dr. E. Douple, Dr. S. Nagataki, Mr. Y. Takayama, Dr. S. Taira, Dr. S. Wolff, Mr. H. Kuroki, Dr. J. Weiss, Dr. S. Kyoizumi; Row three: Dr. M. Soda, Dr. S. Fujiwara, Dr. A. A. Awa, Dr. N. Nakamura, Dr. C. W. Heath, Jr., Dr. K. Mabuchi, Dr. M. Akahoshi, and Dr. T. Satoh.

April 29 Former RERF Vice Chairman and Chief of Research Seymour Abrahamson was decorated with the Third Order of the Sacred Treasure.

May

- 19 RERF and *Niseikyo* signed letters of confirmation for the health effects study of the children of A-bomb survivors.
- 20–June 23 Dr. Saeko Fujiwara, assistant chief of the Department of Clinical Studies, and Mr. Tadaaki Watanabe, General Affairs Section chief of the Secretariat, joined the first team of the twelfth biennial health examination of atomic-bomb survivors residing in North America. Dr. Kojiro Koyama, Tumor and Tissue Registry Office chief of the Department of Epidemiology, and Mr. Kazunari Yamanaka, group leader of the Department of Information Technology joined the second team. This program has been carried out jointly by the Hiroshima Prefectural Medical Association and RERF with the support of the Ministry of Health and Welfare (MHW), Hiroshima Prefecture, Hiroshima City, and the Hiroshima Atomic-bomb Casualty Council. The first group examined 185 survivors in San Francisco and Seattle between May 20 and June 2, and the second team 229 survivors in Los Angeles and Honolulu between June 9 and 23.

May 19 At the Hiroshima laboratory auditorium, Mr. Nobuto Hirano (left), president of *Niseikyo*, and RERF Chairman Shigenobu Nagataki exchanged letters of confirmation for the health effects study of the children of A-bomb survivors.

June 11 Administrative Advisor Richard Sperry was recognized for his 40 years of service to the National Academy of Sciences in Washington. From left to right: William Colglazier, Richard Sperry, Warren Muir (Commission on Life Sciences executive director), and Evan Douple (Board on Radiation Effects Research director).

June 21 Former Consultant and Associate Chief of Research Akio A. Awa was honored with National Academy of Sciences plaque. From left to right: Associate Chief of Research Clark W. Heath, Jr., Evan Douple, Akio A. Awa, and Vice Chairman Sheldon Wolff.

June 23-25 33rd Board of Directors Meeting
Pictured from left to right, front to back: Row one: Dr. M. Oike, Dr. K. Arichi, Dr. S. Wolff, Dr. S. Nagataki, Dr. R. B. Setlow, Dr. P. A. Buffler, Dr. S. Taira, Dr. I. Shigematsu; Row two: Mr. K. Kunitoshi, Dr. M. Soda, Dr. K. Mabuchi, Dr. T. Hirohata, Mr. R. D. Sperry, Mr. D. Williams; Row three: Dr. C. W. Heath, Jr., Dr. E. Douple, Ms. C. S. Berkley, Mr. J. Hall, Dr. M. Akahoshi, and Mr. H. Kuroki.

June

- 11 Administrative Advisor Richard D. Sperry was recognized for his 40 years of service to the National Academy of Sciences (NAS). An award was presented to Mr. Sperry by National Research Council Executive Officer William Colglazier in a ceremony held at NAS in Washington D.C. Since he joined the staff of the Atomic Bomb Casualty Commission (ABCC) as an administrative assistant in 1958, Mr. Sperry has contributed to ABCC-RERF and NAS as an assistant chief of the Secretariat and as a business administrator.
- 11 Hiroshima retirement ceremony for the first half of fiscal year 1999
Tsuneyuki Isaka, administrative assistant department chief, Department of Information Technology
Kyoko Katagami, administrative assistant department chief, Department of Epidemiology
Iwao Osaki, administrative assistant department chief, Department of Clinical Studies
- 21 Former Consultant and Associate Chief of Research Akio A. Awa was presented with a plaque of appreciation by Dr. Evan Douple, director of the Board on Radiation Effect Research of the Commission on Life Science of NAS, at an award ceremony at RERF. Dr. Awa's 32 years of dedicated service to ABCC-RERF, and his contributions to NAS were acknowledged. His achievements and leadership in cytogenetics and radiobiology were highlighted.
- 23-25 The 33rd meeting of the Board of Directors was held in Nagasaki. (See Appendix Two for meeting minutes.)
- 25 Nagasaki retirement ceremony for the first half of fiscal year 1999
Yoko Sakuma, group leader, Clinical Administration Section, Department of Clinical Studies
- 29 At the 44th Annual Meeting of the Health Physics Society (June 26-July 2, 1999, Philadelphia, U.S.A.), RERF Chairman Shigenobu Nagataki was presented with the 1999 G. William Morgan Award in recognition of his distinguished

achievements in radiation protection. In accepting this award, Dr. Nagataki spoke on the "Prospect for RERF Studies to Influence Radiation Regulations in the Next Millennium."

July

- 1 Dr. Masazumi Akahoshi, acting chief of the Department of Clinical Studies in Nagasaki was promoted to the position of chief.
- 8 A meeting was held with *Niseikyo* at RERF's Nagasaki laboratory.

August

- 20 The Third Meeting of the Japanese Association for the Management of Radiation Accidents and the Third Forum on Medical Management for Radiation Accident Emergencies were held at Hiroshima International Conference Hall. They were jointly sponsored by the Japanese Association for the Medical Management of Radiation Accidents, the Hiroshima International Council for Health Care of the Radiation Exposed (HICARE), the Nuclear Safety Research Association, and RERF. Representatives of the Ministry of Health and Welfare (MHW) and the Science and Technology Agency participated in the meeting. Representatives of the World Health Organization (WHO) and IAEA also gave lectures.

September

- 21 Dr. Donald G. MacPhee assumed the post of chief of the Department of Radiobiology.

October

- 1 At MHW's request, RERF dispatched Dr. Kazuo Neriishi, chief of the Division of Medicine; Dr. Masayuki Hakoda, chief of the Division of Clinical Laboratories; Ms. Michiko Kuwamoto, assistant chief of nurses; and Mr. Shinsuke Matsuura, senior technician of the Division of Clinical Laboratories, to conduct health examinations on residents in the area surrounding the criticality accident site of JCO, the nuclear fuel reprocessing facility in Tokaimura, Ibaraki Prefecture. The accident occurred on September 30.
- 1 Dr. Akihiko Suyama assumed the post of chief of the Department of Epidemiology in Nagasaki.
- 1 Ms. Margaret A. Irwin assumed the post of information specialist of the Archive Office at the Publication and Documentation Center.
- 5 A meeting was held with *Niseikyo* at RERF's Nagasaki laboratory.

November

- 1-3 A multinational peer review for the Department of Genetics was held. (See Appendix Three for peer review report.)

June 29 RERF Chairman Shigenobu Nagataki received the 1999 G. William Morgan Award at the Health Physics Society meeting in Philadelphia.

August 20 The Third Meeting of the Japanese Association for the Management of Radiation Accidents and the Third Forum on Medical Management for Radiation Accident Emergencies were held at Hiroshima International Conference Hall.

November 1-3 Multinational Peer Review of the Department of Genetics
Pictured from left to right, front to back: Row one: Dr. S. Nagataki, Dr. N. Niikawa, Dr. A. Shima, Dr. T. Nomura, Dr. H. J. Evans, Dr. J. W. Gray, Dr. A. T. Natarajan, Dr. Y. Nakamura, Dr. S. Wolff; Row two: Mr. K. Kunitoshi, Dr. M. Clegg, Dr. E. Douple, Dr. K. Mabuchi, Dr. N. Takahashi, Dr. D. G. MacPhee, Dr. C. W. Heath, Jr., Dr. S. Taira, Dr. M. Itoh, Dr. S. Fujiwara, Dr. A. Suyama; Row three: Dr. A. A. Awa, Dr. D. L. Preston, Dr. J. Asakawa, Dr. N. Nakamura, Dr. Y. Kodama, Dr. M. Kodaira, Dr. K. Ohtaki, Dr. M. Nakano, and Dr. I. Danjo.

November 17 Senior Research Scientist Jun-ichi Asakawa, Department of Genetics, received the 38th Kodama Award at the 50th general meeting of the Japanese Electrophoresis Society.

November 23 At the third open house in Nagasaki laboratory, visitors stained their own buccal mucosal cells for examination under the microscope.

February 1 Dr. James V. Neel, RERF consultant emeritus and professor emeritus of the University of Michigan Medical School, died in Ann Arbor.

- 17 Dr. Jun-ichi Asakawa, senior research scientist in the Department of Genetics, received the 38th Kodama Award at the 50th General Meeting of the Japanese Electrophoresis Society, in recognition of the study, "The Search for Mutations at the Protein and Gene Level Using Two-Dimensional Electrophoresis."
- 23 Two hundred and thirty-three people attended the Nagasaki laboratory's third open house. The demonstration of observing stained and fixed buccal mucosal cells under a microscope was very popular with the visitors.
- 27 Four hundred and sixty-six people attended the Hiroshima laboratory's fifth open house. Department of Genetics Chief Nori Nakamura gave a lecture entitled "What is Radiation?" RERF's new promotional video was also featured.

December

- 7 The Nagasaki Local Liaison Council held its third meeting since re-establishment. This was the 11th meeting since the Council's establishment.
- 7 Nagasaki retirement ceremony for the latter half of fiscal year 1999
Yasutaka Ohgushi, assistant chief, Secretariat
- 13 The first meeting of the Scientific Committee, which consists of external researchers who review and give advice on the contents of the health effects study on A-bomb survivors' children, was held at RERF's Hiroshima laboratory.
- 17 The Hiroshima Local Liaison Council held its second meeting since re-establishment. This was the 8th meeting since the Council's establishment.
- 20 Hiroshima retirement ceremony for the latter half of fiscal year 1999
Chizuko Kato, assistant section chief, Master File Section, Department of Epidemiology
Sachiko Nagatani, assistant section chief, General Affairs Section, Secretariat
Donald A. Pierce, senior research scientist, Department of Statistics
Katsusuke Sasaki, maintenance staff, Supply and Property Section, Secretariat
Tomiko Sasaki, unit supervisor, Supply and Property Section, Secretariat
Ginko Yamashita, group leader, Tumor and Tissue Registry Office, Department of Epidemiology
- 31 Dr. Clark W. Heath, Jr., associate chief of research, resigned.

January 2000

- 1 Dr. Gen Suzuki assumed the post of chief of the Department of Clinical Studies in Hiroshima.
- 24 The first meeting of the Ethics Committee, which reviews and gives advice on the health effects study of A-bomb survivors' children from an ethical viewpoint, was held at RERF's Hiroshima laboratory.

February

- 1 Dr. James V. Neel, RERF consultant emeritus and professor emeritus of the University of Michigan Medical School, passed away in Ann Arbor. He was 84 years old. In 1947, Dr. Neel came to Japan as a chief of the first field survey team the U.S. National Research Council organized for ABCC. He continued the survey until 1948. Subsequently, he served as a consultant of the ABCC-RERF Departments of Clinical Studies and Genetics for a long time, and played a central role in establishing the Laboratory of

Biochemical Genetics in 1976. He was one of the founders of the U.S. Human Genetics Society, and together with Dr. William J. Schull, former RERF vice chairman, Dr. Neel contributed to the progress of human genetics in Japan, and trained many Japanese geneticists.

- 16 A meeting was held with *Niseikyo* at RERF's Nagasaki laboratory.
- 17-18 The 2nd International Chernobyl Symposium under the auspices of the Ministry of Foreign Affairs was held at RERF's Hiroshima laboratory.
- 23 U.S. Ambassador to Japan Thomas S. Foley visited RERF. Ambassador Foley together with Osaka Consul General Robert Ludan, Consul Joanne Livingston, and Ms. Jane Heller, ambassadorial aid, heard an explanation by Chairman Shigenobu Nagataki on the history and research of ABCC-RERF. Following the question and answer session with the directors and research scientists, they toured some of the research facilities.

March

- 13-14 The U.S.-Japan Dosimetry Reassessment Workshop was held under the auspices of RERF at the ANA Hotel in Hiroshima. Over 60 researchers from Japan and abroad participated. (See Appendix Four for workshop report.)
- 29 A meeting was held with *Niseikyo* at RERF's Nagasaki laboratory.

Regular committee meetings

Various regular committee meetings and research audits were held as shown below:

Regularly scheduled Executive Committee meetings:

April 13, May 11 and 25, June 8, July 7 and 27, August 12, September 14, October 14 and 28, November 9 and 25, December 16, January 11 and 27, February 8 and 22, and March 7 and 23.

Enlarged Operating Committee meetings:

May 25, July 27, September 14, October 28, November 25, December 16, January 27, February 22, and March 23.

February 23 U.S. Ambassador to Japan Thomas S. Foley (center) visited RERF with Osaka Consul General Robert Ludan (right). Pictured at left is Ms. Fumiko Gregg, an interpreter for the ambassador.

March 13-14 The U.S.-Japan Dosimetry Reassessment Workshop was held at the ANA Hotel in Hiroshima.

Ad-hoc Executive Committee meetings:

May 19, October 12, 18, and 20.

Research Protocol meetings:

May 11, July 26, September 13, November 8 and 30, and December 27.

Research Audit:

May 27 and 28.

Section One: RERF Study Programs

Active Research Protocols by Study Program

1 April 1999–31 March 2000

The 64 research protocols (RPs) that were active during the fiscal year are listed below with brief progress reports prepared by primary investigating departments and listings of publications and oral presentations emanating from related work.

Investigating departments and laboratories are identified by the following codes:

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

The following designations are used for publications and oral presentations presented with RPs:

- ◆ Publications
- ✂ Manuscripts in Press
- ❖ Oral Presentations

Protocols are presented by study program in reverse chronological order, and entries include the protocol title, investigators, and a brief description of the RP.

Each protocol is followed by a listing of any publications that emanated from its research as well as manuscripts accepted for publication during the fiscal year. These are presented in alphabetical order by first author.

Manuscripts or presentations emanating from *inactive or terminated RPs are also listed, though detailed protocol information is not included.

Most outside authors are RERF consultants or expert advisors and are not listed with their affiliations. Separate departmental lists of consultants and expert advisors appear with the respective departments' staff listings in the following section of the annual report.

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

Oral presentations are included by RP after publications and listed chronologically by meeting date.

Research Protocols 1-75 (Platform Protocol), 14-78*, 11-69*, 2-61

Life Span Studies

RP 1-75 (Supersedes ABCC RP 14-60) Research plan for RERF studies of life span of atomic-bomb survivors, Hiroshima and Nagasaki

Shimizu Y (EH), Mabuchi K (EH), Preston DL (S), Shibata Y, Pierce DA (S)

For the full text of this platform protocol, see ABCC Technical Report 4-59.

This is a long-term follow-up of the fixed cohort of 93,000 atomic-bomb survivors and 27,000 unexposed individuals. The follow-up began in 1950 using the family registration system, the *koseki*, which assures virtually complete mortality ascertainment. It also serves as the sampling frame for the Adult Health Study clinical subcohort. Periodical analyses of the LSS mortality data have resulted in a series of reports. *LSS Report 12, Part 1* on cancer mortality, updated through 1990, was published in 1996. Recently, through tumor registries in Hiroshima and Nagasaki, it has also become possible to study cancer incidence in a subset of the LSS. The first comprehensive LSS cancer incidence data were published in 1994. As of 1995, about 50% of LSS subjects and about 85% of those exposed before age 30 were alive. Because of the uncertainty of the current risk estimates based on the incomplete follow-up of those exposed early in life, continuation of the follow-up, in terms of both mortality and cancer incidence, is essential. The latest published LSS mortality data also demonstrated an excess risk of death from noncancer causes, largely from cardiovascular and digestive diseases, associated with radiation exposure. Further research is needed to elucidate the nature and magnitude of the excess noncancer risk. *Part 2 of LSS Report 12* on noncancer mortality was published in 1999. Preparation will soon begin for the next LSS report, which will include updated (possibly through 1995) incidence and mortality data.

RP 1-75 Publications

◆ Chomentowski M, Kellerer AM, Pierce DA. Radiation dose dependences in the atomic bomb survivor cancer mortality data: A model-free visualization. *Radiation Research* 2000 (March); 153(3):289–94.

◆ Pierce DA, Mendelsohn ML. A model for radiation-related cancer suggested by atomic bomb survivor data. *Radiation Research* 1999 (December); 152(6):642–54. (RERF Report 11-99)

◆ Shibata Y, Shimizu Y, Suyama A. Estimation of attributable risk of radiation exposure in cancer mortality and cancer incidence among A-bomb survivors. FY-1999 Welfare Science Research Subsidy Report of Welfare Science Special Research Projects. Reassessment of A-bomb Radiation Dosimetry System and Study of Health Effects. Hiroshima: Study Team of the Reassessment of A-bomb Radiation Dosimetry System and Health Effects;

2000 (March 31), pp 41–50. (Japanese)

◆ Shimizu Y, Pierce DA, Preston DL, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part II. Noncancer mortality: 1950–1990. *Radiation Research* 1999 (October); 152(4):374–89. (RERF Report 11-98) (J)

RP 1-75 Oral Presentations

❖ Izumi S, Ohtaki M. Multiple regression analysis of survival time data using Weibull-gamma model. *Joint Annual Meeting of the Biometric Society of Japan and the Japanese Society of Applied Statistics, FY1999, 6–7 May 1999, Tokyo, Japan*

❖ Mabuchi K. The significance of long-term epidemiological studies about the health effects of atomic-bomb exposure. *The 40th Late A-bomb Effects Research Meeting, 6 June 1999, Hiroshima, Japan*

❖ Preston DL. Radiation effects on the atomic bomb survivors. *The 11th International Congress of Radiation Research, 18–23 July 1999, Dublin, Ireland*

❖ Shimizu Y, Pierce DA, Preston DL, Mabuchi K. Studies of the noncancer mortality of atomic bomb survivors: 1950–1990. *The 11th International Congress of Radiation Research, 18–23 July 1999, Dublin, Ireland*

❖ Shimizu Y. Epidemiological study on health effects of atomic bomb survivors. *The 11th International Conference of Women Engineers and Scientists, 24–27 July 1999, Chiba, Japan*

❖ Pierce DA. On the relation between frequency inference and likelihood. *The 52nd Session of the International Statistical Institute, 15–18 August 1999, Helsinki, Finland*

❖ Nagataki S. Thyroid cancer in atomic-bomb survivors. *The 26th Annual Meeting of the European Thyroid Association, 28 August–1 September 1999, Milan, Italy*

❖ Shimizu Y, Pierce DA, Preston DL, Mabuchi K. Noncancer disease mortality among atomic bomb survivors, 1950–1990. *The 42nd Annual Meeting of the Japan Radiation Research Society, 1–3 September 1999, Hiroshima, Japan*

❖ Mabuchi K. Epidemiological characteristics of the cancer risks in atomic-bomb survivors. *The 58th Annual Meeting of the Japanese Cancer Association, 29 September–1 October 1999, Hiroshima, Japan*

❖ Nakamura N. Molecular mechanisms of cancer deduced from data of A-bomb survivors. *The 58th Annual Meeting of the Japanese Cancer Association, 29 September–1 October 1999, Hiroshima, Japan*

*RP 14-78 Mail questionnaire survey for epidemiologic data on the Life Span Study extended sample, 1978

This research protocol was terminated on 16 July 1982, but following papers use data collected from that research.

*RP 11-69 Mail questionnaire survey for epidemiologic data on females in the JNII-ABCC Life Span Study sample

This research protocol was superseded by RP 14-78 (terminated on 16 July 1982) on 3 December 1978.

RPs 14-78 and 11-69 Publication

◆ Key TJ, Sharp GB, Appleby PN, Beral V, Goodman MT, Soda M, Mabuchi K. Soya foods and breast cancer risk: A prospective study in Hiroshima and Nagasaki, Japan. *British Journal of Cancer* 1999 (December); 81(7):1248–56.

RPs 14-78 and 1-98 (Special Cancer Studies) Manuscript in Press

⌘ Nagano J, Kono S, Preston DL, Moriwaki H, Sharp GB, Koyama K, Mabuchi K. Bladder-cancer incidence in relation to vegetable and fruit consumption: A prospective study of atomic-bomb survivors. *International Journal of Cancer*.

RP 2-61 Study of mortality in children exposed *in utero*

Preston DL (S), Mabuchi K (EH)

See *ABCC Technical Report 21-60* for full protocol text.

This is an ongoing long-term follow-up of a cohort of about 3,000 persons who were *in utero* at the time of the atomic bombings. Mortality follow-up for most cohort members began in 1946 and, thus, allows studies starting from birth of health effects associated with radiation exposure occurring during embryonic and fetal development. The cohort has recently been expanded to 3,289 persons by integrating several RERF overlapping *in utero* cohorts. The earlier follow-up data showed no evidence of childhood leukemia and cancer risks associated with radiation exposure in contrast to high risks associated with *in utero* exposure to X-rays given for diagnostic purposes. However, there is emerging evidence of an excess risk of adult-type cancers. Analyses of the latest mortality data have demonstrated significant excess risks of leukemia and solid cancer occurring between ages 17 and 46, and the magnitude of the risk is comparable to that seen among those exposed during early childhood (prior to age six). As the number of background cancer risks will increase rapidly in the next few decades, it is important to continue the follow-up using both mortality and cancer incidence as the endpoints. Because exposure occurred during the period of organogenesis, it is also important to study the risk of noncancer diseases since the background rate of such diseases will increase as the subjects age.

Research Protocol 2-75**Adult Health Study—Platform Protocol****RP 2-75 (Supersedes ABCC RP 1-63) Research plan for RERF Adult Health Study, Hiroshima and Nagasaki**

Kodama K, Fujiwara S (CH), Neriishi K (CH), Yamada M (CH), Nobuyoshi M (CH), Shimizu M, Murakami H, Akahoshi M (CN), Soda M (EN), Usa T (CN), Hida A (CN)

The primary purpose of the Adult Health Study (AHS) has been to determine the types of diseases and abnormalities in physiologically or biochemically determined values occurring as a consequence of atomic-bomb exposure and to relate this information with other life experiences and death. The AHS has also long provided information on nonfatal as well as fatal events.

The AHS's major research elements may be categorized as (1) characterization of cancer types in relation to various confounders of radiation effects; (2) radiation-related noncancer diseases (benign tumors, cardiovascular diseases, and other chronic diseases); (3) aging associated with exposure; (4) radiation-related changes in physiological measurements; (5) medical dosimetry; (6) psychosocial changes associated with exposure; and (7) health status of the *in utero* exposed.

Since disease morbidity information has depended on examination findings, participation maintenance has been an essential quality control factor. However, because of natural aging, a significant decrease in the participation rate is anticipated in the near future, which will result in less complete data collection on morbidity. To improve health information retrieval, a mail survey followed by telephone contact of nonresponders was introduced in Hiroshima in August 1995 and in Nagasaki in March 1996. In both cities, the response rate to the new surveillance system has been around 90% since the survey started. The response rates were 70% and 80%, respectively, for those AHS members who refused to participate in the biennial medical examination and those who migrated from the contact area, respectively. Moreover, the response rate of those above 70 years old, in which group medical examination participation has been poor, was around 85%. In addition, a substantial amount of information on newly developed diseases was obtained from this surveillance. These findings indicate that morbidity data collection is now more complete as a result of the new system, and future analysis of data on morbidity of various diseases may illuminate the association between morbidity and previous exposure to ionizing radiation.

Special emphasis has been placed on screening for skin, breast, and thyroid cancers, which are often not fatal. Although the AHS sample is limited, exposures to other carcinogens can be obtained through personal interviews and measurements using serum. Using stored serum, case-control studies will be conducted on various cancers related to nutrients and potential carcinogen and/or promoter substances.

Abdominal ultrasonographic techniques are being used to detect various benign tumors, such as uterine myoma, ovarian tumor, prostatic tumor, and liver heman-

gioma.

Storage of serum and other biological materials for future epidemiology has been a high priority. Cryopreservation of serum samples from AHS participants was started in both Hiroshima and Nagasaki in 1969. Routine collection and storage of lymphocytes from AHS participants was initiated in June 1990 (RP 2-90) by the collaborative efforts of the Departments of Clinical Studies and Radiobiology. Lyophilization of blood samples for DNA extraction (RP 2-97, Addendum to RP 2-90; see "Immunology" section) was started in December 1997. Such biological samples are being collected for future epidemiological studies.

To elucidate pathogenic mechanisms of radiation-induced diseases, molecular epidemiological studies on the AHS population have been initiated with international collaboration. For these studies, in addition to the ongoing lymphocyte collection and preservation for AHS subjects, collection of fresh biological materials from surgery, such as tissues of cancers, benign tumors, blood vessels, and skin, through more intensive morbidity surveillance is desirable.

A study of accumulated data to assess the frequency and nature of the social and psychological problems experienced by survivors has been in progress. The prevalence of mental disorders in relation to acute radiation symptoms and the place at the time of bombings were analyzed based on diagnostic criteria for mental disorders. Whether psychological problems themselves ultimately influence the magnitude of the risk through the adoption of lifestyle changes will be investigated in future.

Creation of a computerized data base containing all major AHS clinical and laboratory data, such as patient contact results, clinical diagnoses, and laboratory measurements, was nearly completed in 1999.

RP 2-75 Publications

♦ Kurisu T, Yamada M, Fujiwara S, Kodama K. The contribution of senility to death in the Adult Health Study. *Kosei no Shihyo (Health Welfare Statistics)* 1999 (November); 46(13):10–5. (Japanese)

♦ Nakashima E, Neriishi K. Analysis of inflammatory test measurements in atomic-bomb survivors with principal component analysis. *Hiroshima Igaku (Journal of the Hiroshima Medical Association)* 2000 (March); 53(3):267–9. (Proceedings of the 40th Late A-bomb Effects Research Meeting, 1999) (Japanese)

RP 2-75 Oral Presentations

❖ Nakashima E, Neriishi K. Analysis of inflammatory test measurements in Atomic-bomb survivors with principal component analysis. *The 40th Late A-bomb Effects Research Meeting, 6 June 1999, Hiroshima, Japan*

❖ Fujiwara S, Nakashima E, Kodama K. Diabetes mellitus among atomic-bomb survivors. *The 11th International Congress of Radiation Research, 18–23 July 1999, Dublin, Ireland*

❖ Kasagi F, Kodama K, Fujiwara S, Yamada M. Sudden death in the atomic-bomb survivors, Hiroshima. *The 11th International Congress of Radiation Research, 18–23 July*

1999, Dublin, Ireland

❖ Neriishi K. Clinical laboratory test of atomic-bomb survivors. *The 19th Meeting of the Japan Society of Clinical Chemistry: Summer Seminar, 28–30 July 1999, Hiroshima, Japan*

❖ Kodama K, Kasagi F, Fujita Y, Yamada M, Fujiwara S. Case-control study of short and long lives in the population of atomic bomb survivors. *The 15th Scientific Meeting of the International Epidemiological Association, 31 August–4 September 1999, Florence, Italy*

❖ Neriishi K, Tominaga T, Nakashima E. Analysis of inflammatory tests for chronic thyroiditis among atomic bomb survivors using principal component analysis. *The 42nd Annual Meeting of the Japan Radiation Research Society, 1–3 September 1999, Hiroshima, Japan*

❖ Neriishi K, Nakashima E. Persistent inflammation in atomic-bomb survivors and possible mechanisms. *International Conference of Free Radical Processes: Ecological, Pharmacological and Clinical Aspects, 8–10 September 1999, St. Petersburg, Russia*

❖ Masunari N, Yamada M, Fujiwara S, Matsuoka K. Contribution and limitation of drug information to reliability of diagnoses of Parkinsonism and Hyperuricemia/Gout. *The 58th Annual Meeting of Japanese Society of Public Health, 20–22 October 1999, Beppu, Oita, Japan*

❖ Neriishi K, Nakashima E. Relationship between radiation dose and smoking in inflammation markers in A-bomb survivors. *The 11th Meeting of Vitamin E Research, 28–29 January 2000, Kurashiki, Okayama, Japan*

❖ Hakoda M, Kasagi F, Yamada M, Masunari N, Fujiwara S, Kodama K. The significance of serum uric acid value as a risk factor for cardiovascular disease. *The 33rd Annual Meeting of Japanese Society of Gout and Nucleic Acid Metabolism, 3–4 February 2000, Kyoto, Japan*

Research Protocols 2-97, 1-93, 4-90, 2-90, 11-89*, 7-89, 7-87, 3-87

Immunology Studies

RP2-97(Addendum to, See also RP 2-90) Lyophilization of blood samples to be obtained from Adult Health Study subjects in Hiroshima and Nagasaki for DNA extraction

Hayashi T (R), Kyoizumi S (R), Fujiwara S (CH), Tominaga T (CN), Akahoshi M (CN)

The subjects and scope of studies conducted at RERF on the effects of atomic-bomb radiation on man and the techniques used for those studies are constantly being improved. It is conceivable, then, that, in the future, we will be able to conduct studies not currently possible. Recent developments in molecular biology have allowed investigators to carry out polymerase chain reaction (PCR) analyses using extremely small amounts of DNA. In studying late effects of radiation exposure in A-bomb survivors, analyses of gene alterations due to radiation are essential in investigations of genetic instability, genetic susceptibility, or molecular oncology. This RP was designed to supplement RP 2-90 by providing a means of storing DNA for multiple small-scale molecular analyses that would be wasteful of stored DNA if the only samples available were those obtained in RP 2-90. Blood samples for DNA extraction will be lyophilized for use in future studies of the effects of A-bomb exposure on humans, especially for molecular biological analyses using DNA. We have cryopreserved blood samples from 3,033 AHS participants in Hiroshima and 2,045 AHS participants in Nagasaki. It was determined by PCR amplification that DNA stored in dry paper was not significantly affected by storage for 2 years. We intend to continue collecting blood samples from approximately 2,000 AHS participants in Hiroshima and Nagasaki every year.

RP 1-93 (Addendum to, See also RPs 7-89, 4-87 [not active], and 3-87) Repertoire of T-cell antigen receptors and activity of hematopoietic progenitor cells in peripheral blood of atomic-bomb survivors
Kusunoki Y (R), Hayashi T (R), Kyoizumi S (R), Kasagi F (S), Fujita S (S), Hakoda M (CH)

To elucidate whether atomic-bomb radiation exposure has changed antigen recognition diversity in the immune system, the repertoire of T-cell receptor (TCR) variable-region (V) genes of mature T cells in the peripheral blood of about 1,000 A-bomb survivors has been studied by flow cytometry and T-cell responsiveness to the superantigen staphylococcal enterotoxin. Peripheral blood progenitor cells were also tested. A preliminary statistical analysis showed a dose-dependent decrease of the CD4 T-cell fraction. An age- but not dose-dependent increase was observed in the frequency of individuals showing skewed TCR V β usage (individuals who had T cells expressing any TCR V β family at a frequency of more than three standard deviations from the mean of about 1,000 examinees). Further, a dose-dependent decrease was seen in the responsiveness to each of all superantigens examined in the study. These results sug-

gest that previous radiation exposure reduced production of overall CD4 T cells but not production of those bearing a specific TCR V β family. As for stem cells, there was a significant dose-related increase of CD34 stem cells as well as colony-forming cells in female survivors, suggesting enhanced myelopoiesis in female survivors.

We investigated whether any immunological parameters examined in this study were associated with myocardial infarction (MI) in atomic-bomb survivors. Of 1,006 survivors examined for CD4 T-cell proportion in peripheral blood lymphocytes, 18 persons had histories of MI. The proportion of CD4 T cells was significantly decreased with increased radiation dose. Further, the prevalence of MI was significantly higher in individuals with a lower proportion of CD4 T cells. These results suggest that MI in A-bomb survivors is partly due to defects of CD4-helper T cells, which may contribute a reduced immune defense against bacterial infections, possibly causing atherosclerosis, such as *Chlamydia pneumoniae* infections.

To test whether defects of CD4-helper T cells in A-bomb survivors are related to inflammation signs, levels of inflammatory cytokines, C-reactive proteins (CRP), and immunoglobulins classes in the plasma were examined. Plasma levels of IL-6, CRP, IgM, and IgG were all found to increase with radiation dose. A strong correlation was observed between IL-6 and CRP levels. Further, both plasma IL-6 and CRP levels were negatively correlated with the percentage of CD4 T cells in peripheral blood lymphocytes. These results suggest that pre-clinical inflammatory status may be associated with the observed CD4-T-cell impairment in A-bomb survivors.

In response to a suggestion from the Multi-national Peer Review Committee, we commenced examining the expression of the costimulatory molecules CD80 and CD86 in peripheral blood B cells and monocytes, as well as expression of their receptor (CD28) in T cells among the A-bomb survivors. Signals resulting from interactions between these molecules are believed to play crucial roles in the differentiation of antigen-stimulated naive cells into Th1 and Th2 subsets, as well as in regulating the functions of overall T-cell populations. Results from this study should help us to understand the long-lasting nature of the radiation-induced abnormalities of T-cell functions that have been found to affect many A-bomb survivors.

As a result of several discussions at the RERF workshop on immunology (March 10 and 11, 1999), we are continuing to evaluate the relative proportions of lymphocyte subsets in our study subjects, and to test for correlations between immunological parameters and the onset of illnesses such as chronic liver diseases, thyroid diseases, and monoclonal gammopathy in A-bomb survivors.

RP 1-93 Publications

◆ Hayashi T, Kusunoki Y, Maki M, Kubo Y, Yamaoka M, Kyoizumi S, Kasagi F, Fujiwara S, Kodama K. Effects of atomic-bomb radiation on human immune responses: (15) Plasma IL-6 and immunoglobulin levels in atomic-bomb survivors. *Hiroshima Igaku* (Journal of the Hiroshima

Medical Association) 2000 (March); 53(3):253–5. (Proceedings of the 40th Late A-bomb Effects Research Meeting, 1999) (Japanese)

◆ Kusunoki Y, Kyoizumi S, Yamaoka M, Kasagi F, Kodama K, Seyama T. Decreased proportion of CD4 T cells in the blood of atomic bomb survivors with myocardial infarction. *Radiation Research* 1999 (November); 152(5):539–43. (RERF Report 2-99) (J)

RP 1-93 Manuscript in Press

✂ Kusunoki Y, Hayashi T, Hamatani K, Kyoizumi S. T-cell function and disease development: Implications for future immunological studies involving A-bomb survivors (Report of the RERF Immunology Workshop, March 10–11, 1999, Hiroshima) (RERF Commentary and Review Series 1-99) (J)

RPs 1-93 and 3-87 Publications

◆ Kusunoki Y, Hayashi T, Kyoizumi S. Immunity polarization in atomic-bomb survivors: From the viewpoint of the Th1/Th2 paradigm. *Hiroshima Igaku* (Journal of the Hiroshima Medical Association) 1999 (May); 52(5):509–11. (Japanese)

◆ Kusunoki Y, Kyoizumi S. Study of radiation effects on immunocompetence. FY-1999 Welfare Science Research Subsidy Report of Welfare Science Special Research Projects. Reassessment of A-bomb Radiation Dosimetry System and Study of Health Effects. Hiroshima: Study Team of the Reassessment of A-bomb Radiation Dosimetry System and Health Effects; 2000 (March 31), pp 91–107. (Japanese)

RP 1-93 Oral Presentations

✧ Hayashi T, Kusunoki Y, Maki M, Kubo Y, Yamaoka M, Kasagi F, Fujiwara S, Kodama K, Kyoizumi S. Late effects of atomic-bomb radiation on human immune responses. (15) Plasma IL-6 and immunoglobulin levels in atomic-bomb survivors. *The 40th Late A-bomb Effects Research Meeting, 6 June 1999, Hiroshima, Japan*

✧ Hayashi T, Kusunoki Y, Kasagi F, Kodama K, Kyoizumi S. A dose-dependent increase of plasma IL-6 level in atomic-bomb survivors. *The 11th International Congress of Radiation Research, 18–23 July 1999, Dublin, Ireland*

✧ Hayashi T, Kusunoki Y, Kubo Y, Maki M, Yamaoka M, Kasagi F, Fujiwara S, Kodama K, Seyama T, Kyoizumi S. Late effects of atomic-bomb radiation on cytokine and immunoglobulin production. *The 42nd Annual Meeting of the Japan Radiation Research Society, 1–3 September 1999, Hiroshima, Japan*

✧ Kusunoki Y, Hayashi T, Onishi H, Kubo Y, Morishita Y, Yamaoka M, Fujiwara S, Kodama K, Seyama T, Kyoizumi S. Hypothesis on the relationship between A-bomb radiation-induced immunity polarization and disease development. *The 42nd Annual Meeting of the Japan Radiation Research Society, 1–3 September 1999, Hiroshima, Japan*

✧ Hayashi T, Kusunoki Y, Kyoizumi S, Seyama T. Reactive oxygen and Bcl-2 in radiation-induced apoptosis. *International Conference of Free Radical Processes: Ecological, Pharmacological and Clinical Aspects, 8–10*

September 1999, St. Petersburg, Russia

❖ Hayashi T, Kusunoki Y, Seyama T, Kyoizumi S. Role of caspase and active oxygen in radiation-induced apoptosis. *The 29th Annual Meeting of the Japanese Society for Immunology, 1–3 December 1999, Kyoto, Japan*
❖ Kyoizumi S, Kusunoki Y, Hayashi T, Hakoda M, Seyama T. Decrease of CD4 T-cell ratio in the peripheral blood of A-bomb survivors with a history of myocardial infarction. *The 29th Annual Meeting of the Japanese Society for Immunology, 1–3 December 1999, Kyoto, Japan*

RP 4-90 Establishment of a method for HLA-DQ and DP gene typing using the polymerase chain reaction

Hayashi T (R), Kusunoki Y (R), Kyoizumi S (R), Fujiwara S (CH), Cologne JB (S), Nakashima E (S)

The objectives of this study are to establish a method of human leukocyte antigen (HLA) genotyping at RERF and to test for a possible population bias among atomic-bomb survivors on the assumption that different persons' survival abilities may have differed during the period of reduced immune function after the atomic bombing. Our analytical results using HLA data from 1,018 atomic-bomb survivors suggest that the frequency of DQA1*0103 males decreased with increasing dose. It is unclear whether this trend is real or due to statistical fluctuation. If it is real, then it implies population bias among the A-bomb study cohort. Diabetes mellitus (DM) prevalence is significantly increased with radiation dose in A-bomb-survivors who were younger than 20 years old at the time of the bombing. In most autoimmune disease, susceptibility is linked most closely with HLA class II alleles. DM, especially, insulin-dependent diabetes mellitus (IDDM), is associated with DR3 or DR4. Recently, some papers on the association of HLA types with non-insulin dependent diabetes mellitus (NIDDM) have appeared but the significance of this association is not yet clear. In A-bomb survivors, most DM patients are NIDDM-type due to age. We examined the effect of radiation on DM development depending on HLA haplotype. There were 109 DM patients among 901 persons with DM and HLA data. There was a dose-dependent increase in the odds ratio (OR) of DM in these subjects (Trend $p = 0.0006$). The OR of the high-dose exposed group (>1.5 Gy) with DQA1*0401/DR8 or DQA1*0301/DR9 haplotypes was significantly higher (OR = 3.43) than that of the control and low-dose groups with these haplotypes (OR = 0.64 and 1.07, Trend $p < 0.0001$). Most people with these haplotypes in the high-dose exposed group were less than 20 years old at the time of the bombing. On the other hand, the OR without DQA1*0401/DR8 or DQA1*0301/DR9 was not significantly increased with increasing dose (ORs of control, low-dose, and high-dose exposed groups = 1.18, 1.51, and 1.33; Trends $p = 0.20$). These results suggested that radiation effects may be different in different genetic backgrounds. Further statistical analysis of the relationship between the HLA type and the data on diabetes mellitus and inflammation will be carried out in collaboration with the Department of Statistics.

RP 2-90 (See also RP 2-97) Cryopreservation of blood cells from Hiroshima and Nagasaki Adult Health Study participants

Kyoizumi S (R), Hirai Y (R), Kusunoki Y (R), Hamatani K (R), Kodama K, Akahoshi M (CN)

Because atomic-bomb survivors are now reaching advanced ages, we propose to cryopreserve live blood cells from all AHS participants in order to have an available source of material for future studies. We have cryopreserved lymphocytes from 289 AHS participants from Hiroshima and 1,024 from Nagasaki this year. The lymphocytes of approximately 6,900 survivors have been preserved, and medical histories of these subjects have been recorded in the Department of Clinical Studies. About 1,400 of these subjects developed cancers before or after preservation of their lymphocytes. The effects of atomic-bomb radiation have been studied for about 2,000 subjects for various endpoints, such as immune functions and somatic mutations. Analytic techniques have continuously improved, and we expect that studies of hitherto immeasurable effects will become possible in the future. Molecular epidemiological analysis of genetic susceptibility to cancer and other diseases is one of the most important study subjects in the near future. We continue to cryopreserve blood cells from 3,200 Hiroshima AHS participants who have been sampled fewer than three times. The blood from about 4,000 AHS participants has not yet been collected for various reasons. It is desirable to resolve this problem.

***RP 11-89 A pilot study for detecting somatic mutations at the HLA-A locus in lymphocytes**

This research protocol was terminated 31 December 1997, but the following oral presentations made during this fiscal year were based on those study findings.

RP 11-89 Oral Presentations

❖ Kusunoki Y, Honma M, Hayashi T, Kyoizumi S. Radiation-induced *in vivo* generation of mutant cells lacking MHC class I alleles and their suppression by NK cells. *The 58th Annual Meeting of the Japanese Cancer Association, 29 September–1 October 1999, Hiroshima, Japan*

❖ Kusunoki Y, Kyoizumi S, Honma M, Hayashi T, Seyama T. NK-mediated elimination of mutant lymphocytes that have lost expression of MHC class I molecules. *The 29th Annual Meeting of the Japanese Society for Immunology, 1–3 December 1999, Kyoto, Japan*

RP 7-89 (See also 1-93) Screening for stem cell mutation in lymphoid lineage among atomic-bomb survivors and its characterization

Kyoizumi S (R), Kusunoki Y (R), Hayashi T (R), Kodama Y (G), Kodama K

The purpose of this study is to identify individuals in whom mutations have occurred in hematopoietic stem cells due to atomic-bomb radiation and elucidate the *in vivo* kinetics of the mutant stem cells by estimating frequencies of their progeny in different cell lineages. Two survivors have so far been identified as such individuals. In one case (1.99 Gy), mutants bearing the same

alteration (HPRT) in both T and B cells at a high frequency (10^{-4} – 10^{-3}) had a unique TCR pattern or Ig gene rearrangement. In the other case (1.95 Gy), the same chromosome aberration was observed at 10% of *in vitro* colonies from peripheral CD34 cells as well as T- and B-cell colonies. This is the first evidence for a chromosome aberration occurring in a multipotent hematopoietic stem cell of an A-bomb survivor. In addition, several survivors have so far been found to have clonal T-cell populations that resulted from massive expansion of a single peripheral T cell. Although it is unclear whether such clonal expansion is a reflection of the normal course of immunological memory or was caused by abnormal cell proliferation possibly leading to malignant transformation, it is an excellent tool for investigating the mechanisms of human lymphopoiesis and carcinogenesis. We will continue our attempt to identify additional persons showing mutations or chromosome aberrations in stem cells and to accumulate information on the kinetics of stem cells participating in hematopoiesis and lymphopoiesis in humans. Leukemia studies in A-bomb survivors indicate a possibility that excess cases of acute myelocytic leukemia and myelodysplastic syndrome can be observed even at present. By retrospective analysis of pre-existing clonal expansion in such cases, we will seek a possible mechanism for radiation-induced leukemogenesis in humans. For this purpose, availability of cryopreserved blood samples before onset of such diseases should be estimated by comparing frozen lymphocyte data with the leukemia registry data base. Based on this estimation, we will prepare a new RP investigating the significance of clonal expansion of stem cells for radiation-induced leukemogenesis in humans.

RP 7-89 Publication

♦ Iwamoto KS, Mizuno T, Seyama T, Kyoizumi S. Mutant p53: Epigenetic mutator of the T-cell receptor via induction of methylation. *Molecular Carcinogenesis* 1999 (June); 25(2):113–21. (RERF Report 6-98)

RPs 7-89 and 3-87 Publication

♦ Kyoizumi S, Kusunoki Y. Study of somatic cell mutations in A-bomb survivors. FY-1999 Welfare Science Research Subsidy Report of Welfare Science Special Research Projects. Reassessment of A-bomb Radiation Dosimetry System and Study of Health Effects. Hiroshima: Study Team of the Reassessment of A-bomb Radiation Dosimetry System and Health Effects; 2000 (March 31), pp 108–20. (Japanese)

RP 7-87 (Addendum to RP 3-86, terminated 1 January 1993) X ray radiosensitivity of lymphocytes *in vitro* from A-bomb survivors. Part 3: Transformation of B cells by Epstein-Barr virus and their cryopreservation

Kyoizumi S (R), Hirai Y (R), Kusunoki Y (R)

For this study, it was initially proposed to cryopreserve EBV-transformed B-cell lines from high-dose and control survivors for future cell biology studies, such as those dealing with radiosensitivity. However, the usefulness of these B-cell lines in many other fields, in-

cluding studies on immune functions and genetic background in disease development, has now become apparent. From 1987, cell lines from 807 Hiroshima Adult Health Study (AHS) participants have been cryopreserved for future studies. As recommended by the peer review panel, we have accelerated EBV transformation of lymphocytes from AHS participants starting from June 1998. The AHS subjects for this study are the high-dose (1 Gy or more) and control (less than 0.005 Gy) groups and total about 3,500 in Hiroshima and Nagasaki. About 400 Hiroshima samples have already been immortalized. About 500 samples that overlap with the F₁ Study have already been immortalized and stored in the Department of Genetics. Consequently, about 2,600 samples will be newly transformed in the Department of Radiobiology. We transformed lymphocytes with EBV from about 500 Hiroshima AHS subjects in 1999. The total number of subjects whose lymphocytes were successfully immortalized is about 700 (June 1998–December 1999). We will continue immortalization of lymphocytes from AHS participants.

RP 3-87 (See also RP 1-93 and related publications above) Cellular immune function and its relationship to *in vitro* T-lymphocyte radiosensitivity and MN blood group locus mutation frequency in A-bomb survivors: Precursor frequency analysis of mitogen- and antigen-responsive blood lymphocytes

Kusunoki Y (R), Kyoizumi S (R), Hayashi T (R)

Measurements for all subjects have been completed. This study has clearly demonstrated that atomic-bomb radiation decreased CD4 T-cell fraction as well as the frequency of T cells capable of producing IL-2 and, in contrast, increased the B-cell fraction. These changes are evident even more than 50 years after the bombings. These results raise the possibility of a radiation-induced shift of T-cell function to Th2-type responses. During the course of this study, we found mature T cells with rare phenotypes, such as CD4⁺8⁺ αβ T and CD3⁺4⁺ T cells. We also found that the frequency of CD4⁺8⁺ αβ T cells is increased in atomic-bomb survivors and that these populations are frequently clonal. CD3⁺4⁺ T cells were found to be mutant T cells lacking T-cell-receptor α or β chains (TCR mutants). Extensive studies have been conducted on radiation-induced *in vivo* and *in vitro* TCR mutations, and they have demonstrated that the TCR mutation assay using flow cytometry is a sensitive indicator of recent radiation exposure. The TCR mutation assay has already been applied to a group of individuals in the Chelyabinsk contaminated area, and a significant increase of TCR Mf with estimated cumulative exposure dose was found. Further, it has been revealed that expression of mutant p53 suppresses transcription of TCR β gene not through induction of gene mutation but through methylation of TCR β promoter region.

Following requests from the Ministry of Health and Welfare and Ibaraki Prefecture, we analyzed lymphocyte subsets in the peripheral blood of 195 residents who were near JCO Company (Tokai-mura, Ibaraki) at the time of the nuclear accident (September 30, 1999). Although the

precise radiation doses of these people have not yet been made available and the validity of the our lymphocyte subset data is untested, our experience with this project suggests that we have the capability to analyze at least 100 blood samples per day in the unfortunate event that a similar accident happens again.

Measurements of TCR mutations and various immunological parameters will be conducted on persons exposed to radiation (and possibly also other mutagens) as and when requests are received from outside agencies/investigators.

RP 3-87 Publication

See RPs 1-93 and 3-87, and RPs 7-89 and 3-87.

RP 3-87 Oral Presentation

❖ Kusunoki Y. Roles of T cell subsets in bone marrow transplantation—Rejection prevention, GVHD, and immune reconstitution. *The 22nd Annual Meeting of Japanese Society of Hematopoietic Cell Transplantation, 16–17 December 1999, Hiroshima, Japan*

Research Protocols 2-00, 1-00, 2-99, 1-95, 5-93, 9-92, 5-92, 3-91, 3-90, 3-89, 2-89, 1-89, 11-86, 5-86, 4-86, 6-85, 4-85, 1-83*

Special Clinical Studies

RP 2-00 Studies on microbial infection and cell-mediated immunity in the Adult Health Study population

Hakoda M (CH), Kusunoki Y (R), Yamada M (CH), Kasagi F (S), Hayashi T (R), Shimizu M, Kodama K, Kyoizumi S (R), Katayama H (IT), MacPhee DG (R), Fujiwara S (CH), Suzuki G (CH), Akahoshi M (CN)

It has been demonstrated that the mortality from and incidence of atherosclerotic diseases, such as ischemic heart disease and cerebrovascular diseases, are increased among atomic-bomb survivors with radiation dose. However, biological mechanisms relating radiation exposure to atherosclerotic diseases among atomic-bomb survivors remain unclear. Recently, it has been suggested that inflammatory process may play important roles in the initiation and progression of atherosclerosis, with microbial infection regarded as a plausible trigger. A number of reports investigating the relationship between infection with *Chlamydia pneumoniae*, *Helicobacter pylori*, or cytomegalovirus and atherosclerotic diseases have been published. Of note is that cell-mediated immunity, important for antimicrobial defense, has been reported as impaired in atomic-bomb survivors. Accordingly, it seems important to analyze the inter-relationships among radiation dose, microbial infection, and cell-mediated immunity among the survivors to explain mechanism for development of atherosclerotic diseases in the survivors. To evaluate the infection with *Chlamydia pneumoniae*, *Helicobacter pylori*, and cytomegalovirus, specific antibodies to these pathogens will be measured in the sera of AHS participants in this study. Cell-mediated immunity will be evaluated on several subsets of T-cells, especially on T-helper subsets. This study has been initiated in Hiroshima in March 2000 and will be initiated in Nagasaki in April 2000.

RP 1-00 Molecular mechanisms of radiation-induced hyperparathyroidism

Fujiwara S (CH), Arnold A, Mallya S, Ezaki H

Primary hyperparathyroidism (HPT) is a common endocrine disorder and most often is due to a solitary adenoma in one of the parathyroid glands. Irradiation of the head and neck is an established risk factor for the development of primary HPT. This Research Protocol will apply to future all cases of hyperparathyroidism detected in the AHS cohort that require surgical removal of the parathyroids. The studies proposed here will analyze radiation-induced human parathyroid tumors for chromosomal alterations using molecular genetic and cytogenetic approaches in a way that is intimately complemented by and intertwined with Dr. Arnold's ongoing murine studies. Thus, our studies are designed to localize and/or identify novel tumor suppressor genes/ oncogenes that play a role in radiation-induced human parathyroid neoplasia.

RP 2-99 Thyroid diseases in Hiroshima and Nagasaki atomic bomb survivors

Tominaga T (CN), Akahoshi M (CN), Soda M (EN), Neriishi K (CH), Fujiwara S (CH), Yamada M (CH), Ezaki H, Kodama K, Nakashima E (S), Shibata Y, Okubo M, Ashizawa K, Sera N, Yokoyama N, Eguchi K

The effect of atomic bomb radiation on thyroid diseases will be analyzed in approximately 5,489 Adult Health Study (AHS) participants in Hiroshima and Nagasaki to elucidate thyroid disease incidence. All subjects will undergo the thyroid gland palpation, function testing, autoantibodies testing, and ultrasound examination. The previous thyroid study conducted in Nagasaki from 1984 to 1987 demonstrated increased thyroid tumor prevalence and a radiation-dose-response relationship in autoimmune hypothyroidism among atomic-bomb survivors. This study will assess whether there is a closer relationship between these diseases and radiation dose after more than ten years. This is the first thyroid disease prevalence study of the Hiroshima AHS since 1971. Previously detected solitary thyroid nodules will be investigated by precise nodule-volume measurement. This study will be continued till the end of 2004.

RPs 2-99 and 1-83 Publication

◆ Akahoshi M. Study of the effects of A-bomb radiation exposure on thyroid diseases. FY-1999 Welfare Science Research Subsidy Report of Welfare Science Special Research Projects. Reassessment of A-bomb Radiation Dosimetry System and Study of Health Effects. Hiroshima: Study Team of the Reassessment of A-bomb Radiation Dosimetry System and Health Effects; 2000 (March 31), pp 57–62. (Japanese)

RP 1-95 Effects of menopause on risk factors for ischemic heart disease—A longitudinal study of the Nagasaki Adult Health Study sample

Akahoshi M (CN), Soda M (EN), Tominaga T (CN), Rose TP, Nakashima E (S), Saimei M, Seto S, Yano K

It is well known that serum cholesterol increases after menopause due to a decrease in estrogen. A longitudinal study has disclosed that serum cholesterol begins to increase approximately three years prior to menopause. However, there has been no study to follow up serum cholesterol and estrogen for a long period of time. To clarify the relation between the two with the lapse of time, measurements of estrogen as well as serum cholesterol, Apo AI, Apo B, and Lp(a) are conducted every six months. At present, follow-up study is being conducted on 35 subjects whose menopause has not been confirmed.

RP 5-93 Longitudinal study of hormone indicators of menopause in premenopausal atomic-bomb survivors

Yamada M (CH), Cologne JB (S), Soda M (EN), Sasaki H, Akahoshi M (CN), Kodama K, Mabuchi K (EH)

This protocol was developed to measure biochemical indicators to estimate the incidence of early menopause in premenopausal AHS participants in Hiroshima and Nagasaki. Occurrence of menopause is monitored with

two perimenopausal hormones, follicular stimulating hormone (FSH) and estradiol (E2), at six-month intervals. Two hundred and eleven women were enrolled in this study in early 1994. Information on menstrual cycle and changes in menopausal symptoms has been documented. The follow-up examination of participants whose E2 levels have not decreased will be continued. A quality control study was undertaken of 20 women to evaluate the sources of variability in hormone assays.

RP 9-92 Study of liver diseases in the Adult Health Study sample—Relationship between radiation dose and infection by B and C hepatitis virus

Fujiwara S (CH), Cologne JB (S), Kodama K, Akahoshi M (CN), Mabuchi K (EH), Kusumi S, Yoshizawa H

The most recent incidence study of noncancer diseases in the AHS has demonstrated a significant dose-response relationship in the incidence of chronic hepatitis and cirrhosis. To elucidate whether infection with hepatitis C (HCV) or B (HBV) viruses contribute to an increased incidence of chronic liver diseases with radiation dose, HCV, HBs antigen and antibody, and HBe antigen were measured among all AHS participants in Hiroshima and Nagasaki. The statistical analysis has almost been completed. Paper on HCV prevalence is in press for the Radiation Research.

RP 9-92 Manuscript in Press

✎ Fujiwara S, Kusumi S, Cologne JB, Akahoshi M, Kodama K, Yoshizawa H. Prevalence of anti-hepatitis C virus antibody and chronic liver disease among atomic bomb survivors. Radiation Research.

RP 5-92 Study on senile dementia among the Adult Health Study subjects

Yamada M (CH), Kodama K, Mimori Y, Sasaki H, Akahoshi M (CN), Nakamura S, Nagataki S (D), Kasagi F (S), Shibata Y, White LR, Shimizu Y (EH), Ohara JL, Schull WJ

The objective of the senile dementia study is to determine if there is an association between exposure to ionizing radiation and subsequent impairment of cognitive function and the occurrence of senile dementia. It will also provide cross-cultural comparisons of the prevalence of senile dementia since the same neuropsychological test batteries and diagnosis criteria are used in ongoing cohort studies in Honolulu, Hawaii and Seattle, Washington.

RP 5-92 Publications

◆ Mimori Y, Ikeda J, Nakamura S, Yamada M, Sasaki H. Prevalence of dementia and its subtypes in the Japanese and Japanese American population: Comparison between Hiroshima, Honolulu and Seattle. Ronen-ki Chiho (Journal of Senile Dementia) 1999 (April); 13(2):173–9. (Japanese)

◆ Yamada M, Mimori Y, Sasaki H, Ikeda J, Nakamura S, Kodama K. Cognitive dysfunction among the elderly evaluated by the cognitive abilities screening instrument (CASI). Nippon Ronen Igakkai Zasshi (Japanese Journal of Geriatrics) 2000 (January); 37(1):56–62. (Japanese)

RP 3-91 (See also RP 3-89) A comparative study of vertebral fracture prevalence among Japanese, Japanese-Americans in Hawaii, and Caucasians in Minnesota

Fujiwara S (CH), Ross PD, Melton III LJ, Huang C, Davis JW, Epstein RS, Wasnich RD, Kodama K

The objective of the osteoporosis study is to determine if previous exposure to radiation influences the occurrence of aging-related disorders. Osteoporosis is a common consequence of aging, and bone loss is influenced by menopause and parathyroid hormone levels, which are radiation-related. Bone mineral density is being measured with dual X-ray absorptiometry among AHS participants. Measurements of an individual's bone mass and its temporal changes provide the relation between radiation and aging.

RP 3-91 Publication

◆ Fujiwara S, Huang C, Ross PD, Yamada M, Kodama K, Davis JW, Wasnich RD. Differences in health characteristics between native Japanese and Japanese-Americans. *Journal of Cross-Cultural Gerontology* 1999 (September); 14(3):273–87. (RERF Report 23-94) (J)

RPs 3-91 and 3-89 Publications

- ◆ Fujiwara S. An evaluation of the factors which influence osteoporosis. Life style. *Horumon to Rinsho (Clinical Endocrinology)* 2000 (February); 48(Special issue):98–102. (Japanese)
- ◆ Fujiwara S. Current status of fracture due to osteoporosis in Japan. *Nihon Konenki Igakkai Zasshi (Journal of Japan Menopause Society)* 1999 (April); 7(1):91–6. (Japanese)
- ◆ Fujiwara S. Epidemiology of osteoporosis. *Sanka to Fujinka (Obstetrics and Gynecology)* 1999 (December); 66(12):1728–34. (Japanese)
- ◆ Fujiwara S. Estimated number of patients with osteoporosis. *Clinical Calcium* 1999 (September); 9(9):1162–5. (Japanese)
- ◆ Fujiwara S. Guideline of therapy for osteoporosis—Prevention for osteoporosis. *Shindan to Chiryo (Diagnosis and Treatment)* 1999 (June 1); 87(6):979–83. (Japanese)
- ◆ Fujiwara S. Osteoporosis. The points of medical interview, considering risk factors. *Current Therapy* 2000 (February); 18(2):217–21. (Japanese)
- ◆ Fujiwara S. Risk factors for osteoporosis. *The Bone* 2000 (February); 14(1):47–51. (Japanese)
- ◆ Fujiwara S. The relationship between secular trends in the incidence of vertebral fractures and changes in Japanese life style. *Seikei Saigai Geka (Orthopaedic Surgery and Traumatology)* 1999; 42(10):1007–13. (Japanese)
- ◆ Fujiwara S. The ways of medical treatments for asymptomatic osteoporosis. *Medical Practice* 2000 (March); 17(3):411–4. (Japanese)
- ◆ Nakamura T, Fujiwara S. Vertebral and hip fractures in Japan. *Bulletin of the World Health Organization* 1999; 77(5):430–1.

RPs 3-91 and 3-89 Manuscript in Press

※ Fujiwara S. Epidemiology of osteoporosis. *Kotsu Kansetsu Jintai (Journal of Musculoskeletal System)*.

RPs 3-91 and 3-89 Oral Presentations

- ❖ Fujiwara S. Osteoporosis and Fractures—An approach from epidemiological studies. *The 6th Meeting for Osteoporosis and Fracture, 13 November 1999, Matsumoto, Nagano, Japan*
- ❖ Fujiwara S. International comparison on osteoporosis-related fractures. *The 8th Meeting of Metabolic Bone Diseases, 11 March 2000, Tokyo, Japan*

RP 3-90 The association of serum cholesterol with noncardiovascular mortality and morbidity in the Adult Health Study population

Yamada M (CH), Kasagi F (S), Kodama K, Fujiwara S (CH), Shimizu M, Soda M (EN), Sasaki H

Earlier analysis showed that the serum cholesterol level in exposed people was significantly elevated compared to that in unexposed people. Since January 1997, analyses for estimating whether radiation affects levels of total cholesterol have been conducted by Dr. Wong *et al.* (See below.) The major objectives of this study are to assess the association of serum cholesterol with subsequent mortality and morbidity and evaluate the effects of ionizing radiation on such an association.

RP 3-90 Publication

◆ Wong FL, Yamada M, Sasaki H, Kodama K, Hosoda Y. Effects of radiation on the longitudinal trends of total serum cholesterol levels in the atomic bomb survivors. *Radiation Research* 1999 (June); 151(6):736–46. (RERF Report 17-97)

RP3-89 (See description under RP 3-91) Osteoporosis in Hiroshima atomic-bomb survivors

Fujiwara S (CH), Kodama K, Fukunaga M, Orimo H

RP 3-89 Publication

See RPs 3-91 and 3-89.

RP 3-89 Manuscript in Press

See RPs 3-91 and 3-89.

RP 3-89 Oral Presentations

- ❖ Fujiwara S, Kodama K, Nagataki S. Checkup for osteoporosis in a cohort study population and its effects. *The 25th General Assembly of the Japanese Association of Medical Sciences, 2–4 April 1999, Tokyo, Japan*
 - ❖ Fujiwara S, Naito K, Masunari N, Kasagi F, Kodama K, Nagataki S, Fukunaga M, Nakamura T. Bone mineral density of the lumbar/femur neck, and spinal fracture risk. *The 17th General Meeting of Japanese Society for Bone and Mineral Research, 29–31 July 1999, Osaka, Japan*
 - ❖ Fujiwara S, Kasagi F, Masunari N, Morihara Y. The quality of life for the elderly and for osteoporosis patients. *The 1st Annual Meeting of Japan Osteoporosis Society, 27–30 October 1999, Kurashiki, Okayama, Japan*
 - ❖ Fujiwara S, Masunari N, Kasagi F, Naito K, Kodama K. Prediction of spinal fracture by bone mineral density. *The 10th General Meeting of Japan Epidemiological Association, 27–28 January 2000, Yonago, Tottori, Japan*
- See RPs 3-91 and 3-89.

RP 2-89 (Addendum to, See also RP 11-86) Hypercalcemia in atomic-bomb survivors, Hiroshima and Nagasaki

Fujiwara S (CH), Nakashima E (S), Ezaki H, Kodama K, Akahoshi M (CN), Shiraki M

A radiation-related increase in occurrence of hyperparathyroidism is one of the most recent findings in a prevalence study. Continuation of this study should provide not only incidence data for hyperparathyroidism but also a clue to the cause of slightly elevated levels of serum calcium, parathyroid hormone, and calcitonin among those exposed to higher doses. In addition, a molecular biological study of parathyroid adenoma to elucidate pathogenic mechanisms has been initiated in cooperation with the Department of Radiobiology (See also RP 1-00).

RP 1-89 Prevalence of radiation-related skin lesions in the Adult Health Study population, Hiroshima and Nagasaki

Yamada M (CH), Yamamoto S, Soda M (EN), Kodama K

Studies of skin cancer among persons exposed to radiation due to occupational or medical therapeutic exposures showed that skin was vulnerable to radiation carcinogenesis. In this study, dermatological examinations are carried out during the biennial AHS health examinations to detect not only skin cancer but precancerous lesions, such as senile keratosis. Information concerning ultraviolet radiation, burns, and trauma scars will be taken into consideration.

RP 11-86 (See description above under RP 2-89) Prevalence of hyperparathyroidism in atomic-bomb survivors during AHS cycle 15 in Hiroshima and Nagasaki

Fujiwara S (CH), Nakashima E (S), Ezaki H, Akahoshi M (CN), Kodama K

RP 5-86 (Addendum to RP 8-83) Dietary habit survey using a simple and computerized diet survey system

Yamada M (CH), Hayabuchi H, Kodama K, Sasaki H, Fujiwara S (CH)

Diet is considered a confounding factor in studies of radiation effects in atomic-bomb survivors. In the past, old-fashioned dietary habit surveys, including a 24-hour recall survey, have been conducted. Recently, a computerized diet survey system has become available that offers simple and accurate methods to assess values for analysis of risk factors on the prevalence or incidence of certain diseases in A-bomb survivors.

RP 4-86 Evaluation of index of physiological measurements as a predictor of mortality or morbidity associated with aging

Fujita S (S), Sasaki H, Kasagi F (S), Kodama K, Yamada M (CH)

This study is intended to determine whether the physiological measurement indices made on the Adult Health Study (AHS) population between 1970 and 1972 are reliable predictors of normal or radiation-induced ac-

celerated aging as manifested by morbidity and mortality findings in the exposed and control persons in the AHS. A report on the relationship between estimated physiological age in 1970–72 and mortality over the next 25 years is undergoing internal review. Upon completion of this paper, this RP will be terminated.

RP 6-85 (Addendum to RP 9-79) Study of M-proteinemia in the Adult Health Study sample

Neriishi K (CH), Yoshimoto Y, Carter RL, Kawamura S, Iwato K, Kawano M, Fujimura K, Kuramoto A

Uncertainties exist regarding the apparent dose-related increase of multiple myeloma. Clinical studies to detect a precursor state of multiple myeloma by protein electrophoresis have been employed in the AHS biennial examinations since 1985. A previous study suggested a marginal increase in the prevalence of benign monoclonal gammopathy in exposed persons. A longitudinal study in 1985–1995 revealed an increased incidence in exposed persons but only among those less than 80 years old at the time of examination. The incidence study is continuing for aging subjects at high risk for monoclonal gammopathy.

RP 6-85 Publication

◆ Neriishi K, Ezaki H, Arihiro K, Okamoto H. Thyroid lymphoma of mucosa-associated lymphoid tissue with monoclonal gammopathy occurring in an atomic bomb survivor: Report of a case. *Surgery Today* 2000 (January 25); 30(2):202–6. (RERF Report 8-96)

RP 4-85 (Addendum to Research Plan TR 12-71) Incidence and risk factors of coronary heart disease (CHD) in Japanese men living in Japan and Hawaii, 1966–78

Yamada M (CH), Kodama K, Shimizu Y (EH), Kasagi F (S), Sasaki H, Shimizu M, Fujiwara S (CH), Curb JD, Rodriguez B, Yano K

The two major objectives of this study are to examine the association between radiation exposure and cardiovascular diseases (CVD) in the Adult Health Study (AHS) cohort and to analyze the morbidity, mortality, and risk factors for CVD in the NI-HON-SAN (Nihon-Honolulu-San Francisco) cohort of the AHS and compare findings with those of the cohort of the Honolulu Heart Program in Hawaii.

The epidemiologic methodology developed by this project has been effective in indicating a weak, but very consistent association between radiation dose and various endpoints of atherosclerosis, including myocardial infarction, thromboembolic stroke, calcification of the aortic arch, retinal arteriosclerosis, isolated systolic hypertension, and abnormal pulse wave velocity.

A study on the ankle-arm blood pressure ratio is currently under way in Hiroshima, and a new study on infection of *Chlamydia pneumoniae*, *Helicobacter pylori*, and cytomegalovirus as a confounder of radiation effects on CVD has been initiated.

RP 4-85 Publication

◆ Yano K, Kodama K, Shimizu Y, Chyou P, Sharp DS,

Tracy RP, Rodriguez BL, Curb JD, Kusumi S. Plasma fibrinogen and its correlates in elderly Japanese men living in Japan and Hawaii. *Journal of Clinical Epidemiology* 1999 (December); 52(12):1201-6. (RERF Report 7-97)

***RP 1-83 Thyroid diseases in atomic bomb survivors in Nagasaki**

This research protocol was terminated 16 January 1990, but the results based on that research were published during this fiscal year. See RP 2-99.

Research Protocol 5-89

Histopathology—Platform Protocol

RP 5-89 (formerly RP 3-75) Pathology studies in Hiroshima and Nagasaki. Revised research plan
Tokuoka S (EH), Tokunaga M, Mabuchi K (EH)

The pathology program started at the inception of ABCC has undergone several major revisions through the years. At the beginning, it consisted almost entirely of an autopsy program in the cities of Hiroshima and Nagasaki with emphasis on the procurement of "exposed" individuals. In 1961, the pathology population was defined as a subset of the Life Span Study (LSS) sample to include adequate controls. An active and aggressive autopsy procurement effort was introduced, resulting in increased autopsy rates. Autopsy rates peaked between 40 to 45% in the early 1960s but subsequently declined. In 1979, active autopsy solicitation was terminated in favor of the completely voluntary cooperation of local physicians. In 1987, the program was redesigned to place major emphasis on pathoepidemiological follow-up studies of atomic-bomb survivors in the search for specific histologic, cytologic, or other tissue changes directly or indirectly attributable to irradiation. The present RP reflects the latest change. Under the newly developed "Guidelines for the conduct of site-specific cancer incidence studies among atomic-bomb survivors, Hiroshima and Nagasaki" (RP 9-88; See Special Cancer Studies), a number of site-specific studies have been initiated and are in progress. The autopsy program at RERF was terminated in 1988. However, through the ABCC-RERF pathology program, a large number of LSS autopsy (about 7,500 cases) and surgical tissue samples (about 13,000 cases) have been collected over the years. These archived tissues have been found to be useful for molecular studies. However, for recently diagnosed cases, we must seek tissue samples from outside hospitals. Tissues used for a series of site-specific studies and molecular studies at RERF are obtained under an agreement signed for the pathology program. For future research in this field, it is essential that we establish a mechanism to identify and secure important tissue samples, especially located outside RERF. Detailed plans of each site-specific and molecular study under way are described under specific research protocols.

Research Protocols 2-94, 7-93, 3-93, 7-92, 18-81 Cell Biology Studies

RP 2-94 (See also RPs 5-90 and 2-92, Special Cancer Studies) Molecular analysis of hepatocellular carcinoma among atomic-bomb survivors

Work was finished on this research protocol in 1999 and following paper was published.

RP 2-94 Publication

♦ Iwamoto KS, Fujii S, Kurata A, Suzuki M, Hayashi T, Ohtsuki Y, Okada Y, Narita M, Takahashi M, Hosobe S, Doishita K, Manabe T, Hata S, Murakami I, Hata S, Itoyama S, Akatsuka S, Ohara N, Iwasaki K, Akabane H, Fujihara M, Seyama T, Mori T. p53 mutations in tumor and non-tumor tissues of Thorotrast recipients: A model for cellular selection during radiation carcinogenesis in the liver. *Carcinogenesis* 1999 (July); 20(7): 1283-91. (RERF Report 10-98)

RP 7-93 Molecular analysis of thyroid cancers among atomic-bomb survivors

Hamatani K (R), Mizuno T (R), Kyoizumi S (R), Shimizu Y (EH), Tokuoka S (EH), Mabuchi K (EH), MacPhee DG (R)

We investigated whether a specific type of RET/PTC rearrangement was induced by X-rays *in vivo* and *in vitro*. In human normal thyroid tissues transplanted into and maintained in scid mice, the RET/PTC1 rearrangement was predominantly detected throughout the observation period (up to 60 days) after an X-ray exposure of 50 Gy. On the other hand, RET/PTC3 was detected only in the samples taken 7 days after X-irradiation, and no transcript of RET/PTC2 was detected in any sample. These results are supported by the results of an *in vitro* study. The RET/PTC1 rearrangement was preferentially induced in four cell lines in a dose-dependent manner by X-rays over a relatively high dose range (10, 50 and 100 Gy). On the other hand, RET/PTC3 was induced at a much lower frequency, and no induction of RET/PTC2 was observed. These results suggest that the induction of the RET/PTC1 rearrangement may play an important role in the early stages of acute X-ray induced thyroid carcinogenesis. Interestingly, recent observations of an increase in the frequency of RET/PTC1 in post-Chernobyl childhood papillary thyroid carcinomas can be contrasted with previous claims that RET/PTC3 rearrangements are much more common in these Chernobyl-associated cases than are either RET/PTC1 or RET/PTC2. It could be that the high initial prevalence of RET/PTC3 reflects the fact that radiation-associated papillary thyroid carcinomas with a relatively short latency were being studied in these early post-Chernobyl cases, whereas the RET/PTC1 rearrangement may be more common among papillary thyroid carcinomas of a somewhat longer latency. If it turns out that the particular type of RET/PTC rearrangement that occurs is a function of the time between radiation exposure and the development of a tumor, we might expect to find that a high proportion of the papillary thyroid carcinomas occurring among high exposure group A-bomb survivors will prove to be of the RET/PTC1 type. We have

therefore analyzed thyroid micro-carcinomas (tumors with a diameter of 10 mm or less) as well as papillary carcinomas. The activated *RET* oncogene was detected in 3 of 6 micro-carcinomas from A-bomb survivors with 0.25 Gy or more and 2 of 7 control cases. Two papillary carcinomas from those exposed to 0.25 Gy or more were positive for RET rearrangements and one of 3 controls was positive. We were able to show that we could recover RNA that was suitable for characterizing the RET rearrangements in 75% of a set of formalin-fixed, paraffin-embedded micro-carcinomas whose sizes ranged from 2 to 9mm in diameter. Successful extraction of RNA from archival thyroid micro-carcinomas was independent of tissue size. After collecting larger numbers of thyroid cancer samples from among the A-bomb survivors, we will use the techniques we have developed to conduct a much larger study. We also plan to carry out a comprehensive molecular analysis of human thyroid cancer tissues in which cells that are found to contain X-ray induced *RET* oncogene rearrangements will be studied with a view to determining whether or not any other genes appear to be involved in the development of radiation-induced thyroid tumors.

RP 7-93 Publication

♦ Mizuno T, Iwamoto KS, Kyoizumi S, Nagamura H, Shinohara T, Koyama K, Seyama T, Hamatani K. Preferential induction of *RET/PTC1* rearrangement by X-ray irradiation. *Oncogene* 2000 (January); 19(3):438-43. (RERF Report 17-99)

RP 7-93 Oral Presentations

❖ Hamatani K, Mizuno T, Ishikawa N, Ito K, Ito K, Nagataki S. Genetic analysis of thyroid papillary cancers by subtraction method based on polymerase chain reaction (PCR). *The 42nd Annual Meeting of the Japan Thyroid Association, 16-18 November 1999, Nagoya, Japan*

❖ Mizuno T, Asakawa J, Kodaira M, Hirai Y, Ishikawa N, Ito K, Ito K, Nagataki S. Analysis of genes abnormally expressed in human papillary thyroid carcinomas by two-dimensional differential display. *The 42nd Annual Meeting of the Japan Thyroid Association, 16-18 November 1999, Nagoya, Japan*

RP 3-93 Molecular analysis of skin cancers in atomic-bomb survivors

Mizuno T (R), Iwamoto KS (R), Nakashima E (S), Shimizu Y (EH), Tokunaga M, Kishikawa M, Tokuoka S (EH), Mabuchi K (EH)

The purpose of this study is to investigate the roles of the *ras* oncogenes and *p53* tumor suppressor gene in skin cancer in atomic-bomb survivors. In reports regarding solid tumor incidence in A-bomb survivors, an elevated risk of nonmelanoma skin cancer, especially basal cell carcinoma (BCC), has been noted among the survivors. It is also well known that skin cancers generally arise in areas of the body exposed to sunlight. In the case of skin tumors caused by atomic-bomb radiation, all areas of skin should have had an equal chance of being targets for molecular lesions of ionizing radiation. Our general ob-

jectives are to identify the mutational changes caused by A-bomb radiation and differences in the spectra of mutations induced by ionizing radiation and ultraviolet (UV) light. Regarding *p53*, we have analyzed mutations within exons 5 to 8 using polymerase chain reaction-single-strand conformation polymorphism and then direct sequencing, focusing on BCC. The frequency of *p53* gene mutations in BCC was high (about 60%) as reported, but no difference was observed between the low-dose (0–0.2 Gy) and high-dose (≥ 1 Gy) groups. However, a statistically significant difference was observed between the low-dose and high-dose groups at mutational sequence sites in BCC. Because the increased risks of BCC among survivors cannot be explained by only *p53* gene mutations, it is necessary to examine other candidate genes involved in BCC carcinogenesis.

We will expand the molecular analysis of skin cancer to analyze the patched (*PTCH*) gene, which has been identified as another candidate gene of basal cell carcinoma. We have conducted loss-of-heterozygosity (LOH) analysis of the *PTCH* gene in the same BCC samples mentioned above, and are completing the statistical assessment of these results with the Departments of Epidemiology and Statistics. We believe that these results will help elucidate the mechanisms of radiation-induced carcinogenesis.

RP 7-92 Molecular analysis of the p53 tumor suppressor gene in breast cancers of atomic-bomb survivors (with Addendum)

RP 7-92 (Addendum) Molecular analysis of Rb, PHB, and other tumor-suppressor genes in breast cancers among atomic-bomb survivors

Ban S (R), Hirai Y (R), MacPhee DG (R), Mabuchi K (EH), Suyama A (EN), Soda M (EN), Tokunaga M, Tokunaga S (EH), Cologne JB (S), Nakamura N (G), Land CE, Arihiro K, Fujii S, Inai K, Ikeda T, Kawai K, Gray J, Tucker MA, Buetow KH, Iwamoto KS (R)

Epidemiological studies have shown an increased risk of breast cancer among atomic-bomb survivors, especially among those younger than 19 at the time of the bombings. Since germline mutation of *BRCA1* and *BRCA2* genes carries a high risk for developing familial and early-onset breast cancer, there has been considerable interest in the prevalence of such mutations among atomic-bomb survivors with breast cancer, especially with early-onset breast cancer. It is widely regarded as desirable that molecular analysis of tumor cells be performed using precisely defined homogenous tumor cell populations with little or no contamination by non tumor cells. A laser capture microdissection (LCM) method has recently been introduced to reduce the possibility of normal cell contamination. We have established that DOP-PCR amplification can be used to increase the amounts of useable DNA that can be extracted from the small numbers of cells typically produced by LCM of archival tissue specimens. We are currently planning to utilize immunohistochemical staining as one of the simplest screening procedures available to identify *BRCA1*-associated cancers. Because as yet there is no immunohistochemical assay for the detection of reduced *BRCA2* expression, we

have recently established competitive RT-PCR to quantify both *BRCA1* and *BRCA2* mRNAs. Arrangements for tissue collection are still in progress. As soon as breast cancer tissue samples become available, we will initiate immunohistochemical staining to detect cancers that show reductions in *BRCA1* protein expression, as well as competitive RT-PCR studies to identify cases in which *BRCA* mRNA expression is abnormal. DNA sequencing of *BRCA1* and *BRCA2* will be conducted in all exposed, early-onset cases as well as in a large number of (selected) cases where onset is somewhat later.

RP 7-92 Publications

◆ Ban S, Hirai Y, Shinohara T, Moritaku Y, MacPhee DG. Radiation sensitivity of *BRCA1*- or *BRCA2*-defective cultured human cancer cells. Syrota A, Tanada S, eds. Proceedings of the Third Japan-France Workshop on Radiobiology, Imaging and Environmental Sciences. Chiba, Japan: National Institute of Radiological Sciences; 1999 (November), pp 18–24.

◆ Ban S, Shinohara T, Itoh M, Nakamura N. Whole genome amplification to immortalize the DNA extracted from the formalin-fixed and paraffin-embedded tissue sections. Hiroshima Igaku (Journal of the Hiroshima Medical Association) 2000 (March); 53(3):225–8. (Proceedings of the 40th Late A-bomb Effects Research Meeting, 1999). (Japanese)

RP 7-92 Oral Presentations

✧ Ban S, Shinohara T, Itoh M, Nakamura N. Whole genome amplification to immortalize the DNA extracted from the formalin-fixed and paraffin-embedded tissue sections. *The 40th Late A-bomb Effects Research Meeting, 6 June 1999, Hiroshima, Japan*

✧ Ban S, Hirai Y, Shinohara T, Yoshikawa K, Takahashi R. Radiation sensitivity of *BRCA1*- or *BRCA2*-defective cultured human cancer cells. *The 42nd Annual Meeting of the Japan Radiation Research Society, 1–3 September 1999, Hiroshima, Japan*

✧ Ban S, Hirai Y, Yoshikawa K, Takahashi R. *BRCA1* and *RAD51* expression and radiation sensitivity of cultured human breast cancer cells. *The 58th Annual Meeting of the Japanese Cancer Association, 29 September–1 October 1999, Hiroshima, Japan*

✧ Ban S, Hirai Y, Shinohara T, Moritaku Y, MacPhee DG. Radiation sensitivity of *BRCA1*- and *BRCA2*-defective cultured human cancer cells. *The 3rd Japan-France Workshop on Radiobiology, Imaging and Environmental Sciences, 10–12 November 1999, Chiba, Japan*

RP 18-81 Pathophysiology and radiation response of human thyroid cells in culture and in grafts in athymic nu/nu mice

Kyoizumi S (R), Nobuyoshi M (CH), Kusunoki Y (R), Hayashi T (R), Mizuno T (R), Hamatani Y (R)

The radiobiological study of humans has been hampered by a lack of suitable *in vivo* experimental models. To overcome this limitation, we have attempted to create models using small animals that maintain human normal tissues with their active functions. This project

originally sought to implant human thyroid tissues into athymic nude mice, but recently, severe-combined-immunodeficient (SCID) mice were found to be better recipients, i.e., the success rate of human tissue implantation is much higher in SCID than nude mice. Thus, SCID mouse-human chimeras (SCID-hu mice) can be used not only for human thyroid tissue but also various human epithelial and hematolymphoid tissues. We demonstrated the usefulness of a SCID-hu skin model for the study of radiation-induced human epilation (Kyoizumi *et al.* Radiation sensitivity of human hair follicle in SCID-hu mice. *Radiation Research* 1998; 149: 11–18), a SCID-hu cord blood model for human hematopoiesis, and a SCID-hu small intestine model for radiation-induced apoptosis *in vivo*. Furthermore, for the thyroid model, we showed radiation-induced mutagenesis in cancer-associated genes, such as the *RET* oncogene, which is believed to be specifically altered in thyroid carcinogenesis (Mizuno *et al.* Continued expression of a tissue-specific activated oncogene in the early steps of radiation-induced human thyroid carcinogenesis. *Oncogene* 1997; 15: 1455–1460). Using this model, we found that both the *RET/PTC1* (predominantly) and *RET/PTC3* rearrangements were induced by high-dose X-irradiation (see RP 7-93 Publication, Mizuno *et al.*). These approaches should help to clarify the molecular mechanisms of human radiation carcinogenesis, which have not been clear from survivor studies.

RP 18-81 Oral Presentations

❖ Kyoizumi S, Koyama K, Hayashi T, Morishita Y, Tsuyama N, Seyama T. Radiation-induced apoptosis and cell cycle changes in epithelial cells in the human small intestine. *The 42nd Annual Meeting of the Japan Radiation Research Society, 1–3 September 1999, Hiroshima, Japan*

❖ Kyoizumi S, Koyama K, Hayashi T, Morishita Y, Tsuyama N, Seyama T. Uncoupling of DNA synthesis and mitosis in human intestinal crypt stem cells following radiation exposure. *European Molecular Biological Organization Workshop: Stem Cells, Growth Factor and Cancer, 7–10 October 1999, Torino, Italy*

❖ Nobuyoshi M, Kusunoki Y, Seyama T, Kodama K, Fujiwara S, Kimura A, Kyoizumi S. Human dendritic cell precursors in NOD/SCID mice transplanted with human cord blood mononuclear cells. *The 41st Annual Meeting of American Society of Hematology, 3–7 December 1999, New Orleans, USA*

Research Protocols 1-97, 7-85, 5-85 Biochemical Genetics Study

RP 1-97 Pilot study of the genetic background of the Adult Health Study (AHS) population: Identification of markers in potential candidate genes associated with hypertension

Takahashi N (G), Murakami H, Yamada M (CH), Kasagi F (S), Kodama K

The purpose of this study is to test if there is any association between hypertension and polymorphic markers at hypertension-related genes. We examined possible relation between the seven polymorphisms detected at the 5'-flanking region of the angiotensin II type 1 (AT₁) receptor gene and hypertension. A case-control study was performed on 156 normal and 149 hypertensive individuals to find one marker showed a significantly higher frequency in hypertensive than in normotensive subjects. Further, evidence was obtained that this polymorphism showed a synergistic effect on the risk of hypertension with a polymorphism of angiotensin I converting enzyme. Frequencies for other markers on AT₁ gene were similar in both groups. A manuscript describing the results was approved by RERF, submitted to *Annals of Human Genetics*, and accepted for publication.

RP 1-97 Oral Presentations

❖ Takahashi N, Murakami H, Kasagi F, Yamada M, Kodama K, Nishishita T, Inagami T. Association of a polymorphism at 5'-region of angiotensin II type 1 receptor with hypertension. *Gordon Research Conferences, 8–13 August 1999, Oxford, UK*

❖ Takahashi N, Murakami H, Kasagi F, Yamada M, Kodama K, Nishishita T, Inagami T. Association of a polymorphism at 5'-region of angiotensin II type 1 receptor with hypertension. *The 44th Meeting of the Japan Society of Human Genetics, 17–19 November 1999, Sendai, Japan*

RP 7-85 Study to develop methods of DNA analysis for detection of mutations in children of atomic-bomb survivors

Asakawa J (G), Takahashi N (G), Kodaira M (G), Danjo I (G), Katayama H (IT), Itoh M (G), Nakamura N (G), Preston DL (S), Kuick R, Neel JV

Cell lines for 100 families, 50 from highest dose-exposed and 50 from control groups, are currently used for pilot studies to test the feasibility of various methods.

Results for repetitive sequences We examined one additional minisatellite locus, pYNH24, in this fiscal year. The results showed that the mutation frequencies were 0% for the exposed and 0.6% in the control groups. Overall, we tested 9 probes for single minisatellite loci and one probe for DNA fingerprint. The mean mutation rates of the whole data at the single loci were 1.6% (9/565) in the exposed gametes and 2.2% (36/1612) in the control, and the rates at DNA fingerprint were 1.3% (14/1080) in the exposed and 1.4% (14/1024) in the control groups. Radiation effect was not observed.

Two-dimensional DNA gel electrophoresis (2-DE method) The 2-DE method labels DNA at *NotI* restriction sites. After successive digestions of DNA by two restriction

enzymes, DNA fragments are visualized as thousands of spots in autoradiograms. Although the nature of the DNA of each spot is not known beforehand, DNA fragments can be recovered from each spot for subsequent characterization after mutation detection. The biggest advantage of the 2-DE method is that no probes are needed for mutation screening.

Results from a small-scale survey in mice indicated that the method was applicable to children of the survivors. To collect information on the frequency and nature of the germ cell mutations, the mouse experiment was expanded. Seventy-nine F_1 mice born to males exposed to 5 Gy of X rays, 237 mice born to males exposed to 3 Gy, and 190 mice in the control were analyzed. The total numbers of the spots examined were 87,589 for 5-Gy group, 238,351 for 3-Gy group, and 190,807 in the control. We found 8 mutant spots in 5-Gy and 3-Gy groups, respectively, and 7 in the control.

We have cloned and characterized the normal and/or mutated DNA fragments. Five mutation spots out of 8 in the 5-Gy group were insertions and three were deletions. One insertion contained an approximately 550-base-pair (bp) sequence of the L1 transposable element and was found in two litters (cluster mutations). Another insertion was also found as a cluster mutation in three litters and the molecular characterization is in progress. Among the three deletion mutations, one carried a large deletion whereas the remaining two had loss of short repeat sequences, one was a 3-base deletion (CTT) and the other was a 4-base deletion (CTCT) in the CTT and CT tracts, respectively.

Among the 8 mutations in 3-Gy group, one was an 8-base insertion (GA)₄ in GA tract. The remaining 7 were deletions, of which three were small deletions consisting of 3-base deletions (GAA) in GAA tract and the remaining four were large deletions. Of these large deletions, two spots were found in one animal as a result of a large deletion affecting two nearby fragments. The remaining two deletions are characterized currently.

Five mutant spots among 7 in the control group were deletions. One of these mutations had a deletion larger than 25 kb including two or more *NotI* sites as revealed by loss of two adjacent fragments, and the mutation was found in two animals of the same litter as a cluster. Therefore, one single mutational event was detected as 4 mutational spots. Another deletion mutation had (CT)₃ deletion in a CT tract. The remaining two non-deletion-type mutations were a base substitution and an insertion of C in a C_n tract.

We also examined children of the survivors (64 in the exposed and 64 in the control) by the 2-DE method and found one mutation in the control (1/28,088 spots) and no mutation in the exposed (0/29,971 spots). This mutation was most likely a deletion. A summary draft is in preparation.

DNA-chip-based comparative genomic hybridization (CGH) DNA microarray or chip technology receives keen interest for various research fields in molecular biology and genetics for understanding cellular functions and screening of genetic alterations related to human disorders. The technique has a potential to examine automatically a large number of genes (several thousands to several tens

of thousand) at a time. We are addressing one application, comparative genomic hybridization on a DNA chip (DNA-chip-based CGH), based from the reports that it can effectively detect gain or loss of one copy of a gene from diploid conditions. In 1999, we performed model experiments using chips carrying DNA of λ -phage or human X-chromosomal genes and found that the method can detect large deletions which are the predominant type of mutations induced by radiation exposure.

RP 7-85 Publications

◆ Asakawa J, Kodaira M, Nakamura N, Satoh C, Fujita M. Chimerism in humans after intragenic recombination at the haptoglobin locus during early embryogenesis. *Proceedings of the National Academy of Sciences of the United States of America* 1999 (August 31); 96(18):10314–9. (RERF Report 12-98)

◆ Kodaira M. Genetic effects of atomic-bomb radiation: Analysis of minisatellite loci detected by DNA fingerprint probes. *Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications)* 1999 (June); 34(2):205–12. (Japanese)

◆ Kodaira M, Nakamura N. Genetic effects of atomic-bomb radiation: mutations at minisatellite loci. FY-1999 Welfare Science Research Subsidy Report of Welfare Science Special Research Projects. Reassessment of A-bomb Radiation Dosimetry System and Study of Health Effects. Hiroshima: Study Team of the Reassessment of A-bomb Radiation Dosimetry System and Health Effects; 2000 (March 31), pp 131–9. (Japanese)

◆ Takahashi N. Denaturing gradient gel electrophoresis. Koike K, Sekiya T, Kondo H, eds. *Molecular Biology Protocols*, 2nd Edition. Tokyo: Nankodo; 1999 (December), pp 41–7. (Japanese)

◆ Takahashi N. Overview of DNA-chip technologies and their application for the study on the potential genetic effects of atomic bomb radiation. *Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications)* 1999 (June); 34(2):232–42. (Japanese)

◆ Takahashi N. Phosphoglucosyltransferase (PGM). *Nippon Rinsho (Japanese Journal of Clinical Medicine)* 1999 (September); 57(Suppl):753–7. (Comprehensive Manual for the Biochemical and Immunological Aspects of Clinical Pathology [2]. 5th edition) (Japanese)

RP 7-85 Oral Presentations

❖ Asakawa J. High resolution two-dimensional electrophoresis of end-labeled genomic DNA fragments. *Meeting of the International Council of Electrophoresis Societies, 1999, 25–28 May 1999, Tokyo, Japan*

❖ Asakawa J, Kodaira M, Ishikawa N, Ito K, Ito K, Nagataki S. Search of genome-wide genetic and epigenetic alterations in papillary thyroid cancer by sequential two-dimensional DNA gel analysis. *The 26th Annual Meeting of the European Thyroid Association, 28 August–1 September 1999, Milan, Italy*

❖ Kodaira M, Satoh C, Shimoichi Y, Nakamoto Y, Imanaka M. Genetic effects of A-bomb radiation: Reanalysis of minisatellites by DNA fingerprints. *The 42nd Annual Meeting of the Japan Radiation Research Society, 1–3 September 1999, Hiroshima, Japan*

❖ Asakawa J, Kodaira M, Ishikawa N, Ito K, Ito K, Nagataki S. Rapid and accurate detection of tissue specific gene expression in human papillary thyroid carcinomas by two-dimensional differential display. *The 72nd Annual Meeting of the American Thyroid Association, 29 September–3 October 1999, Palm Beach, USA*

❖ Kodaira M, Asakawa J, Ishikawa N, Ito K, Ito K, Nagataki S. Analysis of tissue specific gene expression in human papillary thyroid carcinomas by two-dimensional differential display. *The 42nd Annual Meeting of the Japan Thyroid Association, 16–18 November 1999, Nagoya, Japan*

❖ Asakawa J, Kodaira M, Ishikawa N, Ito K, Ito K, Nagataki S. Analysis of gene expression in thyroid carcinomas by two-dimensional differential display. *The 50th Annual Meeting of the Japanese Electrophoresis Society, Satellite Symposium, 17 November 1999, Ube, Yamaguchi, Japan*

❖ Asakawa J. Search of alterations in proteins and genomic DNAs by using two-dimensional electrophoresis. *The 50th Annual Meeting of the Japanese Electrophoresis Society, 18–19 November 1999, Ube, Yamaguchi, Japan*

❖ Asakawa J, Kodaira M, Katayama H, Funamoto S, Tomita S, Ito M, Preston DL, Nakamura N. Spontaneous and X-ray induced germ cell mutations in mice detected by computer assisted two-dimensional DNA gel analysis. *The 50th Annual Meeting of the Japanese Electrophoresis Society, 18–19 November 1999, Ube, Yamaguchi, Japan*

❖ Takahashi N, Tsuyama N, Sasaki K, Kyoizumi S, Ichihara T. Application of DNA microarray system to comparative genomic hybridization. *The 22nd Annual Meeting of the Molecular Biology Society of Japan, 7–10 December 1999, Fukuoka, Japan*

RP 7-85 and RP 8-93 Oral Presentation

❖ Nakamura N. Genetic effects of atomic-bomb radiation: Past, present, and future. *The 40th Late A-bomb Effects Research Meeting, 6 June 1999, Hiroshima, Japan*

RP 5-85 Culture of permanent lymphocyte cell lines as sources of biological samples for investigation of genetic effects of radiation on children of atomic-bomb survivors

Takahashi N (G), Murakami H, Fujiwara S (CH), Akahoshi M (CN), Nakamura N (G)

B-cell lines have been established from 964 families, including 1,399 children. The breakdown of cell lines in relation to gonadal dose of the exposed parents is: 144 families with doses greater than 1 Sv; 170 families with doses of 0.5–1.0 Sv; 173 families with doses of 0.005–0.5 Sv; and 477 families with doses of less than 0.005 Sv. In 1998, it was recognized that there were 317 AHS participants (with their 852 children) whose DS86 doses are greater than 1 Sv but who were not included in the original project to establish permanent cell lines. We decided to collect these additional cases even though unexposed spouses may not be available in all of them. Blood collection started in September 1998 in Hiroshima and February 1999 in Nagasaki. By the end of January 2000, we had obtained blood samples and established cell lines from 61 children (48 families) in Hiroshima and 42 children (26 families) in Nagasaki. We plan to accomplish the additional blood collection by the end of FY2001.

Research Protocol 8-93

Cytogenetics Study

RP 8-93 (Supersedes RP 10-89) Cytogenetic study in the Adult Health Study population by fluorescence *in situ* hybridization (FISH)

Kodama Y (G), Nakano M (G), Ohtaki K (G), Itoh M (G), Awa AA, Nakamura N (G)

This FISH study is expected to provide answers to several questions raised by past cytogenetic studies using conventional staining methods. Mainly, these questions regard city differences among those exposed in Japanese houses, lower dose response of Nagasaki factory workers, and possible bias in cytogenetic dose estimation due to clonal expansion of aberration-bearing cells. Because previous studies were not free from laboratory bias, a full FISH study must be achieved by the Hiroshima laboratory. Since 1994, nearly 750 Hiroshima and 230 Nagasaki survivors have been examined. We started sampling Nagasaki cases in May 1997. High-dose parents (about 140 individuals) of progeny in the F_1 DNA study will also be introduced into this study since it is critical to assess the accuracy of their dose assignments. Further, nearly 90 survivors who donated their teeth extracted for medical reasons will be FISH-examined to compare findings with tooth enamel data collected by electron spin resonance (ESR).

As the Multinational Peer Review held in November 1999 recommended to shift the focus on more basic researches, we plan to reduce the number of survivors for FISH examination from 200–250 to 100–150 per year.

RP 8-93 Publications

◆ Kodama Y, Nakano M, Itoh M, Ohtaki K, Kusunoki Y, Hirai Y, Kyoizumi S, Nakamura N. Origin of clonal chromosome aberrations in atomic-bomb survivors. *Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications) 1999 (June); 34(2):213–22. (Japanese)*

◆ Kodama Y, Ohtaki K, Awa AA, Nakano M, Itoh M, Nakamura N. The F value for chromosome aberrations in atomic bomb survivors does not provide evidence for a primary contribution of neutrons to the dose in Hiroshima. *Radiation Research 1999 (November); 152(5):558–62. (RERF Report 1-98)*

◆ Nakamura N. Is micronucleus derived from chromosome breakage? *Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications) 1999 (June); 34(2):251–8. (Japanese)*

◆ Nakamura N, Funamoto S, Awa AA. Cytogenetic tests for directional asymmetry in radiation dose from Hiroshima atomic bomb. *FY-1999 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japanese Public Health Association); 2000 (March), pp 65–6. (Japanese)*

◆ Ohtaki K. Clonal chromosome aberrations in atomic-bomb survivors: Deletion 5q and inversion 14, characteristics of leukemia-related changes. *Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications) 1999 (June); 34(2):223–31. (Japanese)*

◆ Ohtaki K. Clonal chromosome aberrations in atomic-bomb survivors: Deletion 5q and inversion 14, characteristics

of leukemia-related changes. Hiroshima Igaku (Journal of the Hiroshima Medical Association) 1999 (April); 52(4):388–90. (Japanese)

RPs 8-93 and 1-92 (Atomic-Bomb Dosimetry Studies) Publication

♦ Nakamura N, Kodama Y. Biological dosimetry. FY-1999 Welfare Science Research Subsidy Report of Welfare Science Special Research Projects. Reassessment of A-bomb Radiation Dosimetry System and Study of Health Effects. Hiroshima: Study Team of the Reassessment of A-bomb Radiation Dosimetry System and Health Effects; 2000 (March 31), pp 121–30. (Japanese)

RP 8-93 Oral Presentations

❖ Nakamura N. Somatic mutation in blood cells and human aging. *The 6th Asia/Oceania Regional Congress of Gerontology*, 8–11 June 1999, Seoul, Korea

❖ Nakamura N, Funamoto S, Awa AA. Does the chromosome aberration dose response vary depending on the direction from the hypocenter? *The 24th Chugoku-area Local Radiation Research Meeting*, 3 July 1999, Hiroshima, Japan

❖ Nakamura N, Funamoto S, Awa AA. Does the chromosome aberration dose response vary depending on the direction from the hypocenter? *The 42nd Annual Meeting of the Japan Radiation Research Society*, 1–3 September 1999, Hiroshima, Japan

Research Protocol 4-75

F₁ Study Platform Protocol—Genetic Effects of Atomic Radiation on Children Born to Bombing Survivors

RP 4-75 (Supersedes ABCC RP 22-60) Research plan for RERF studies of the potential genetic effects of atomic radiation: Hiroshima and Nagasaki. Part 1. Mortality study of children born to atomic-bomb survivors

Mabuchi K (EH), Preston DL (S)

See *ABCC Technical Report 4-60* for full text of this platform protocol.

This is a long-term mortality follow-up of a cohort of 77,000 children (F₁) born to parents, one or both of whom were exposed to radiation from the atomic bombs, and to control parents. As with the Life Span Study (LSS), F₁ mortality follow-up is based on ascertainment of deaths through the nationwide family registration system, the *koseki*; the Hiroshima and Nagasaki tumor registries also provide cancer incidence data for a subset of the cohort. Previously published 1945–85 mortality data for diseases excluding external causes showed no significant increase associated with parental radiation exposure. An apparent increase in noncancer mortality prior to attained age 20 in the greater than 2.5-sievert dose category was considered due to worsened socioeconomic conditions in which many survivors lived in the aftermath of the bombings. Tumor registry cancer incidence (through 1982) showed no excess cancer risk associated with parental radiation during the first two decades of life. Through 1990, 4,130 deaths occurred, including 203 cancer deaths in about 67,500 with DS86 dose estimates. Through the tumor registries, 448 cases have been identified, including 60 leukemia and 28 lymphoma cases. Preliminary analyses show no significant relationship between parental exposure and the risk of leukemia or lymphoma. We plan to start analysis of the latest mortality and cancer data shortly.

Research Protocols 1-99, 1-98, 3-94, 1-94, 6-93, 4-92, 2-92, 6-91, 2-91, 5-90, 9-88, 6-86, 2-86, 8-85, 14-79, 7-76, 29-60

Special Cancer Studies

RP 1-99 (Addendum to, See also RP 5-90 below) Primary liver cancer incidence study among atomic-bomb survivors, 1958-87

Sharp GB (EH), Mizuno T (R), Fujiwara S (CH), Cologne JB (S), Mabuchi K (EH), Kodama K

The main objective of this addendum study to the case-control study of primary liver cancer (RP 5-90) is to use standard serum tests for hepatitis B (HBV) and hepatitis C (HCV) viruses to validate tests for these viruses conducted using archival tissue samples. The tissue-based tests for HBV being validated include orcein staining, immunohistological staining, and polymerase chain reaction (PCR); for HCV, the tissue-based test being validated is reverse transcriptase-PCR (RT-PCR).

This protocol involves the testing of frozen and freeze-dried samples for subjects included in RP 5-90 for whom both tissue and serum samples are available. We are restricting serum analysis to subjects with at least two separately stored serum samples.

The protocol was approved in February 1999. Since that time, we identified the subjects for whom dual serum samples were available and conducted the specified serum tests. We were able to obtain and test frozen (-80°C) or freeze-dried serum samples for a total of 51 subjects in this study for whom tissue-based HBV staining or PCR results were available. These samples were tested, under code, for HbsAg in the RERF Department of Clinical Studies using radioimmunoassay procedures and commercially available reagents. All 45 of the persons whose sera were negative for HbsAg were negative by tissue staining or PCR (specificity = 100%); five of the six persons whose sera were HbsAg-positive were positive by tissue-based staining or PCR (sensitivity = 83%). We were able to test frozen serum samples (-80°C) for 43 subjects, for whom HCV results of tissue-based RT-PCR tests were available. These samples were tested, under code, for HCV antibodies by ELISA-2 tests in the RERF Department of Clinical Studies using commercially available reagents. All 43 of these serum samples were also sent to a clinical laboratory in Tokyo (Special Reference Laboratory) where qualitative RT-PCR tests were performed. Fifteen of the 23 subjects testing HCV-negative by either serum-based ELISA-2 or RT-PCR were confirmed (specificity = 65%); the other eight subjects tested positive by the tissue-based RT-PCR. Of the 20 subjects testing positive by ELISA-2 or serum-based RT-PCR, 14 were positive by tissue-based RT-PCR (sensitivity = 70%), the other six being negative. This information was used to determine which of the subjects to classify as HBV- and HCV-positive in the analysis of data collected for protocol RP 5-90. A report on this work is now under preparation.

RP 1-98 A prospective study of bladder cancer and diet

Nagano J, Kono S, Preston DL (S), Moriwaki H (EH),

Sharp GB (EH), Fujita S (S), Mabuchi K (EH)

The relation between consumption of 22 dietary items and subsequent bladder cancer incidence was examined in the Life Span Study cohort. Subjects were 38,540 people who responded to a mail survey carried out between 1979-1981 and who had no known cancer diagnosed before the start of follow-up (1 January 1980 for men and 1 February 1981 for women). Consumption frequencies for 22 dietary items were ascertained with precoded answers. As of the end of 1993, there were 114 (83 men and 31 women) incident cases of bladder cancer among 450,326 person-years at risk. Statistical analysis was done using Poisson regression for grouped survival data. Consumption of green-yellow vegetables and fruit were protectively associated with risk. Adjusted for sex, age, radiation exposure, smoking status, educational level, body mass index, and calendar time, relative risks (RRs) for those consuming green-yellow vegetables 2-4 times per week and almost everyday were 0.62 (95% confidence interval 0.39-0.98) and 0.54 (0.30-0.94), respectively, compared with those consuming once per week or less. The corresponding RRs for fruit consumption were 0.50 (0.30-0.81) and 0.62 (0.39-0.99), respectively. The findings add to evidence that high consumption of vegetables and fruit are protective against bladder cancer. A report on the results was accepted for publication by *International Journal of Cancer* as of 9 November 1999, and this study was completed.

RP 1-98 Manuscript in Press

See RP 14-78, Life Span Study.

RP 3-94 Incidence of lymphoid malignancies among the atomic-bomb survivors, 1950-90

Namba K, Matsuo T, Tokunaga M, Jubashi T, Fujita Y (EH), Soda M (EN), Dohy H, Kamada N, Tomonaga M, Travis LB, Preston DL (S), Mabuchi K (EH), Land CE, Tokuoka S (EH)

The relationship between lymphopoietic malignancies and radiation exposure is complicated because of variability of diagnostic categories and uncertainty about the potential for radiation carcinogenesis for certain important categories. For instance, the risk for acute lymphocytic leukemia was markedly elevated among atomic-bomb survivors, particularly children, during the early years, while there is no convincing evidence of a radiation-induced excess of chronic lymphocytic leukemia. Multiple myeloma, derived from terminally differentiated B cells, has been identified as a radiation-induced cancer in the analysis of the LSS mortality data, but recently published incidence data demonstrated only a weak association with radiation exposure. Studies of non-Hodgkin's lymphoma in the LSS have also demonstrated variable and inconsistent results, at least in part because of different sources of diagnostic data and diagnostic variability. On the other hand, recent advances in immunological studies of malignant lymphoma are remarkable. Surface markers to tumor cells can be used to distinguish B and T cells involved in malignant lymphomas, and a new classification has replaced the conventional classification of lymphomas.

The objective of the present study is to investigate all lymphopietic tumors (lymphomas, multiple myeloma, and lymphocytic leukemias) that occurred between 1950 and 1990 in the LSS. Emphasis is on confirmation and classification of cases using modern techniques and classification applied to cases ascertained from all sources. The study will involve both hematologists and pathologists engaged in lymphoid tumor research. Non-Hodgkin's lymphomas will be classified by immunohistochemical studies into T- or B-cell lymphomas, and diagnosis of adult T-cell leukemia will be based on detection of proviral DNA of HTLV-I in archived tissues. Screening is under way on several thousand potential cases with a wide range of diagnoses to which lymphoid tumors may be misclassified. It is expected to take at least another year to complete this phase and a pathology review.

RP 1-94 Studies of lung cancer incidence among the atomic-bomb survivors, 1950–90

Egawa H, Matsuo T, Yonehara S, Fujita Y (EH), Nakashima E (S), Soda M (EN), Tokunaga M, Tokuoka S (EH), Akiba S, Mabuchi K (EH), Preston DL (S), Land CE

Lung cancer is a well established late effect of radiation exposure in various irradiated populations, including the atomic-bomb survivors. However, several specific issues and questions remain, including the specificity of various cell types involved in radiation- versus smoking-related cancers, confounding and joint effects of smoking in relation to radiation exposure, delineation of temporal trends with allowance given to age at exposure, and attained-age effects. The International Commission on Radiological Protection (ICRP) has also recently published a new report on the risk of lung cancer from inhaled radionuclides modeled anatomically in terms of lung "Compartments." New information on the anatomical distribution of lung cancers resulting from uniformly distributed radiations may be useful for evaluating the ICRP model. This RP was developed to address these questions and issues. The study will evaluate lung cancer incidence in the Life Span Study for the period 1950–90. Pathology reviews are expected to be completed in the coming year.

RP 6-93 Breast-cancer incidence among atomic-bomb survivors, 1950–90

Tokunaga M, Land CE, Tokuoka S (EH), Ikeda T, Soda M (EN), Mabuchi K (EH)

This is the latest of a series of breast cancer incidence surveys conducted by Drs. Tokunaga and Land. A previously completed fourth survey (RP 1-90) included 807 primary breast cancer cases and 20 second breast cancer cases from 1950 to 1985. A strong linear radiation-dose response was found, with the highest excess relative risk averaged over the entire observation period occurring among women who were younger than 20 at the time of radiation exposure from the bombings. A much lower, marginally significant dose response was seen among women exposed after age 40. A strikingly high risk per unit of radiation for early-onset breast cancer cases led the authors to suspect the possible presence of a genetically susceptible subgroup. A new research pro-

tol expands the breast cancer series through 1990. Data collection for this series has been completed, adding 261 newly accessed cases (250 from 1986 through 1990 and eleven prior to 1986). Of these, 58 cases were exposed prior to age ten, and this should strengthen risk estimates for this age-at-exposure group. A paper is being prepared for publication.

RP 4-92 Incidence study of tumors of the central nervous system among atomic-bomb survivors

Yonehara S, Fujii H, Kishikawa M, Kobuke T, Thompson DE, Soda M (EN), Tokunaga M, Tokuoka S (EH), Mabuchi K (EH), Ron E, Preston DL (S), Land CE

Tumors of the nervous system have been associated with late effects of medical radiation at all ages, although detailed risk assessment has been difficult primarily due to the smaller number of cases. Until recently, there was very limited information on brain and other tumors of the nervous system in the LSS cohort. In the recent solid cancer incidence report, a suggestive dose response was found for tumors of the nervous system except for the brain among those exposed before age 20. These findings prompted the present study. The objective is to ascertain malignant and benign tumors of the central nervous system in the LSS between 1950 and 1991 under the guidelines established for the conduct of site-specific studies. All the work related to case finding and histological review has been completed, and 374 benign and malignant tumors have been identified. Of these, 282 (75%) are histologically confirmed. Meningioma is most frequent (41%), followed by schwannoma (or neurilemmoma) of the cranial and spinal nerves (25%), cerebrospinal glioma (19%), and pituitary adenoma (11%). Preliminary analysis shows a significant dose response for neurilemmoma. Two papers are being prepared for publication, and this RP will be terminated upon their publication.

RP 2-92 Studies of ovarian tumor incidence among the RERF Extended Life Span Study cohort, 1950–87

Tokuoka S (EH), Kawai K, Inai K, Shimizu Y (EH), Nakashima E (S), Tokunaga M, Soda M (EN), Mabuchi K (EH), Land CE

An increased risk of ovarian cancer among atomic-bomb survivors has been reported from an earlier site-specific study of ovarian cancer as well as from analyses of LSS mortality and incidence. No clear evidence exists for any specific histologic type being particularly associated with radiation exposure. In the previous study, the frequency of benign tumors of the ovary detected at autopsy was also found to increase with radiation dose. The present study extends the previous ovarian cancer series by seven years (1950–80) and includes a systematic ascertainment of benign tumors. All work related to case identification and histological verification is completed. Seven hundred and twenty-seven primary ovarian tumors (Hiroshima, 503; Nagasaki, 224) have been identified, of which 605 cases (83.2%) were histologically confirmed, 185 cases of malignant tumors (including 46 cases of borderline malignancy) and 420 cases of benign tumors. The most preponderant type of malignant tumor

was the common epithelial tumor (Group I; 168/185 cases, 90.8%). Cases of sex-cord stromal tumors (Group II; 12 cases, 6.5%) and germ-cell tumors (Group IV; 5 cases, 2.7%) were rare. Among benign tumors, cases of Group I tumors were predominant (251/420 cases, 59.8%), followed by cases of Group IV (117 cases, 27.9%), Group II (50 cases, 11.9%), and others (2 cases, 0.5%). There were 146 multiple ovarian tumors encountered in 71 persons. Among the 28 malignant tumor cases, Group I tumors were predominant (26 cases, 92.9%), and of 118 benign tumor cases, Group I (77 cases, 65.3%) and Group IV (35 cases, 29.7%) tumors were preponderant. Among the 573 exposed cases, malignant as well as benign tumors showed a dose-response relationship, and this tendency was especially remarkable in the serious tumors of Group I. Data analysis is under way. The study is expected to be complete in one to two years.

RP 6-91 Studies of thyroid tumor incidence among the RERF Extended Life Span Study cohort, 1950–87

Hayashi Y, Tsuda N, Akiba S, Fujita S (S), Tokunaga M, Tokuoka S (EH), Ron E, Land CE, Mabuchi K (EH)

Thyroid cancer was one of the earliest solid cancers found to be increased in atomic-bomb survivors, and several thyroid cancer studies have been conducted among survivors over the last 40 years. The aim of the present investigation is to update and expand the earlier thyroid cancer incidence series (through 1979), including both benign and malignant tumor cases diagnosed between 1950 and 1990. An increased number of cases over an extended study period should allow more detailed risk analyses. All the work related to case ascertainment and histological grouping has been completed. Two thousand six hundred and thirty-seven potential cases were reviewed, from which 915 thyroid tumor cases were identified. Histological verification was possible for 851 (93%) of these cases, 558 with malignant tumors and 293 with benign tumors. The majority of malignant thyroid carcinomas are of the papillary type (96%), followed by the follicular type (1%), malignant lymphoma (<1%), medullary (<1%), and undifferentiated carcinoma (<1%). The 537 papillary carcinomas include 297 microcarcinomas detected primarily at autopsy. Data analysis has begun, and papers will be written and submitted for publication in the next two years.

RP 2-91 Studies of skin cancer incidence among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950–87

Kishikawa M, Kobuke T, Iseki M, Sadamori N, Yamamoto S, Soda M (EN), Tokunaga M, Tokuoka S (EH), Mabuchi K (EH), Ron E, Preston DL (S), Land CE

An elevated risk of skin cancer, mostly basal cell carcinoma, has been reported from the follow-up of children treated with radiation for tinea capitis, enlarged thymus, and various head and neck diseases. The LSS solid cancer incidence report demonstrated for the first time an increased risk of skin cancer in atomic-bomb survivors. Because the completeness of the ascertainment of skin cancer from tumor registries is questionable and diag-

noses of skin cancer are highly variable among physicians and pathologists, the present study is designed to provide extended case finding and a standardized pathology review for diagnosis and histological typing of skin tumors. All work related to case ascertainment has been completed, and analyses have almost been completed. Three hundred and forty-four skin cancer cases were identified for the study period from 1950 to 1987, 302 (88%) of which have been histologically verified by a panel of pathologists. Basal cell carcinomas comprise 36% of the cases; squamous cell carcinomas, 33%; Bowen disease, 13%; malignant melanomas, 5%; and other types, 13%. A significant dose response is demonstrated for nonmelanoma skin cancers as a group and especially for basal cell carcinomas and other epithelial cancers (nonbasal, nonsquamous cell). There is no evidence of a dose response for squamous cell carcinoma. Noteworthy is the absence of a suspected combined effect of ultraviolet and ionizing radiation exposure and a strong effect of age at exposure on basal cell carcinoma. A paper on risk estimates was published in *Cancer Causes and Control* in 1998, and a second paper on histological characteristics of skin cancer is in preparation.

RP 5-90 (See also RP 1-99 above, and RP 2-94 [Cell Biology]) Primary liver cancer incidence study among atomic-bomb survivors, 1958–87

Fukuhara T, Itakura E, Yamamoto M, Tokuoka S (EH), Mabuchi K (EH), Seyama T, Nakamura N (G), Akiyama M, Cologne JB (S), Soda M (EN), Tokunaga M, Beebe GW

Elevated risk of liver cancer among atomic bomb survivors was first reported from the LSS tumor registry solid cancer incidence paper published by Thompson *et al* (1994). Since the liver is a frequent site of metastasis for cancer from other sites, careful review of clinical and pathological materials is especially important. The present study was conducted to obtain more definitive evidence on the relationship of this cancer to radiation exposure and to characterize the histopathological features of liver cancer by a more detailed, standardized investigation.

Case-ascertainment and diagnostic confirmation has been completed. The total number of primary liver cancer cases in the LSS for the period 1958–1987 was 830, of which 364 (44%), mostly hepatocellular carcinomas (HCC), were histologically verified. We frequency matched 897 controls to the 307 HCC and 53 cholangiocarcinoma cases who were histologically verified. Hepatitis B virus (HBV) tests were performed for 86% of controls and 82% of cases; hepatitis C virus (HCV) tests were performed for 62% of controls and 57% of cases. Non-tested subjects had insufficient tissue or tissue of too poor a quality to permit testing. By surveying Adult Health Study interviews and three of the LSS mail surveys, we were able to obtain cigarette smoking information for 65% of controls and 63% of cases. T. Mizuno, formerly in the Department of Radiobiology, *et al.*, wrote a paper describing the HCV testing (Mizuno T, Nagamura H, Iwamoto KS, Ito T, Fukuhara T, Tokunaga M, Tokuoka S, Mabuchi K, Seyama T. RNA from decades-

old archival tissue blocks for retrospective studies. Diagnostic Molecular Pathology 1998;7:202–208).

Although the use of PCR and RT-PCR on archival liver tissue samples is innovative, one problem with using this technique is that it has not been used previously and lacks validation. Therefore, a new smaller project was developed to utilize serum samples stored in the Adult Health Study to validate PCR and RT-PCR of liver tissue as a means of detecting HBV and HCV. This addendum research protocol was developed jointly by staff from the RERF Departments of Epidemiology, Radiobiology, Clinical Studies and Statistics to compare tissue-based tests for HBV and HCV against standard serum measures. During the past year, we compared HBV test results for 51 subjects and HCV test results for 43 subjects for whom both tissue and serum samples were available.

Most of our effort undertaken this year has been in preparation of reports for publication. As expected, a large proportion of liver cancer cases were identified through death certificates only. Since accuracy of death-certificate diagnosis is poor for liver cancer, information from the pathology review was used to adjust the numbers of cases used for incidence analysis. Background incidence of liver cancer rose dramatically among males between the ages of 40 and 60 between 1958 and 1987. Excess relative risk from radiation exposure was linear: 0.81 per Sv (95% CI: 0.32, 1.43). Males and females had similar relative risks so that, given a threefold higher background incidence for males, the radiation-induced excess incidence was substantially higher in males. The paucity of cholangiocarcinoma and hemangiosarcoma cases suggested that they are not the types primarily associated with uniform radiation exposure from the atomic bombs, as they are with internal exposure from thorotrast. This information was recently published (see Cologne *et al.* below).

The pathology reviews served to characterize the histology of liver cancer and liver lesions accompanying cancer. Among histologically verified cases, 85% were HCC cases and 14% were cholangiocarcinoma. The majority of HCCs are of the trabecular type (81%), followed by tumors of the compact (13%), pseudoglandular (4%) and sclerotic types (1%). Liver cirrhosis accompanying cancer was found in 74% of HCC cases and 8% of cholangiocarcinoma cases. The most frequent type of cirrhosis was the mixed type (69%) followed by macronodular (15%), micronodular (13%) and undetermined types. A paper describing these histopathological features of liver tumors in association with hepatitis B and C infections has passed RERF internal review and been submitted for publication. A paper describing the HCC case-control analysis is currently under preparation.

RP 5-90 Publication

♦ Cologne JB, Tokuoka S, Beebe GW, Fukuhara T, Mabuchi K. Effects of radiation on incidence of primary liver cancer among atomic bomb survivors. Radiation Research 1999 (October); 152(4):364–73. (RERF Report 6-99)

RP 5-90 Oral Presentation

♦ Sharp GB, Mizuno T, Cologne JB, Tokuoka S, Mabuchi K. Does atomic-bomb radiation increase the risk of hepatocellular carcinoma and cholangiocarcinoma among persons with viral hepatitis? *The 11th International Congress of Radiation Research, 18–23 July 1999, Dublin, Ireland*

RP 9-88 Guidelines for the conduct of site-specific cancer incidence studies among atomic-bomb survivors

Tokunaga M, Mabuchi K (EH), Tokuoka S (EH), Land CE

These guidelines are intended to simplify the preparation of research plans for site-specific cancer incidence studies and provide uniformity in basic study design and operation. The guidelines state that case ascertainment be undertaken through the Hiroshima and Nagasaki tumor registries supplemented by an extended case-finding search. Histopathological verification should be achieved by a panel of collaborating pathologists specializing in pertinent areas. Tumor types are to be classified using internationally accepted tumor classification systems. Data analyses should be performed by RERF and/or other participating epidemiologists and statisticians. Under these guidelines, the following site-specific cancer incidence studies are currently undertaken: liver (RP 5-90); skin (RP 2-91); thyroid (RP 6-91); ovary (RP 2-92); central nervous system (RP 4-92); breast (RP 6-93); lung (RP 1-94); and lymphoid tissues (RP 3-94). The salivary tumor study has been terminated. A paper on skin cancer has been accepted for publication. In addition, draft papers on central nervous system tumors and liver cancer will be prepared and submitted for internal review. Most current site-specific studies are expected to be completed in the next three to four years. A new study on cancers of the colon/rectum will be started. Other sites of interest will likely be identified.

RP 6-86 Ultrasonographic screening of Adult Health Study participants to detect cancer and other diseases

Yamada M (CH), Naitoh K, Akahoshi M (CN), Kasagi F (S), Fujiwara S (CH)

The increased incidence of uterine myoma among heavily exposed subjects was reported in *AHS Report 7*. To avoid potential bias in diagnosis, abdominal ultrasonographic examinations were conducted in Hiroshima between 1992 and 1993. The prevalence of uterine nodules increased significantly with radiation dose, with an odds ratio of 1.6 for those exposed to one gray. This result suggested that benign tumors, such as uterine myomas, may be induced by exposure to radiation, although the pathogenesis remains unclear. Further studies are needed to clarify whether the association is the result of radiation.

RP 2-86 Collection of surgically removed cancer tissues from A-bomb survivors: Special reference to thyroid and breast cancers

Hirai Y (R), Ban S (R), Hamatani K (R), MacPhee DG (R)

This research protocol proposes the collection and cryopreservation in liquid nitrogen of possibly radiation-induced thyroid and breast cancer tissues to be used as a resource for future studies on oncogene and tumor suppression genes. These tissues will also be useful for the preparation of DNA and possibly mRNA for studies of oncogenes and other molecular biological aspects of cancer. However, despite our continuing interest, it is very difficult to collect not only fresh but also archival tissue samples from A-bomb survivors. The current status of the collection of archival tissue samples of thyroid and breast cancers in Hiroshima is 103 of thyroid cancer (A-bomb survivors = 56; unexposed controls = 47) and 75 cases of breast cancer (A-bomb survivors = 37; unexposed controls = 24; early entrant = 7; exposure status unknown = 7), respectively.

We will submit a new RP for collecting archival tissues from A-bomb survivors with the cooperation of outside pathology laboratories, and we will continue to make efforts for the collection of fresh tissue samples. We plan to examine new candidate genes of breast cancers of Japanese women using fresh surgical breast cancer materials from non-AHS members. This is a pilot and collaborative study with the Second Department of Surgery of the Hiroshima University School of Medicine and RERF's Department of Genetics. To date, we have collected fresh samples from 40 cases (normal tissue, tumor tissue, and blood cells for each case). We will use fresh materials to evaluate the usefulness of the DNA two-dimensional electrophoresis method applied to breast cancer.

RP 8-85 Incidence study on malignant and benign genital tumors among females, Hiroshima and Nagasaki, 1950–80

Tokuoka S (EH), Kawai K, Shimizu Y (EH), Inai K, Ohe K, Mabuchi K (EH)

Several reports suggest genital cancer as a late effect of local irradiation, but evidence on genital cancers induced by whole-body irradiation is limited. This RP intends to determine the incidence of tumors of various female genital organs in the LSS. A study of ovarian tumors has been superseded by RP 2-92. A separate RP will be prepared for uterine tumors.

RP 14-79 Interaction between radiation dose and host factors. An epidemiological case-control study of female breast cancer in atomic-bomb survivors

Mabuchi K (EH), Cologne JB (S), Shibata Y, Tokunaga M, Land CE

This ongoing case-control study nested in the LSS cohort is intended to evaluate the effects, if any, of host factors other than age on radiation carcinogenesis in women. These have included traditional risk factors, such as reproductive histories, ovarian activity, and use of exogenous hormones. In a recently published case-control study of 196 breast cancer cases and 566 controls, risk was found to be positively associated with age at first full-term pregnancy, while negative associations were observed with number of births and total cumula-

tive period of breastfeeding. Significant positive associations were also found with histories of treatment for dysmenorrhea and uterine or ovarian surgery. Neither age at menarche nor age at menopause was significantly associated with breast cancer. Radiation exposure (from the atomic bombs) was associated in a multiplicative manner with age at first full-term pregnancy, number of children, and cumulative total period of lactation. More recently, special attention has been given to family predisposition because of the rapidly increasing knowledge on BRCA-1, -2, and ATM, other genes that may possibly play an important role in heritable forms of breast cancer. Preparations are currently under way for a new study of early- versus late-onset breast cancer cases to investigate family pedigrees and inherited mutations in the genes mentioned above using tissues and blood samples. Preparation of a research protocol is under way.

RP 14-79 Oral Presentation

❖ Cologne JB, Langholz B. Selecting controls for assessing interaction in nested case-control studies. *The 32nd Annual Meeting of Society for Epidemiologic Research, 10–12 June 1999, Baltimore, USA*

RP 7-76 The value of Adult Health Study family history records in the determination of genetic influences on the development of cancer and other disorders

Cologne JB (S), Yamada M (CH), Izumi S (S), Grant EJ (EH), Mabuchi K (EH)

This project was originally undertaken to ascertain the feasibility of using AHS family history information to study genetic influences on cancer and other diseases. For many years, there was little or no activity on this project, and data collected in early years were not stored in computer data bases. Recent advances in the understanding of genetic effects on disease and development of improved methods for genetic epidemiology and statistical genetics have led to specific hypotheses concerning genetic susceptibility to radiation effects. By combining data on familial relationships with information in diagnostic data bases and taking advantage of our molecular genetics capabilities, RERF is in a unique position to investigate some of these hypotheses. Family data on 7,352 Hiroshima AHS participants and their relatives (36,035 individuals) have been entered into a computer data base and verified. Data from Nagasaki participants is in the checking/identification phase. Computer programs to produce family pedigrees and link them to the tumor/tissue registry, AHS clinical diagnoses, and cause-of-death data bases are near completion. Work is also underway to make the data base compatible with RERF's database interface and to implement functions allowing extraction of useful pedigree information. At this point, it is reasonable to conclude that the original intent of the RP could not foresee the current state of the art of genetic epidemiology or the complexity involved in producing reliable family pedigrees from the available information. Nevertheless, a system is nearly in place by which the value of the information can finally be assessed and, hopefully, genetic epidemiology studies can be initiated.

RP 29-60 Detection of leukemia and related disorders

Mabuchi K (EH), Tomonaga M, Kimura A, Kodama K, Kamada N, Dohy H, Soda M (EN), Shibata Y, Preston DL (S)

This case-finding program, known as the leukemia registry, was started in 1948, with collaborations of hematologists and physicians involved in the treatment and care of leukemia patients in Hiroshima and Nagasaki. It is designed to detect, document, evaluate, and diagnose cases of leukemia and certain closely related hematological disorders occurring among the LSS and other RERF cohorts. In the early years, case-finding was based on a wide variety of sources, including reports from participating physicians, ABCC clinical examinations, death certificates, obituaries, and others. With the recent improvement in the Hiroshima and Nagasaki tumor registries, leukemia case ascertainment currently relies primarily on the tumor registries' activities. In the mid-1980s, more than 60% of leukemia cases in the leukemia registry were reclassified using modern diagnostic criteria and nomenclature, including the French-American-British (FAB) classification for acute leukemias. The latest published report results from comprehensive analyses of LSS incidence data for 1950–1987, involving analyses of a dose response and modifying effects for major leukemia types (acute lymphocytic leukemia, acute myelocytic leukemia, chronic myelocytic leukemia, and adult T-cell leukemia) and lymphoma and multiple myeloma. An important question remaining relates to the risk for multiple myeloma. (See RP 3-94, Special Cancer Studies.) A new site-specific protocol to be undertaken jointly by hematologists and pathologists has been developed to investigate all lymphoid tumors, including multiple myeloma, so that more definitive data can be obtained on the risk of these tumors. This new lymphoid tumor study will be a major focus of this research protocol in the next few years. (See detailed plan under RP 3-94, Special Cancer Studies.)

Research Protocol 18-61

Hiroshima and Nagasaki Tumor, Tissue, and Leukemia Registries

Note that RERF studies related to the tumor and tissue registries include RPs 3-94, 1-94, 6-93, 4-92, 2-92, 6-91, 2-91, 5-90, 9-88, 8-85, and 29-60 (all discussed under Special Cancer Studies).

RP 18-61 Tumor registry study in Hiroshima and Nagasaki

Mabuchi K (EH), Soda M (EN), Fujita Y (EH), Koyama K (EH)

See ABCC Technical Report 2-61 for full text of protocol.

This research protocol provides the framework for the operation of the Hiroshima and Nagasaki tumor registries, which provide for the systematic collection and management of tumor cases in the populations of the cities of Hiroshima and Nagasaki. These registries are undertaken under the auspices of each city's medical association with technical support provided by RERF. The registries are linked with the master file for the major RERF cohort samples (LSS, *In utero*, and F₁) and, thus, serve as the source of RERF cancer incidence studies in each cohort. The Hiroshima and Nagasaki tumor registries are the first population-based registries in Japan. Case ascertainment and data collection are based on abstraction of medical records conducted by trained personnel at regularly scheduled hospital visitations. This active approach is reflected in a high quality of incidence data not typically seen for other tumor registries in Japan, most of which rely on passive case notifications by physicians. The Hiroshima and Nagasaki tumor registry data have regularly been included in recent volumes of *Cancer Incidence of Five Continents*, compiled by the International Association of Cancer Registries (IACR) at the International Agency for Research on Cancer (IARC) in Lyon, France. The cancer incidence from the two cities was included in Volume VII of this monograph, which was published in 1997. The latest data will be included in Volume VIII to be published in 2002. The latest childhood cancer incidence data in Hiroshima and Nagasaki are included in the latest volume of *International Incidence of Childhood Cancer*, also compiled by the IARC, in 1998.

RP 18-61 Publications

- ◆ Arisawa K, Soda M, Endo S, Kurokawa K, Katamine S, Shimokawa I, Koba T, Takahashi T, Saito H, Doi H, Shirahama S. Evaluation of adult T-cell leukemia/lymphoma incidence and its impact on non-Hodgkin lymphoma incidence in southwestern Japan. *International Journal of Cancer* 2000 (February 1); 85(3):319–24.
- ◆ Soda H, Oka M, Tomita H, Nagashima S, Soda M, Kohno S. Length and lead time biases in radiologic screening for lung cancer. *Respiration* 1999 (November); 66(6):511–7.

RP 18-61 Oral Presentation

- ❖ Soda M, Akahoshi M, Ichimaru S, Soda H. Evaluation on usefulness of lung cancer screening based on a cohort

study. *The 21st Annual Meeting of the International Association of Cancer Registries, 29 September–1 October 1999, Lisbon, Portugal*

No RP Number Tissue Registry Studies

Mabuchi K (EH), Soda M (EN), Fujita Y (EH)

Tissue registries were undertaken in April 1973 under the auspices of Hiroshima's prefectural medical association and in September 1974 by Nagasaki's city medical association. Pathology slides and pathology reports are collected for each tumor, malignant and benign. Tissue registry and tumor registry data from each city are processed at RERF and entered into a common data base. These registries provide a supplemental source for tumor case ascertainment for the tumor registries and were especially valuable in the early years, when there was difficulty in seeking collaboration from certain hospitals in Hiroshima. A large number of pathology slides collected and stored at one location greatly facilitate the conduct of a large number of site-specific studies involving pathology reviews of cases diagnosed over many years.

Research Protocols 1-92, 10-86, 18-59

Atomic-Bomb Dosimetry Studies

RP 1-92 Radiation dose estimates using tooth samples. Part 2. Use of electron spin resonance on tooth enamel from Hiroshima atomic-bomb survivors

Nakamura N (G), Miyazawa C, Awa AA

Results for interlaboratory comparison of ESR measurements of teeth from Mayak nuclear workers were published in January 2000 (see Romanyukha *et al.* below).

Another international comparison task was organized by IAEA. Tooth samples were exposed to gamma rays, mainly below 0.5 Gy, that were decoded only after reporting ESR measurement data. Our ESR-estimated doses were consistently lower than the exposed dose by about 0.1 Gy. Subsequently, we measured remaining halves of each tooth that were not exposed to radiation and found that these non-exposed samples had slightly smaller background signal intensity compared with the mixed enamel samples that were used to create the calibration curve several years ago. The difference was nearly 0.1 Gy and hence the net increase was very close to the exposed dose. The results from 30 participating laboratories were summarized and presented at 9th International Conference on Luminescence and Electron Spin Resonance (September 1999, Rome), and will be published in *Radiation Measurements* as conference proceedings.

Measurements of tooth samples from Kyrgyzstan were also completed and the results were sent to Dr. Brimkulov. The ESR-estimated doses of six Kyrgyzstan cleanup workers at the Chernobyl accident were between 0 Gy to 0.8 Gy. The results were highly appreciated and further collaboration was asked. However, as isolation of enamel from teeth takes time and labor, it was agreed that the separation process to be performed in Kyrgyzstan according to the protocol developed at RERF.

As for the teeth from atomic-bomb survivors, we measured 46 enamel samples from 26 teeth during the past one year. We have encountered three exceptional cases whose estimated ESR doses are over 10 Gy. The first sample was a front tooth from a welder. As electric sparks release electromagnetic waves of various wavelengths, the observed results may be attributable to his occupational UV exposures. We could not find any possible causes including radiotherapy for the remaining two cases.

RP 1-92 Publication

♦ Romanyukha AA, Ignatiev EA, Vasilenko EK, Drozhko EG, Wieser A, Jacob P, Keirim-Markus IB, Kleschenko ED, Nakamura N, Miyazawa C. EPR dose reconstruction for Russian nuclear workers. *Health Physics* 2000 (January); 78(1):15–20. (RERF Report 4-99)
See RPs 8-93 and 1-92, Cytogenetic Studies.

RP 10-86 Radiation dose estimates using tooth samples. Part 1. Collection of tooth samples from A-bomb-exposed people in Hiroshima and

Nagasaki

Nakamura N (G)

The purpose of this research protocol is to collect A-bomb survivors' teeth extracted for medical reasons. RERF has not been involved in Nagasaki collections because before this protocol was approved in 1986, the Nagasaki University group had already sent letters to proximally exposed individuals requesting that they donate their extracted teeth. Recently, nearly 100 teeth have been received each year from Hiroshima survivors, giving rise to more than 900 specimens. About 30% to 50% of collected materials are suitable for subsequent study.

RP 18-59 Shielding survey and dosimetry study

Fujita S (S), Funamoto S (S), Preston DL (S), Cullings H (S), Watanabe T (EH)

See ABCC Technical Report 7-67 for full text.

The DS86 Dosimetry System provides the dose estimates that are used as the basis for all current RERF analyses of radiation effects. Computation of individual doses requires computer programs and data bases developed for the US-Japan Joint Committee for Reassessment of Atomic-bomb Dosimetry, additional computer programs developed at RERF, and extensive data on location and shielding of atomic-bomb survivors at the time of the bombings. In early 1995, the DS86 computer programs and data bases were moved to RERF's new workstation-based computer system. Fundamental installation and validation of the DS86 system on the new computers is complete. However, a major effort to review and restructure all dose-estimation-related data continues. The review has included development of an expanded comprehensive roster of persons alive at the time of the bombings whose dose estimates and exposure status are relevant to RERF studies. This roster, which includes members of the LSS cohort, mothers of members of the *in utero* cohort, and parents of F₁ cohort members, contains about 250,000 people (roughly 100,000 people more than the current DS86 master list). Shielding and acute effects data have been reviewed and placed in relational database tables, and a major goal in designing the new tables has been the development of documented and consistent data on the nature of the shielding and acute injuries for all cohort members. The new information has been incorporated into the main RERF data base. Documentation of the implementation and use of the DS86 system at RERF is incomplete, but we hope to complete an updated version within the year. We are also nearing completion of a program that would allow researchers outside RERF to compute DS86 doses estimates based on simple descriptions of (hypothetical) distance and shielding conditions.

In the decade since the introduction of DS86, it has become apparent that there are problems with both the DS86 neutron- and gamma-dose estimates in Hiroshima. In addition, a reassessment of the chromosome aberration data for Nagasaki survivors suggests that DS86 estimates for Nagasaki factory workers are too large. In response to a letter in *Radiation Research*, we published an assessment of the potential impact of changes in the Hiroshima neutron doses on cancer risk estimates. A

paper about the chromosome aberration data for Nagasaki survivors has been prepared for publication. We are making progress on the DS86 measurement data base, which now includes data on almost 600 published measurements of gamma-ray and neutron activation. Dr. Cullings, who came to work at RERF in the fall of 1999, has primary responsibility for the development of this data base and analyses of the activation measurement data. These data are being used in the US-Japan assessment of measurement quality being carried out in conjunction with the formal dose reassessment. These analyses are being carried out by RERF staff on behalf of the NAS dosimetry committee.

In December 1998 Drs. Lowder, Maruyama, and Cullings visited laboratories in Hiroshima and Kanazawa Universities and at NIRS in Japan to obtain direct information on the nature of the DS86-related measurements. This group also visited SAIC in January 1999 to discuss aspects of the DS86 computations. In December 1999 Drs. Cullings and Maruyama visited Dr. Nakanishi at Kanazawa University for further discussions of measurement issues. In January 2000, Drs. Fujita, Cullings, and Preston met with Drs. Kaul and Egbert of SAIC for discussions on the computation of updated DS86 estimates for the physical samples being used in the dose reassessment and the use of mapping (GIS) software for studying shielding issues. As a result of these discussions, RERF has acquired GIS software and has developed detailed maps showing survivor and physical sample locations. The software is also being used to identify discrepancies between the old (US Army) and new city maps.

The U.S.-Japan Joint Committee met in May 1996 to discuss the neutron issue, and data on the factory workers' dose estimates problem was brought to the committee attention at that time. The U.S. has created a new dosimetry committee managed by NAS. This committee met for the first time in June 1998. Both Drs. Fujita and Preston made presentations to the committee at that time and at subsequent meetings in January 1999 and January 2000. In March 2000 RERF hosted an international meeting on DS86 that involved Japanese, US, and European scientists to discuss the dose reassessment. The major areas on which the reassessment is focusing are: a) the possibility of distance-dependent modifications to Hiroshima neutron doses as suggested data from various activation measurements; b) new computations based on improved computer codes (including three dimensional transport models) and improved theoretical models for the bombs; and c) updated and more complete descriptions of survivor shielding (including efforts to deal with the Nagasaki factory worker issue, allowance for the effects of local terrain shielding, and incorporation of additional data on frontal shielding for people exposed in houses or other light structures). The consensus of the workshop participants was that efforts need to be made to complete DS86-related activation measurements in the near future, to complete a report on issues related to uncertainties and possible biases in these data, and to develop and review an updated survivor dosimetry system over the next two years.

RP 18-59 Publications

- ◆ Endo S, Iwatani K, Oka T, Hoshi M, Shizuma K, Imanaka T, Takada J, Fujita S, Hasai H. DS86 neutron dose: Monte Carlo analysis for depth profile of ^{152}Eu activity in a large stone sample. *Journal of Radiation Research* 1999 (June); 40(2):169–81.
- ◆ Fujita S, Watanabe T. Collection of materials exposed to atomic bomb radiation in Hiroshima. FY-1999 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japanese Public Health Association); 2000 (March), pp 50–2. (Japanese)
- ◆ Hoshi M, Endo S, Takada J, Ishikawa M, Nitta Y, Iwatani K, Oka T, Fujita S, Shizuma K, Hasai H. A crack model of the Hiroshima atomic bomb: Explanation of the contradiction of “Dosimetry System 1986”. *Journal of Radiation Research* 1999 (December); 40(Suppl):145–54.
- ◆ Taira S, Maruyama T, Preston DL, Fujita S. Study of the reassessment of A-bomb radiation dosimetry. FY-1999 Welfare Science Research Subsidy Report of Welfare Science Special Research Projects. Reassessment of A-bomb Radiation Dosimetry System and Study of Health Effects. Hiroshima: Study Team of the Reassessment of A-bomb Radiation Dosimetry System and Health Effects; 2000 (March 31), pp 8–23. (Japanese)

Research Protocols 5-91, 8-87, 8-86, 7-86 Medical Dosimetry Studies

In any assessment of atomic-bomb radiation effects, the contribution of medical radiation exposures must be considered. Information concerning therapeutic and diagnostic radiation exposures has been obtained by interviewing Adult Health Study participants. To determine organ doses, some of the medical radiation exposures have been experimentally reproduced using technical exposure factors obtained from hospital and clinic surveys. Information concerning medical radiation exposure is useful for determining the relative amounts of medical and atomic-bomb radiation doses received by survivors.

RP 5-91 (Addendum to RP 7-81) Radiation-therapy-related cancer among Life Span Study subjects

Kato K, Antoku S, Sawada S, Yamada M (CH), Fujiwara S (CH), Kodama K, Mabuchi K (EH)

RP 8-87 (Addendum to RP 8-84) Organ doses from medical X-ray exposures

Kato K, Sawada S, Antoku S, Russell WJ, Fujita S (S), Yamada M (CH), Fujiwara S (CH), Kodama K

RP 8-86 Ionizing radiation exposure for medical reasons reported by Adult Health Study participants, Hiroshima and Nagasaki

Yamada M (CH), Fujita S (S), Fujiwara S (CH), Kodama K

RP 7-86 Doses to Adult Health Study participants from RERF radiological examinations, Hiroshima and Nagasaki

Yamada M (CH), Fujita S (S), Kato K, Fujiwara S (CH), Kodama K

Collaborative and Institutional Publications

The following manuscripts are not based on research connected to specific protocols. Rather, they represent collaborative work and institutionally authored publications. They are arranged by department, and a separate section is included for Chernobyl-related research.

Directors

- ◆ Forrow L, Sidel VW (Supervised and commented by Nagataki S). Medicine and nuclear war: From Hiroshima to mutual assured destruction to abolition 2000. JAMA (Japanese version) 1999 (April 15); 4:103-11. (Japanese)
- ◆ Kawasaki E, Yamaguchi Y, Nagataki S. Insulinitis in an autoimmune-mediated patient originally classified as having type 2 diabetes. Diabetes Care 1999 (April); 22(4):541-2.
- ◆ Nagataki S. Health effects of radiation. Gen-ankyo Dayori (Tidings of Nuclear Safety Research Association) 2000 (February); No. 174:1-2. (Japanese)
- ◆ Nagataki S. Reassessment of A-bomb radiation dosimetry system and study of health effects. FY-1999 Welfare Science Research Subsidy Report of Welfare Science Special Research Projects. Reassessment of A-bomb Radiation Dosimetry System and Study of Health Effects. Hiroshima: Study Team of the Reassessment of A-bomb Radiation Dosimetry System and Health Effects; 2000 (March 31), pp 1-7. (Japanese)
- ◆ Nagataki S. The comment of the chairperson on the symposium "Research on late atomic-bomb effects and welfare of atomic-bomb survivors—importance, reconsideration, and prospects." Hiroshima Igaku (Journal of the Hiroshima Medical Association) 2000 (March); 53(3):153. (Proceedings of the 40th Late A-bomb Effects Research Meeting, 1999) (Japanese)
- ◆ Nagataki S, et al. A-bomb Disease Research Project with Support from the Health and Welfare Ministry Research Entrustment Fund. Studies on A-bomb diseases: Summary report. FY-1999 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japanese Public Health Association); 2000 (March), pp 3-6. (Japanese)
- ◆ Nagataki S, Kasuga M. A talk on research and its background. Diabetes Frontier 1999 (June); 10(3):377-86. (Japanese)
- ◆ Sera Y, Kawasaki E, Abiru N, Ozaki M, Abe T, Takino H, Kondo H, Yamasaki H, Yamaguchi Y, Akazawa S, Nagataki S, Uchigata Y, Matsuura N, Eguchi K. Autoantibodies to multiple islet autoantigens in patients with abrupt onset type 1 diabetes and diabetes diagnosed with urinary glucose screening. Journal of Autoimmunity 1999 (September); 13(2):257-65.

Directors and Clinical Studies, Hiroshima

- ◆ Nagataki S, Neriishi K. Issues involved in long-term follow-up of persons after radiation exposure. Haraguchi Y, Tomoyasu Y, Kojima M, eds. Nuclear or Radiation Disaster: A Simulation Model and a Scenario for Disaster Drills and a Manual-2000. Tokyo: The Clinical Research Institute, National Hospital Tokyo Disaster Medical Center; 1999 (December), pp 74-7. (Japanese)

Clinical Studies, Hiroshima

- ◆ Fujiwara S. Liver diseases among A-bomb survivors. FY-1999 Welfare Science Research Subsidy Report of Welfare Science Special Research Projects. Reassessment of A-bomb Radiation Dosimetry System and Study of Health Effects. Hiroshima: Study Team of the Reassessment of A-bomb Radiation Dosimetry System and Health Effects; 2000 (March 31), pp 78-83. (Japanese)
- ◆ Neriishi K. Latest findings of ophthalmological diseases. FY-1999 Welfare Science Research Subsidy Report of Welfare Science Special Research Projects. Reassessment of A-bomb Radiation Dosimetry System and Study of Health Effects. Hiroshima: Study Team of the Reassessment of A-bomb Radiation Dosimetry System and Health Effects; 2000 (March 31), pp 84-90. (Japanese)
- ◆ Yamada M. Study of benign tumors. FY-1999 Welfare Science Research Subsidy Report of Welfare Science Special Research Projects. Reassessment of A-bomb Radiation Dosimetry System and Study of Health Effects. Hiroshima: Study Team of the Reassessment of A-bomb Radiation Dosimetry System and Health Effects; 2000 (March 31), pp 51-6. (Japanese)

Clinical Studies, Hiroshima, Epidemiology, Hiroshima, and Statistics

- ◆ Fujita Y, Kodama K, Kasagi F, Fujita S, Kishimoto M, Tanihara S, Ojima T, Oki I, Nakamura Y, Yanagawa H, Nose T. Building aging level indices based on ability to perform personal care and household management activities. Nippon Eiseigaku Zasshi (Japanese Journal of Hygiene) 1999 (July); 54(2):467-73. (Japanese)
- ◆ Kodama K, Toshima H, Yazaki Y, Toyoshima H, Nakagawa H, Okada R, Kitabatake A, Serizawa T, Tanaka H, Hosoda S, Yano K, Yokoyama M, Fujita Y, Kasagi F, Yokoyama T, Tanaka H, Kawamura T, Ohno Y, Hashimoto T. Life-style related factors and idiopathic dilated cardiomyopathy. A case-control study using pooled controls. Journal of Epidemiology 1999 (November); 9(5):286-96.

Epidemiology, Hiroshima and Nagasaki, and Radiobiology

- ◆ Inai K, Yamashita S, Tanaka H, Dohi H, Fujii S, Shibata Y, Takamura N, Naito S, Fujita Y, Kyoizumi S, Hirai Y. Storage of biological samples: Summary report. FY-1999 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japanese Public Health Association); 2000 (March), pp 7-33. (Japanese)

Genetics

- ◆ Nakamura N. Future directions of low dose-low dose rate studies. Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications) 1999 (June); 34(2):243-50. (Japanese)

◆ Nakamura N. Genetic effects of atomic-bomb radiation: Past, present and future (Review). Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications) 1999 (June); 34(2):153–69. (Japanese)

◆ Nakamura N. Genetic effects of atomic-bomb radiation—past, present, and future. Hiroshima Igaku (Journal of the Hiroshima Medical Association) 2000 (March); 53(3):147–9. (Proceedings of the 40th Late A-bomb Effects Research Meeting, 1999) (Japanese)

◆ Tauchi H, Endo S, Eguchi-Kasai K, Furusawa Y, Suzuki M, Matsuura S, Ando K, Nakamura N, Sawada S, Komatsu K. Cell cycle and LET dependence for radiation-induced mutation: A possible mechanism for reversed dose-rate effect. Journal of Radiation Research 1999 (December); 40(Suppl):45–52.

Radiobiology

◆ Hoffmann GR, MacPhee DG. Editorial: Reflections of Zhores Medvedev. Mutation Research 2000 (January); 462(1):1–2.

◆ Ogawa T, Hayashi T, Kyoizumi S, Ito T, Trosko JE, Yorioka N. Up-regulation of gap junctional intercellular communication by hexamethylene bisacetamide in cultured human peritoneal mesothelial cells. Laboratory Investigation 1999 (December); 79(12):1511–20.

◆ Trosko JE, Chang CC, Wilson MR, Upham B, Hayashi T, Wade M. Gap junctions and the regulation of cellular functions of stem cells during development and differentiation. Methods 2000 (February); 20(2):245–64.

Statistics

◆ Barlow WE, Ichikawa L, Rosner D, Izumi S. Analysis of case-cohort designs. Journal of Clinical Epidemiology 1999 (December); 52(12):1165–72.

◆ Pierce DA, Peters D. Improving on exact tests by approximate conditioning. Biometrika 1999 (June); 86(2):265–77.

Statistics and Clinical Studies, Hiroshima

◆ Kasagi F, Kodama K. Prevalence and incidence of acute myocardial infarction in Japan. Shindan to Chiryo (Diagnosis and Treatment) 1999 (September); 87(9):1622–7. (Japanese)

◆ Kasagi F, Kodama K. Prevalence of angina pectoris in Japan. Shindan to Chiryo (Diagnosis and Treatment) 1999 (September); 87(9):1493–7. (Japanese)

RERF-authored Articles

◆ RERF. RERF bibliography of publications, 1998. Hiroshima Igaku (Journal of the Hiroshima Medical Association) 2000 (February); 53(2):131–5. (Japanese)

◆ RERF. RERF directors, supervisors, and scientific councilors (as of August 1999). Hiroshima Igaku (Journal of the Hiroshima Medical Association) 1999 (October); 52(10):932. (Japanese)

Chernobyl-related Research (Epidemiology, Nagasaki)

◆ Yamashita S, Shibata Y, Hoshi M, Fujimura K, et al. Results of medical examinations of children exposed to radiation from the Chernobyl nuclear power plant acci-

dent—the Chernobyl Sasakawa Health and Medical Cooperation Project 1991–1996 (I). Hoshasen Kagaku (Radiological Sciences) 1999 (September); 42(10):303–9. (Japanese)

◆ Yamashita S, Shibata Y, Hoshi M, Fujimura K, et al. Results of medical examinations of children exposed to radiation from the Chernobyl nuclear power plant accident—the Chernobyl Sasakawa Health and Medical Cooperation Project 1991–1996 (II). Hoshasen Kagaku (Radiological Sciences) 1999 (October); 42(11):338–48. (Japanese)

◆ Yamashita S, Shibata Y, Hoshi M, Fujimura K, et al. Results of medical examinations of children exposed to radiation from the Chernobyl nuclear power plant accident—the Chernobyl Sasakawa Health and Medical Cooperation Project 1991–1996 (III). Hoshasen Kagaku (Radiological Sciences) 1999 (November); 42(12):381–6. (Japanese)

Chelyabinsk-related Collaborative Research (Statistics)

◆ Shilnikova NS, Preston DL, Vassilenko EK, Gilbert ES, Ron E, Koshurnikova NA. Cancer risk among workers at the Russian nuclear complex “Mayak.” In: Moriarty M, Mothersill C, Seymour C, Edington M, Ward JF, Fry RJM, eds. Radiation Research. Volume 2: Proceedings. Lawrence, Kansas, USA: Allen Press; 2000, pp. 766–9. (Proceedings of Eleventh International Congress of Radiation Research, Dublin, Ireland, 18–23 July 1999)

Manuscript in Press (Radiobiology)

✂ Ban S. Mitochondrial DNA-defective cells for the cellular life-science study. Igaku no Ayumi (Journal of Clinical and Experimental Medicine).

Collaborative and Institutional Oral Presentations

The following oral presentations were not linked to specific research protocols but represent collaborative work with outside organizations and general research activities. They are arranged by department.

Directors

- ❖ Nagataki S. Quantitative analysis of radiation effects: A paradigm for studying health effects of environmental disorders. *The 3rd Japan-France Workshop on Radiobiology, Imaging and Environmental Sciences*, 10–12 November 1999, Chiba, Japan
- ❖ Nagataki S. Studies at Radiation Effects Research Foundation. *Bridging Radiation Policy and Science*, 1–5 December 1999, Virginia, USA
- ❖ Nagataki S. Health effects of radiation—atomic bombs, nuclear power plant accidents, and Tokaimura. *The 31st Special Seminar Concerning the Safety of Nuclear Power Plants*, 16–18 February 2000, Tokyo, Japan

Clinical Studies, Hiroshima

- ❖ Hakoda M, Kamatani N. Fc binding activity encoded by every IgG4 molecule. *The 29th Annual Meeting of the Japanese Society for Immunology*, 1–3 December 1999, Kyoto, Japan

Epidemiology, Hiroshima

- ❖ Koyama K. The healthy worker effect in a long-term follow-up population. *The 22nd Meeting of the Japanese Society of Cancer Epidemiology*, 15 July 1999, Tokyo, Japan
- ❖ Koyama K. Disease prevention and epidemiology. *The 8th Japan Preventive Nephrology and Urology Meeting*, 16–17 July 1999, Kurashiki, Okayama, Japan
- ❖ Fujita Y, Kodama K, Kasagi F, Fujita S, Yanagawa H, Nose T. Study of aging level indices based on functional status. *The 15th Scientific Meeting of the International Epidemiological Association*, 31 August–4 September 1999, Florence, Italy

Statistics

- ❖ Kasagi F, Kodama K, Okayama A, Ueshima H. Estimation of the effects of population and high-risk strategies on nationwide downward shift in blood pressure level in Japan. *The 10th General Meeting of Japan Epidemiological Association*, 27–28 January 2000, Yonago, Tottori, Japan

Genetics

- ❖ Nakamura N. Atomic-bomb survivor cancer data and their interpretation. *The 42nd Annual Meeting of the Japan Radiation Research Society*, 1–3 September 1999, Hiroshima, Japan

Radiobiology

- ❖ Ban S. Mitochondrial genome importance in X-ray-induced apoptosis and apoptotic repair. *The 11th Inter-*

national Congress of Radiation Research, 18–23 July 1999, Dublin, Ireland

Scientific Lectures and Seminars Presented at RERF

The following presentations were made during the fiscal year by researchers internal and external to RERF at RERF's Hiroshima laboratory. They appear in chronological order.

14 April 1999, *Carmel Mothersill*, director, Radiation Science Centre, Dublin Institute of Technology, Dublin, Ireland: "Radiation-induced genomic instability in normal human epithelial tissue"

17 May 1999, *P. S. Chauhan*, head of Cell Biology Division, Bhabha Atomic Research Center, Department of Atomic Energy, Government of India, Mumbai, India: "Genetic risks of environmental agents: Role of human epidemiology with radiation as a model (cytogenetic, malformation, and mini- and microsatellite analysis on Kerala population)"

28 May 1999, *Akira Asano*, associate professor, Division of Mathematical and Information Sciences, Faculty of Integrated Arts and Sciences, Hiroshima University, The 175th Hiroshima Statistics Study Group: "Texture analysis using mathematical morphology"

2 June 1999, *Tony Hayter*, associate professor, Department of Industrial Engineering, Georgia Institute of Technology, Georgia, U.S.A.: "An introduction to multiple comparisons data analysis with examples"

25 June 1999, *Donald A. Pierce*, senior scientist, Department of Statistics, RERF, The 176th Hiroshima Statistics Study Group: "Development of multi-stage models for cancer"

28 June 1999, *Song-Feng Wang*, secretary general, Republic of China Atomic Energy Council, Taipei, Taiwan: "Mitigation and prevention of the ^{60}Co -contaminated rebar incident"

22 September 1999, *Jacob A. Brody*, professor, University of Illinois at Chicago School of Public Health, Illinois, U.S.A.: "Age-associated diseases and conditions: Implications for decreasing late life morbidity"

30 September 1999, *Shankar Menon*, programme coordinator, Organization for Economic Cooperation and Development/Nuclear Energy Agency, Sweden: "The regulation of recycling of radioactively contaminated material"

1 October 1999, *Kenichi Satoh*, research associate at the Department of Environmetrics and Biometrics, Research Institute for Radiation Biology and Medicine, Hiroshima University, The 177th Hiroshima Statistics Study Group: "Modification of AIC-type criterion in multivariate linear regression with a future experiment"

18 October 1999, *Kiyoshi Miyagawa*, professor, Department of Molecular Pathology, Research Institute for Radiation Biology and Medicine, Hiroshima University: "The BRCA/RAD protein complex: Linkage of double-strand break repair to tumor formation"

18 October 1999, *Robert Ullrich*, Vincent P. Collins distinguished professor, Radiation Oncology Research, director of the Biology Division, Department of Radiation Oncology, University of Texas Medical Branch, Texas, U.S.A.: "Radiation-induced genomic instability and radiation carcinogenesis"

29 October 1999, *Masaaki Matsuura*, associate professor, Department of Environmetrics and Biometrics, Research Institute for Radiation Biology and Medicine, Hiroshima University, The 178th Hiroshima Statistics Study Group: "Survival analysis for dynamic population and carcinogenesis modeling"

10 November 1999, *Andrew J. Grosowsky*, associate professor, Environmental Toxicology Program, University of California, California, U.S.A.: "Radiation-induced genomic instability"

15 November 1999, *Masahiro Sugawara*, professor, Department of Medicine, University of California at Los Angeles School of Medicine, Center for the Health Sciences, California, U.S.A.: "Future aspect of telomerase"

19 November 1999, *Saeko Kusanobu*, Faculty of Integrated Arts and Sciences, Hiroshima University, The 179th Hiroshima Statistics Study Group: "Spatial smoothing method to reduce stripe noise in Landsat TM images"

24 November 1999, *Shoichiro Tsugane*, chief, Epidemiology and Biostatistics Division, National Cancer Center Research Institute, Chiba: "A population-based cohort on diet and chronic diseases: JTHC study"

8 December 1999, *Samir M. Hanash*, professor, Department of Pediatrics, University of Michigan Medical School, Michigan, U.S.A.: "Integrating genomic and expression analysis in cancer investigation"

24 December 1999, *Eiji Nakashima*, research scientist, Department of Statistics, RERF, The 180th Hiroshima Statistics Study Group: "A regression analysis of a clustered ordered polytomous data—An application of GEE to the arteriosclerosis obliterans (ASO) data"

18 January 2000, *Kanehisa Morimoto*, professor, Department of Social and Environmental Medicine, Course of Social Medicine, Osaka University Graduate School of Medicine: "Lifestyle, chromosome alterations, and immunological potentials"

28 January 2000, *Ryuei Nishii*, professor, Faculty of Integrated Arts and Sciences, Hiroshima University, The 181st Hiroshima Statistics Study Group: "Spatial discriminant analysis based on a penalized likelihood"

31 January 2000, *Lee Frank*, professor of medicine and pediatrics, University of Miami School of Medicine,

Florida, U.S.A.: "Development of the antioxidant defense systems of the lung"

10 February 2000, *Catherine Sauvaget*, research scientist, Department of Epidemiology, RERF: "Health-expectancies in the elderly"

23 February 2000, *Margaret R. Karagas*, associate professor, Department of Community and Family Medicine, Section of Biostatistics and Epidemiology, Dartmouth Medical School, New Hampshire, U.S.A.: "A population-based study of non-melanoma skin cancers in New Hampshire: Incidence trends, radiotherapy exposure and genetic factors"

3 March 2000, *Masamoto Kanno*, professor, Department of Immunology and Parasitology, Hiroshima University School of Medicine: "Chromatin silencing and its function by polycomb group genes—in immune system and tumorigenesis"

6 March 2000, *Kenji Wakai*, lecturer, Department of Preventive Medicine, Nagoya University Graduate School of Medicine: "Seasonal allergic rhinoconjunctivitis and fatty acid intake"

10 March 2000, *Nobuhiro Uchida*, research scientist, Laboratory of Experimental Radiology, Aichi Cancer Center Research Institute: "Mismatch repair and microsatellite instability in esophageal cancer cell"

17 March 2000, *Duncan Thomas*, professor, Department of Preventive Medicine, School of Medicine, University of Southern California, California, U.S.A.: "Age-at-exposure and dose-rate effects for radiation-related cancer: Mechanistic models and measurement errors"

International Collaborative Activities

Participation in International Collaborative Activities by RERF Directors and Staff Members (excluding participation in international scientific meetings)

Chernobyl-related collaborative activities

Japanese Ministry of Foreign Affairs

Kazuo Neriishi, chief of Division of Medicine, Department of Clinical Studies, and Tomonori Hayashi, research scientist of Department of Radiobiology, conducted on-site research and made a report concerned, as part of the exchange program for sending and inviting Chernobyl nuclear plant accident experts supported by the Japanese Ministry of Foreign Affairs. (Minsk, Republic of Belarus, September 1999)

Chelyabinsk-related cooperation

RERF-URCRM-FIB-1 Agreement

Under a collaborative agreement between RERF, the Urals Research Center for Radiation Medicine (URCRM, Chelyabinsk, Russian Federation), and Branch N1 of the Institute of Biophysics (FIB-1, Ozyorsk, Russian Federation), Dale L. Preston, chief, Department of Statistics, visited Russia twice and conducted analyses in collaboration with researchers at URCRM and FIB-1. (Chelyabinsk and Ozyorsk, Russian Federation, June–July 1999 and March 2000) (See the following description of the collaboration.)

Epidemiologic Studies of the Mayak and Techa River Cohorts in the Russian Federation (NIH Contract N01-CP-81034)

Primary Investigators: Ron E (NCI), Gilbert E (NCI), Preston DL (RERF), Mabuchi K (RERF), Koshurnikova N (FIB-1), Mushkacheva G (FIB-1), Kossenko M (URCRM)

The contract between RERF, National Cancer Institute (NCI), FIB-1, and URCRM supports improvements to the epidemiological follow-up and data-risk estimation procedures for the Techa River resident and Mayak worker cohorts. In 1997, the contract was expanded to include a small-scale clinical pilot study related to thyroid function in adults who were young children living in Ozyorsk at the time of the releases of ^{131}I in the early and mid-1950s. Work carried out during the initial three-year contract (which ended in September 1998) resulted in significant improvement in the completeness and quality of follow-up data for the two main cohorts. In the fall of 1998, the contract was extended for three more years. A brief paper on solid cancer risks in the Mayak worker cohort was published this past year. We have now begun analyses of leukemia and solid cancer risks (including some comparisons with Life Span Study results) in both the Mayak and Techa River cohorts using updated follow-up data. We anticipate the publication of several more papers over the next year or two.

Semipalatinsk-related collaborative activities

Research Institute for Radiation Biology and Medicine, Hiroshima University

Hiroaki Katayama, assistant chief, Department of Information Technology, had a meeting and collected information for the purpose of establishing a dosimetry data base. (Semipalatinsk, Republic of Kazakhstan, January 2000)

Other collaborative activities

1) Health examination project for the atomic-bomb survivors residing in US (Japan Public Health Association, Hiroshima Prefectural Medical Association, Hiroshima Prefecture, Hiroshima City, Hiroshima Atomic Bomb Casualty Council and RERF)

As noted in the Chronology (see page 5), Saeko Fujiwara, assistant chief, Department of Clinical Studies, and Tadaaki Watanabe, General Affairs Section chief, Secretariat, joined the San Francisco–Seattle team, and Kojiro Koyama, Tumor and Tissue Registry Office chief, Department of Epidemiology, and Kazunari Yamanaka, group leader, Department of Information Technology, joined the Los Angeles–Honolulu team. (USA, May–June 1999)

2) ICRP-related collaborative activities

Donald A. Pierce, research scientist, Department of Statistics, participated in International Commission on Radiological Protection's (ICRP's) activities. (Munich, Germany, March 2000)

3) IAEA-related collaborative activities

After the radiation accident in Thailand, Gen Suzuki, chief, Department of Clinical Studies, Hiroshima, was dispatched as a member of the International Atomic Energy Agency (IAEA) medical team and engaged in the medical treatment of the exposed. (Samutprakarn, Thailand, February 2000)

4) WHO-related collaborative activities

The World Health Organization (WHO) has designated RERF as a WHO Collaborating Center for Radiation Effects on Humans since 1979 and a member of the WHO Radiation Emergency Medical Preparedness and Assistance Network (REMPAN) since 1988. The eighth meeting of REMPAN was originally scheduled for November 1999 at the National Radiological Protection Board in the United Kingdom, but it was postponed to June 2000.

Acceptance of Visitors from Overseas for Briefing and Training

(Total in FY1999: 115 persons, excluding general visitors)

RERF Hiroshima: 88 persons

Visitors related to Hiroshima International Council for Health Care of the Radiation Exposed (HICARE) (23 persons)

20 visitors related to Chernobyl

1) RERF

One specialist from St. Petersburg, Russian Federation on 12 October 1999, one specialist from Kiev, Ukraine from 1 to 12 November 1999 and from 22 November to 10 December 1999, one specialist from Riga, Republic of Latvia from 17 to 18 January 2000, and one specialist from Moscow, Russian Federation from 17 to 19 January 2000.

2) Japanese Ministry of Foreign Affairs

Two specialists from Minsk, Republic of Belarus, from 14 to 18 February 2000, and twelve participants in the Special Open Symposium 2000, "Health Condition of Residents after Chernobyl Nuclear Plant Accident", from Russian Federation, Ukraine, and Republic of Belarus from 17 to 18 February 2000.

3) Hiroshima Branch, Japanese Red Cross Society

Two doctors from Minsk, Republic of Belarus on 17 March 2000.

Two visitors related to Chelyabinsk

One specialist from Chelyabinsk, Russian Federation from 20 to 22 October 1999 and one specialist from Chelyabinsk, Russian Federation from 20 October to 16 November 1999.

One visitor related to Semipalatinsk

One doctor from Semipalatinsk, Republic of Kazakhstan from 2 to 8 June 1999.

Visitor related to HICARE and Hiroshima Prefectural Medical Association (one person)

One specialist from Republic of South Africa on 25 October 1999.

Visitor related to HICARE and Japan International Cooperation Agency (JICA) (one person)

IAEA

One specialist from Sofia, Bulgaria from 24 August to 10 September 1999.

Visitors related to HICARE and Nagasaki Association for Hibakushas' Medical Care (NASHIM) (two persons)

Two visitors related to Chernobyl

Two doctors from Gomel, Republic of Belarus on 29 July 1999.

Visitors related to JICA (58 persons)

1) Japan Chemical Analysis Center

Five trainees from the "Course of Environmental Radioactivity Analysis and Measurement, FY1999" from the South American and Asian countries on 8 October 1999.

2) Faculty of Medicine, Osaka University

Eight trainees from the "Advanced Medical Radiological Technology Course, FY1999" from the Southeast Asian, Middle and Near Eastern, South American, and African countries on 14 October 1999.

3) National Cardiovascular Center Research Institute

Seven trainees from the "Cardiovascular Disease Course, FY1999" from the Southeast Asian, African, and South American countries on 11 November 1999.

4) Japan International Medical Technology Foundation (JIMTF)

13 trainees of clinical laboratory technologists from the Oceanian, South American, Southeast Asian, African, and East European countries on 3 December 1999.

5) Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association

17 trainees from the "Group Training Course in National Tuberculosis Programme Management, FY1999" from the Southeast Asian, South American and Middle and Near Eastern countries on 1 February 2000.

6) Aichi Cancer Center

Eight trainees from the "Community-Based Cancer Prevention Course, FY1999" from the Southeast Asian, Oceanian, and South American countries on 17 March 2000.

Visitor related to the Science and Technology Agency (STA) Fellowship Program through Japan Science and Technology Corporation (JST) (one person)

One doctor from Obninsk, Russian Federation from 15 to 18 February 2000 and from 6 March to 11 April 2000.

Other visitors (two persons)

IAEA and Japanese Ministry of Foreign Affairs

One specialist from Vienna, Austria on 15 April 1999 and one specialist from Vienna, Austria on 19 August 1999.

RERF Nagasaki: 27 persons

Visitors related to NASHIM (two persons)

1) Red Cross Society, Republic of Korea

One doctor from Seoul, Republic of Korea on 23 November 1999.

2) Welfare Society of Atomic-bomb Victims, Republic of Korea

One nurse from Hyopchon, Republic of Korea on 23 November 1999.

Visitors related to JICA (25 persons)

1) National Cancer Center

11 trainees from the "Group Course of Clinical Oncology II, FY1999" from the Southeast Asian, South American and African countries on 16 October 1999.

2) JIMTF

14 trainees from the "Course of Total Medical Imaging and Radiation Therapy Technology, FY1999" from the South American, African and Southeast Asian countries on 25 February 2000.

Section Two: RERF Departments

Organization of the Laboratories

(Departments and their major sections are reflected in this chart. Further subdivisions of sections are not shown.)

Hiroshima

Nagasaki

Departments of Clinical Studies, Hiroshima and Nagasaki

The Adult Health Study (AHS) biennial examinations initiated in 1958 continue. Their primary purposes have been to determine the types of diseases and abnormalities in physiologically or biochemically determined values that may have occurred as a consequence of previous exposure to ionizing radiation and to collate this information with other life experiences and death. The AHS clinical examination is the only point of direct contact with the survivors and functions as a source of biological materials for various special studies.

The AHS has greatly increased in importance in recent years as a result of the accumulation of an enormous body of data from serial medical examinations, with and without the superimposed radiation aspects. Particularly noteworthy is the accumulating evidence of the radiation-dose-related increase in noncancer disease morbidity, such as cardiovascular disease, hyperparathyroidism, thyroid diseases, uterine myoma, and chronic liver disease. The potentially important and largely unexpected relationship could never be properly studied using death certificate data alone. Another unexpected finding is the retrospective evidence that radiation is associated with premature menopause, and this, in turn, may result in earlier onset of other conditions, such as an increase in cholesterol levels and cardiovascular disease. In addition, most recent findings suggest that diabetes mellitus increases with radiation dose among younger survivors in Hiroshima. Given the increasing age of survivors, the time for such studies is limited, and it is imperative that these opportunities be exploited soon.

The Departments of Clinical Studies in Hiroshima and Nagasaki follow exactly the same procedures for clinical examination and laboratory testing (history taking, physical examination, electrocardiography, chest x ray, abdominal ultrasonography, and hematological and biochemical examination as well as computer data entry) for AHS participants based on AHS platform protocol 2-75, allowing analysis of combined AHS cohort data in the two cities.

In addition to their collaborative efforts on RP 2-75, the two departments also cooperate as primary investigators in nine special clinical studies (RPs 2-99, 9-92, 5-92, 3-90, 2-89, 1-89, 11-86, 5-86, and 6-85), four medical dosimetry studies (RPs 5-91, 8-87, 8-86, and 7-86), and a special cancer study (RP 6-86). Nagasaki Clinical Studies is working independently on one special clinical study, RP 1-95, and the Hiroshima department is working on special clinical studies RPs 1-00, 3-91, 3-89, and 4-85 independent of the Nagasaki department.

Department of Clinical Studies, Hiroshima

Gen Suzuki, MD, DMSc, department chief (employed 1 January 2000)

Saeko Fujiwara, MD, DMSc, assistant department chief (senior scientist)

Iwao Osaki, administrative assistant department chief (retired 30 June 1999)

Kanjuro Hidaka, administrative assistant department chief

Division of Medicine

Kazuo Neriishi, MD, DMSc, division chief

Masaharu Nobuyoshi, MD, DMSc, research scientist (resigned 31 March 2000)

Hideko Murakami, visiting scientist (concurrent assignment)

Naomi Masunari, pharmacist (concurrent assignment)

Division of Radiology

Michiko Yamada, MD, DMSc, division chief (senior scientist)

Yuko Morihara, assistant chief of technicians

Kazumi Yamane, associate senior technician

Yuji Yoneyama, clinical radiology technician (concurrent assignment)

Clinical Laboratory

Masayuki Hakoda, MD, DMSc, division chief (employed 1 June 1999)

Shinsuke Matsuura, senior technician

Yae Yamamoto, senior technician

Misae Sora, associate senior technician

Mayumi Inoue, associate senior technician

Takeshi Kishi, clinical laboratory technician

Hidetoshi Tominaga, clinical laboratory technician (employed 1 April 1999)

Sae Karino, laboratory hygiene technician

Ruriko Horiguchi, technician helper (temp)

Nursing Section

Kunie Matsuoka, chief of nurses

Michiko Kuniyama, assistant chief of nurses

Juniko Kato, assistant chief of nurses

Michiko Kuwamoto, assistant chief of nurses

Yukimi Kurihara, assistant chief of nurses

Masae Yamashita, assistant chief of nurses

Mitsuko Shinmoto, senior nurse

Nobuko Shiota, nurse

Clinical Administration Section

Masahiro Wada, section chief

Machiko Nishio, assistant section chief

Naomi Masunari, unit supervisor

Emiko Matsuyama, unit supervisor

Hiromi Nakamichi, unit supervisor

Eiko Matsuura, group leader

Mahoko Fujiwara, group leader

Toshinori Kurisu, group leader

Naoko Yamada, assistant group leader

Yasuko Katayama, assistant group leader

Clinical Contacting Section

Naoya Kagimoto, section chief

Chizuru Kimura, unit supervisor

Haruyo Sasaki, unit supervisor

Sayoko Sakamoto, unit supervisor

Hiromi Tsuji, group leader

Tetsuyuki Hashiba, group leader

Miwako Nakaji, assistant group leader

Kaori Shiba, public health nurse

Part-time Professionals

Ann B Cox, research physiologist, Biotechnology Branch, Radiofrequency Radiation Division, USAF Armstrong

Laboratory

Tetsuaki Hara, assistant, Hiroshima University Hospital
Junko Ikeda, graduate student, Graduate School, Hiroshima University School of Medicine

Kazuo Katoh, assistant professor, Suzugamine Women's Junior College

Masayuki Kinutani, assistant, Hiroshima University Hospital

John T Lett, professor, Department of Radiological Health Sciences, Colorado State University

Norio Mihar, lecturer, Hiroshima University Hospital
Yasuyo Mimori, assistant professor, Third Department of Internal Medicine, Hiroshima University School of Medicine

Kenji Oda, director, Health Control Center, Hiroshima Citizens' Hospital

Kazushi Shigemasa, assistant, Hiroshima University Hospital

Shinji Sudo, research resident, Department of Dementia Research, National Longevity Medical Research Center

Satoru Yamada, head physician, Department of Dermatology, National Kure Hospital

Department of Clinical Studies, Nagasaki

Masazumi Akahoshi, MD, DMSc, department chief

Division of Medicine

Masazumi Akahoshi, MD, DMSc, acting division chief (concurrent assignment)

Midori Soda, MD, research scientist (concurrent assignment)

Tan Tominaga, MD, DMSc, research scientist (concurrent assignment) (resigned 1 November 1999)

Ayumi Hida, MD, research scientist (employed 1 April 1999)

Toshiro Usa, MD, DMSc, research scientist (employed 1 November 1999)

Shin-ichiro Ichimaru, unit supervisor

Division of Radiology

Masazumi Akahoshi, MD, DMSc, acting division chief (concurrent assignment)

Isao Sakamoto, assistant chief of technicians

Ichiro Koba, clinical radiology technician (temp)

Sachie Mizuta, technician helper (temp)

Division of Clinical Laboratories

Masazumi Akahoshi, MD, DMSc, acting division chief (concurrent assignment)

Tan Tominaga, MD, DMSc, division chief (resigned 1 November 1999)

Nobuaki Taira, assistant chief of technicians

Kunio Yamaguchi, assistant chief of technicians

Mikiko Mizogoshi, senior technician

Yoshiro Saitsu, clinical laboratory technician

Noriko Oka, clinical laboratory technician

Takahiro Suga, clinical laboratory technician

Nursing Section

Yumiko Yamashita, assistant chief of nurses

Yuko Watanabe, associate senior nurse

Miwako Tasaki, associate senior nurse

Tomoko Mitsuoka, nurse

Junko Nagatomi, public health nurse (concurrent assignment)

Clinical Administration Section

Kazuyoshi Yamashita, section chief

Megumi Yoshizumi, unit supervisor

Seiko Kogano, unit supervisor

Yoko Sakuma, group leader (retired 30 June 1999)

Kuniaki Matsunaga, group leader

Kaoru Yoshida, clerk (concurrent assignment)

Clinical Contacting Section

Kuniyo Yamaguchi, section chief

Fukiko Kondo, assistant section chief

Atsuko Yada, unit supervisor

Kaoru Yoshida, unit supervisor

Fukiko Kondo, unit supervisor (concurrent assignment)

Sayumi Yamakawa, group leader

Hiroko Shinohara, group leader

Toyomi Takeda, associate senior public health nurse

Junko Nagatomi, associate senior public health nurse

Kaori Miura, public health nurse

Part-time Professionals

Yasuko Amasaki, physician, Amasaki Internal Medicine Clinic

Masayuki Hayashida, graduate student, Graduate School, Nagasaki University School of Medicine

Ryuji Hazama, director, Hazama Internal Medicine Clinic

Kensaku Horikami, graduate student, Graduate School,

Department of Clinical Studies, Hiroshima

Department of Clinical Studies, Nagasaki

Nagasaki University School of Medicine
Akiko Irita, physician, Nagasaki Prefectural Saiseikai Hospital
Kiyotaka Matsuo, physician, Third Department of Internal Medicine, Nagasaki University School of Medicine
Tatsuki Matsuo, assistant department chief (lecturer), Blood Transfusion Department, Nagasaki University Hospital
Naoki Matsuoka, director, Gotokai Hospital
Yasutake Miyamura, physician, Department of Obstetrics and Gynecology, Nagasaki University School of Medicine
Mitsuo Okazaki, graduate student, Department of Obstetrics and Gynecology, Nagasaki University School of Medicine
Shinji Seto, lecturer, Third Department of Internal Medicine, Nagasaki University School of Medicine
Masako Tsuruta, director, Tsuruta Hospital
Yuichi Yakata, medical doctor, Department of Sequela Therapy, Atomic Disease Institute, Nagasaki University School of Medicine

Consultants, Hiroshima and Nagasaki

Shigetoshi Antoku, emeritus professor, Kyushu University
Eric Boerwinkle, professor and center director, Human Genetics Center, The University of Texas Health Science Center at Houston
Kanji Choshi, director, Onomichi General Hospital
Jess D Curb, professor, John A Burns School of Medicine, University of Hawaii
Katsumi Eguchi, professor, First Department of Internal Medicine, Nagasaki University School of Medicine
Haruo Ezaki, consultant, Hiroshima Thyroid Clinic
Shuichi Hatano, professor, Kumamoto Gakuen University
Kuniaki Hayashi, professor, Department of Radiology, Nagasaki University School of Medicine
Yutaka Hosoda, research consultant, Radiological Epidemiology Investigation Center, Radiation Effects Association
Michito Ichimaru, director, SAN-REMO Rehabilitation Hospital
Chikako Ito, director, Health Management and Promotion Center, Hiroshima Atomic Bomb Casualty Council
Katsuhide Ito, professor, Department of Radiology, Hiroshima University School of Medicine
Motonori Izumi, director, Nagasaki Prefectural Saiseikai Hospital
Tadashi Kawai, director, International Clinical Pathology Center
Akiro Kimura, professor, Research Institute for Radiation Biology and Medicine, Hiroshima University
Kazunori Kodama, professor, Hiroshima University School of Medicine
Shigeru Kono, professor, Second Department of Internal Medicine, Nagasaki University School of Medicine
Eric B Larson, medical director, University of Washington Medical Center
Shigenobu Nakamura, professor, Third Department of Internal Medicine, Hiroshima University School of Medicine
Kohsoh Ohama, professor, Department of Obstetrics and

Gynecology, Hiroshima University School of Medicine
Hajime Orimo, director, Tokyo Metropolitan Old-aged Medical Center
Shozo Sawada, director, Hiroshima Prefectural Health and Welfare College
Masao Tomonaga, professor, Department of Sequela Therapy, Atomic Disease Institute, Nagasaki University School of Medicine
Mitsuhiro Tsujihata, director, Nagasaki North Hospital
Toshiaki Usui, principal, Nagasaki Prefectural Health Care School
Lon R White, director, Honolulu Heart and Aging Studies
Michio Yamakido, professor, Second Department of Internal Medicine, Hiroshima University School of Medicine
Shoso Yamamoto, professor, Department of Dermatology, Hiroshima University School of Medicine
Shun-ichi Yamashita, professor, Department of Preventive Medicine, Atomic Disease Institute, Nagasaki University School of Medicine
Hiroshi Yanagawa, vice president, Saitama Prefectural University
Katsusuke Yano, professor, Third Department of Internal Medicine, Nagasaki University School of Medicine
Koji Yoshizawa, professor, Department of Hygiene, Hiroshima University School of Medicine

Expert Advisors, Hiroshima and Nagasaki

Hiroo Dohi, chief, First Department of Internal Medicine, Hiroshima Red Cross A-bomb Hospital
Kingo Fujimura, professor, Department of Pharmacy, Hiroshima University School of Medicine
Motonobu Hayano, assistant professor, Third Department of Internal Medicine, Nagasaki University School of Medicine
Shizuyo Kusumi, vice director, Radiological Epidemiology Investigation Center, Radiation Effects Association
Hideo Sasaki, deputy director, Health Management and Promotion Center, Hiroshima Atomic Bomb Casualty Council

Department of Genetics

The Department of Genetics divides its activities between its biochemical genetics program, which centers on the detection of gene mutational events and the development of the requisite technology for such detection, and its cytogenetics program, which focuses on the occurrence of chromosomal abnormalities in atomic-bomb survivors and their offspring. The two programs are carried out respectively in the biochemical genetics and cytogenetics laboratories.

The biochemical genetics program has concentrated its efforts on developing technologies for detecting germ-cell mutations in survivors' children and establishing B-cell lines from 1,000 parent-child trios, half of which include at least one proximally exposed parent.

In the past, screening for chromosomal abnormalities and gene mutations in germ cells were carried out in the two laboratories by examining the children of survivors selected from the F₁ cohort. However, in the last ten years, the cytogenetics program has focused on screening for somatic chromosome abnormalities in survivors to determine if this methodology provides an effective biodosimetry. The demonstration that physical dose estimation through the application of electron spin resonance (ESR) of tooth enamel obtained from survivors is consistent with cytogenetic methods establishes the chromosome technique as an essential biodosimeter.

In the next five years, ongoing projects will continue in each program. In addition, in the biochemical genetics program, fluorescence *in situ* hybridization (FISH) will be used to physically localize mutated genes, and B-cell lines from the 1,000 trios will be examined by multicolor FISH for chromosomal mutations in the offspring.

Genetics is the primary investigating department for six active protocols, (Biochemical Genetics) RPs 1-97, 7-85, and 5-85; (Cytogenetics) RP 8-93; and (Atomic-Bomb Dosimetry) RPs 1-92 and 10-86.

Biochemical Genetics Program

The primary objective of the biochemical genetics program is to determine whether frequency of new mutations, i.e., uninherited mutations, is elevated in the children born to atomic-bomb-exposed parents in Hiroshima and Nagasaki. Extensive past studies have yielded no evidence of genetic effects of radiation regarding untoward pregnancy outcomes, mortality, chromosome aberrations, and electrophoretic variants of plasma and erythrocyte proteins.

Establishment of cell lines from parents-child trios was recommended by the 1984 Genetic Study Conference. It was planned to immortalize B lymphocytes from 1,300 families, half with (a) proximally exposed parent(s). Cell lines from 964 families (1,928 parents with estimated DS86 doses and 1,399 children) are now established and stored in liquid nitrogen. This is the largest population in the world in terms of both parental gonadal dose and population size for studying radiation on human germ cells. The Human Germline Mutagenesis Workshop held in 1991 recommended starting a pilot study using 100 families (50 exposed to highest doses and 50 control families) to compare various DNA markers or genes for detecting germinal mutations because there was no in-

formation about targets sensitive to radiation mutagenesis. According to this recommendation, microsatellites, minisatellites, and functional single-copy sequences of 124 children and both parents of the 100 families have been examined.

We have developed two techniques to detect deletion mutations in single-copy sequences. One is quantitative measurement of band intensity on Southern filters using chemiluminescent probes, and the other is two-dimensional electrophoresis (2-DE) of DNA followed by a quantitative image analysis of ³²P-labeled spots. Each technique can detect a 50% decrease in band or spot intensity that is derived from deletion of one of the two genes in the autosomes.

Recently, the new "DNA-chip" technology has received keen attention from scientists in different fields, including molecular biology and genetics as well as others. This technology will have a more profound impact than other recent major advances, including DNA sequencing and the polymerase chain reaction. Although this technology needs to be examined for its suitability in detecting genetic effects of radiation, the current applications demonstrate the technique's potential in virtually all areas of molecular genetics. To explore the usefulness and applicability of the DNA-chip method for deletion detection, we decided to terminate the chemiluminescent analysis of Southern filters and have shifted to the new technique.

Cytogenetics Program

The cytogenetics laboratory's research activities are two-fold—first, to collect survivors' cytogenetic information to strengthen DS86 dose estimates by either validating them or demonstrating possible biases in them and, second, to determine whether parental exposure to atomic-bomb radiation increased the frequency of progeny carrying chromosomal abnormality through F₁ cytogenetics studies.

Cytogenetics studies of survivors

While conventional Giemsa staining can detect nearly two-thirds of all reciprocal translocations, chromosome aberration data of each survivor scatter quite widely when regressed on individual DS86 doses. This statistical "overdispersion" could be attributed to physical error in the estimation of DS86 dose or in interview information regarding location and shielding conditions at the time of the bombings (ATB). Or, biological factors, including possible differences in individual radioresponses due to genetic composition, age ATB, sex, and lifestyle, such as smoking habits, might be a cause. To estimate the relative contributions of these possible confounding factors, another biodosimetric marker independent of cytogenetics results has long been sought.

As the frequency of mutations in somatic cells seemed to be a good candidate, the Department of Radiobiology investigated several assays as possible biodosimetric tools. However, of five different assays, only glycophorin A (GPA) in erythrocytes can detect radiation exposure from several decades earlier. Nevertheless, the erythrocyte-based GPA mutation assay does not seem capable of serving as an alternative biodosimetric tool because overdispersion of mutant frequency is even greater than that seen in the chromosome data. This is probably

accreditable to a "jackpot-type" event, an occasional large "payoff-type" event stemming from the relatively small number of bone marrow cells actively producing mature red blood cells or target cells to record radiation effect in GPA assay.

Several laboratories have used ESR to detect radicals in tooth enamel as another indicator of past radiation exposure. Since installation of ESR equipment in the cytogenetics laboratory in January 1995, 100 teeth selected from more than 300 samples donated during the last nearly ten years have been examined. Results show a close association with cytogenetic data from tooth donors, so ESR appears to be a promising alternative means to estimate individual doses, in turn supporting survivors' cytogenetic data. However, since ESR can be applied only to extracted teeth that are rarely obtained whereas chromosome tests require only one to two milliliters of blood, which can be obtained from most survivors, ESR cannot supplant cytogenetics tests but serves to emphasize their results.

Cytogenetics studies of survivors' children

Using conventional staining methods, an extensive cytogenetic survey conducted in the past and involving nearly 16,000 persons (8,000 born to exposed parent/s and 8,000 to unexposed) showed only one *de novo* structural rearrangement in each group, although not all parents of aberration-carrying individuals could be cytogenetically examined. Thus, to date, no evidence of a radiation effect on germ cells has been observed.

Department of Genetics

Nori Nakamura, PhD, department chief
Hideko Murakami, visiting scientist

Biochemical Genetics Laboratory

Norio Takahashi, PhD, laboratory chief
Jun-ichi Asakawa, DPharm, senior scientist
Mieko Kodaira, PhD, associate senior scientist
Inaho Danjo, PhD, research scientist (employed 1 August 1999)
Junko Kaneko, chief of technicians
Eiko Nishikori, assistant chief of technicians
Akiko Miura, assistant chief of technicians
Hideo Omine, assistant chief of technicians
Yuko Shimoichi, assistant chief of technicians
Satomichi Kaneoka, assistant chief of technicians
Shoko Nakagawa, unit supervisor
Yoshiko Nakamoto, senior technician
Kiyomi Naito, group leader
Masaaki Imanaka, associate senior technician
Takahiro Tsuji, associate senior technician
Keiko Sasaki, clinical laboratory technician
Shuji Mishima, clinical laboratory technician
Kaizou Shimanaka, technician helper (temp)
Hiroschi Haba, clerk (concurrent assignment)

Cytogenetics Laboratory

Yoshiaki Kodama, PhD, laboratory chief
Mimako Nakano, DMSc, associate senior scientist
Kazuo Ohtaki, DMSc, research scientist
Masahiro Ito, research scientist
Mayumi Utaka, unit supervisor
Miwa Miura, associate senior technician

Kaori Muramoto, associate senior technician
Hiroyuki Ryukaku, clinical laboratory technician
Tomoko Matsumoto, clinical laboratory technician
Mieko Nakamura, technician helper (temp)

Part-time Professional

Keiko Hiyama, assistant, Second Department of Internal Medicine, Hiroshima University School of Medicine

Consultants

Akio Awa, former associate chief of research, RERF
Tasuku Honjo, dean and professor, Kyoto University School of Medicine
Tadashi Inagami, professor, Vanderbilt University School of Medicine
Yoshiyuki Sakaki, professor, Human Genome Analysis Center, Institute of Medical Science, University of Tokyo
Eiichi Soeda, senior research scientist, Gene Bank, Life Science Tsukuba Research Center, RIKEN Institute of Physical and Chemical Research
Takuro Wada, Director, Matsumoto Dental University

Expert Advisor

Rork Kuick, systems project coordinator, Department of Pediatrics, University of Michigan Medical School

Department of Genetics

Department of Radiobiology

There is a wealth of epidemiological data on the effects of radiation exposure on humans. However, the biological reasons underlying the observed effects of atomic-bomb radiation on the development of human diseases, especially cancer, are unknown. To study the biological mechanisms that may have been affected by exposure to atomic-bomb radiation, we propose that future department research efforts focus on 1) molecular oncology and 2) immunological mechanisms. Breast and thyroid cancers are the two major molecular oncology research projects, and the study of lymphocyte function is our major immunology project. We will also continue to collect biological specimens from A-bomb survivors since we realize that these are essential for future departmental and institutional studies.

The survivors of the atomic bombings were exposed to a wide range of doses of ionizing radiation, and it has been RERF primary objective to ascertain the effects that might have been produced in exposed individuals and their children as a result of that exposure and to relate them to dose and subsequent health effects. Consequently, until recently, RERF research has focused primarily on long-term epidemiological studies of atomic-bomb survivors to ascertain morbidity and mortality of the exposed population, specific investigations on health-related effects that might be related to radiation exposure, and genetic studies to ascertain the mutation rate in children of survivors resulting from radiation exposure. Clearly, there is a need for molecular and cellular studies aimed at revealing the biologic bases underlying this morbidity and mortality. Thus, it is important to bear in mind that if RERF is to achieve its goals, it must strive to maintain a balance between mechanistic studies aimed at understanding the biological bases of radiation-induced changes and the statistical description of risk. RERF must therefore continue to establish a credible and strong program in molecular and cellular research if the biological origins of the radiation-related diseases (and other end points, including pre-disease immunological changes) that may have resulted from A-bomb exposure are ever to be properly understood.

The Department of Radiobiology also intends to use its molecular oncological and immunological skills to study the effects of radiations from sources other than the A-bomb, of course, since any program of the sort with which it is currently engaged would be severely hampered if it were unable to conduct many such investigations.

The Department of Radiobiology current studies are being conducted under 12 active protocols, seven immunology studies (RPs 2-97, 1-93, 4-90, 2-90, 7-89, 7-87, and 3-87), four cell biology studies (RPs 7-93, 3-93, 7-92, and 18-81), and one special cancer study (RP 2-86). We collaborated with other departments or outside researchers on another two.

Department of Radiobiology

Donald G MacPhee, PhD, department chief (employed 21 September 1999)

Masatsugu Yano, visiting scientist

Toshiyasu Iwasaki, visiting scientist

Takahiko Ogawa, visiting scientist

Setsuko Nakamura, unit supervisor

Yoko Takemoto, group leader

Mika Yonezawa, clerk

Cell Biology Laboratory

Keisuke S Iwamoto, PhD, senior scientist (resigned 12 November 1999)

Sadayuki Ban, DMSc, associate senior scientist

Terumi Mizuno, PhD, research scientist (resigned 31 January 2000)

Kiyohiro Hamatani, PhD, research scientist

Naohiro Tsuyama, senior technician

Hachiro Shimba, associate senior technician

Tomoko Shinohara, laboratory hygiene technician

Shiho Yano, clinical laboratory technician

Chiyo Saito, technician helper (temp)

Immunology Laboratory

Seishi Kyoizumi, PhD, laboratory chief

Yuko Hirai, PhD, senior scientist

Yoichiro Kusunoki, PhD, associate senior scientist

Tomonori Hayashi, PhD, research scientist

Hisashi Onishi, assistant chief of technicians

Keiko Takahashi, assistant chief of technicians

Yoshiko Kubo, assistant chief of technicians

Yukari Morishita, senior technician

Kazuaki Koyama, associate senior technician

Mayumi Maki, associate senior technician

Hiroko Nagamura, associate senior technician

Mika Yamaoka, associate senior technician

Mayumi Mukai, laboratory hygiene technician

Fusako Hasegawa, technician helper (temp)

Consultants

Kiyohiko Dohi, director/deputy chairman, Hiroshima Prefectural Hospital

Akihiro Itoh, professor, Research Institute for Radiation Biology and Medicine, Hiroshima University

Osamu Nikaido, dean and professor, Faculty of Pharmaceutical Sciences, Kanazawa University

Ko Okumura, professor, Department of Immunology, Juntendo University School of Medicine

Takao Sekiya, chief, Oncogene Research Department, National Cancer Center Research Institute

Eiichi Tahara, professor, First Department of Pathology, Hiroshima University School of Medicine

Kouichi Tatsumi, chief, Department of Biology and Oncology, National Institute of Radiological Sciences

Department of Radiobiology

Radioisotope Facility

The Radioisotope (RI) Facility is a laboratory where the radiation effects for either germ cells or somatic cells are examined by using liquid radioisotopes. Use of eight types of radioisotopes, including ^{32}P , ^3H , ^{51}Cr , and ^{125}I , is permitted. Recently, ^{32}P has been most frequently used for DNA analyses and ^{51}Cr has also been used for analyses of cell functions.

All of RERF's research departments share the RI facility. Eight persons from the Department of Genetics and 14 from the Department of Radiobiology hold the appropriate registration for authorized use of the RI facility, and three persons are facility administrators responsible for safe conduct of experiments.

Legal regulations concerning the facility's safe management are strictly followed. The Japanese Science and Technology Agency, the country's official supervisory authority for such laboratories, monitors operations and issues advisories when violations occur to preclude recurrences. Upon receipt of such notices, we inspect our facility for any inadequacies and make efforts to improve our operations accordingly.

Radioisotope Facility

Norio Takahashi, PhD, division chief (concurrent assignment)

Yuji Yoneyama, assistant chief of technicians

Toshinori Kurisu, clinical radiology technician (concurrent assignment)

Departments of Epidemiology, Hiroshima and Nagasaki

The Department of Epidemiology plays a central role in the conduct of the long-term follow-up of the Life Span Study (LSS), *in utero*, and F_1 cohorts. The follow-up of these cohorts has long relied on mortality surveillance through the use of the *koseki*, the nationwide family registration system. Recently, cancer incidence data from improved tumor registries in Hiroshima and Nagasaki have become available for the follow-up of these cohorts, adding new dimensions to our studies of radiation cancer risks. Continued follow-up of these cohorts is essential in clarifying the temporal patterns of cancer risk as young subjects reach ages when background cancer risk is increased. In view of the increasing evidence of excess noncancer mortality risk, it is also important to note that continued follow-up will provide further data to help elucidate the nature and magnitude of the noncancer risk. Although the numerous mail surveys conducted in the LSS provide potentially valuable data on the role of nonradiation risk factors, little effort has been made in the past to incorporate these data into RERF analyses. We are placing increased emphasis on the studies of nonradiation risk factors in relation to cancer and noncancer disease risks.

Because of the nature of RERF research, the Department of Epidemiology should and will play a key role in the design and conduct of various interdepartmental research activities. As indicated in the Blue Ribbon Panel report, one of the most important multidisciplinary programs at the present time is the molecular epidemiology of cancer, which will require close interdepartmental and interdisciplinary communication. In addition, the Department of Epidemiology must also play a more active role in generating new ideas for studies to answer questions arising from ongoing epidemiological studies.

The epidemiology research activities in Hiroshima and Nagasaki are carried out following the same research protocols and procedures. The professional staff in the Hiroshima epidemiology department currently consists of seven epidemiologists. Nagasaki's epidemiology department professional staff comprises one epidemiologist and one physician. The epidemiology staff work closely with the statistics department staff in study design, data analysis, and major report preparation; they also work with the Departments of Statistics and Information Technology in database design and development.

During the fiscal year, RERF's Departments of Epidemiology have been involved as primary investigators in work on 20 active research protocols, including three platform protocols spanning five research programs: LSS (RPs 1-75 and 2-61); Histopathology (RP 5-89); F_1 (RP 4-75 [with Statistics]); Tumor Registry (RP 18-61 [and a second study with no RP number]); and Special Cancer Studies (RPs 1-99, 1-98, 3-94, 1-94, 6-93, 4-92, 2-92, 6-91, 2-91, 5-90, 9-88, 8-85, 14-79, 7-76 [with Statistics], and 29-60). We were secondary investigators in many other RP investigations.

Department of Epidemiology, Hiroshima

Kiyohiko Mabuchi, MD, DPH, department chief
Yukiko Shimizu, DMSc, assistant department chief (senior scientist)
Yasuyuki Fujita, MD, DMSc, assistant department chief (resigned 31 March 2000)
Donald A Pierce, PhD, senior scientist (concurrent assignment) (retired 31 December 1999)
Gerald B Sharp, DPH, associate senior scientist
Eric J Grant, research scientist
Catherine S Sauvaget, MD, PhD, research scientist (employed 17 January 2000)
Charles E Land, PhD, visiting scientist
Jun Nagano, visiting scientist
Kyoko Katagami, administrative assistant department chief (retired 30 June 1999)
Yukinobu Nakata, administrative assistant department chief
Kyoko Katagami, advisor (employed 1 July 1999)
Hiroko Moriwaki, laboratory chief
Sonoko Ishii, group leader
Mikiko Hayashi, assistant group leader
Nanayo Irifune, assistant group leader
Manami Konda, research assistant
Miyuki Taguchi, clerk (concurrent assignment)
Ritsuko Sato, clerk (concurrent assignment)

Master File Section

Tadaaki Watanabe, section chief
Chizuko Kato, assistant section chief (resigned 31 December 1999)
Yoshitaka Sakamoto, unit supervisor
Fumiko Nakamura, unit supervisor
Kiyofumi Wakamoto, unit supervisor
Tomoko Yamasaki, unit supervisor
Yukie Kan, group leader
Tomoko Hatakeyama, group leader
Keiko Marumo, assistant group leader
Miyuki Taguchi, clerk
Takashi Oda, investigator (employed 1 April 1999)

Pathology Laboratory

Yasuyuki Fujita, MD, DMSc, acting laboratory chief (concurrent assignment) (resigned 31 March 2000)
Mutsumi Mizuno, assistant chief of technicians
Kayo Sugiyama, clinical laboratory technician

Tumor and Tissue Registry Office

Kojiro Koyama, MD, DMSc, office chief
Kyoko Katagami, acting section chief (concurrent assignment) (retired 30 June 1999)
Shoji Nishio, section chief
Nobuko Shimba, assistant section chief
Masahiro Yamaguchi, unit supervisor
Nobuko Shimba, unit supervisor (concurrent assignment)
Ginko Yamashita, group leader (resigned 31 December 1999)
Noriko Shinozuka, group leader
Kazunari Watanabe, group leader
Kaoru Yamada, group leader
Naomi Dodo, group leader
Yumi Yamane, group leader
Kayo Ohno, assistant group leader
Setsuko Mikami, assistant group leader
Aki Tanida, clerk
Ayumi Nakayama, clerk

Part-time Professional

Hitomi Hayabuchi, associate professor, Department of Human Environment, Fukuoka Women's College

Department of Epidemiology, Nagasaki

Akihiko Suyama, MD, DMSc, department chief (employed 1 October 1999)
Midori Soda, MD, assistant department chief
Koji Nakamura, administrative assistant department chief

Master File Section

Tomoaki Yamashita, section chief
Masanobu Hayashida, unit supervisor
Akiko Nagayoshi, unit supervisor
Koichi Maruta, unit supervisor
Katsunori Urakawa, group leader
Hiroshi Fuchi, group leader
Kazuhiko Tagawa, assistant group leader

Pathology Laboratory

Midori Soda, MD, acting office chief (concurrent assignment)
Hirosuke Tasaki, senior technician
Reiko Matsushima, clinical laboratory technician

Department of Epidemiology, Hiroshima

Department of Epidemiology, Nagasaki

Tumor and Tissue Registry Office

Midori Soda, MD, acting office chief (concurrent assignment)

Makiko Hamamatsu, section chief

Shoko Tani, unit supervisor

Toyonobu Yamada, unit supervisor

Sayuri Hayama, assistant group leader

Masayoshi Yoshida, assistant group leader

Yukihiko Inada, assistant group leader

Computer Management Office

Kenji Inoue, group leader

Koichi Maruta, clerk (concurrent assignment)

Part-time Professional

Kokichi Arisawa, assistant professor, Department of Hygienics, Nagasaki University School of Medicine

Consultants, Hiroshima and Nagasaki

Suminori Akiba, professor, Department of Public Health, Kagoshima University Faculty of Medicine

Takayoshi Ikeda, president, Nagasaki University

Kouki Inai, professor, Second Department of Pathology, Hiroshima University School of Medicine

Hideyo Itakura, professor, Institute for Tropical Medicine, Nagasaki University

Nanao Kamada, director and professor, Research Institute for Radiation Biology and Medicine, Hiroshima University

Suminori Kono, professor, Department of Public Health, Kyushu University School of Medicine

Takashi Maruyama, head, Division of Planning, Radiation Effects Association

Koji Nanba, professor, Hiroshima University Faculty of Integrated Arts and Sciences

Otsura Niwa, director and professor, Radiation Biology Center, Kyoto University

Ichiro Sekine, director and professor, Radiation Effect Research Unit, Atomic Disease Institute, Nagasaki University School of Medicine

Yoshisada Shibata, professor, Radiation Effect Research Unit, Atomic Disease Institute, Nagasaki University School of Medicine

Takashi Taguchi, professor, Second Department of Pathology, Nagasaki University School of Medicine

Eiichi Tahara, professor, First Department of Pathology, Hiroshima University School of Medicine

Expert Advisors, Hiroshima and Nagasaki

Hiromi Egawa, chief, Department of Internal Medicine and Pathology, Hiroshima Asa Citizens' Hospital

Megumu Fujihara, chief, Department of Pathology, Hiroshima Red Cross A-bomb Hospital

Hideharu Fujii, chief, Department of Pathology in Clinical Laboratories, National Nagasaki Central Hospital

Toshiyuki Fukuhara, chief, First Department of Laboratory Medicine, Hiroshima Prefectural Hospital

Aya Hanai, chief, Secretariat, Community-based Cancer Registries

Yuzo Hayashi, vice chairman, Department of Clinical Laboratories, Hiroshima Asa Citizens' Hospital

Michinori Kabuto, head of urban environment and health research team, Regional Environment Division, Na-

tional Institute for Environmental Studies

Kioko Kawai, medical chief, Department of Pathology, Nagasaki Citizens' Hospital

Masao Kishikawa, chief, Department of Morphology, Institute for Development Research, Aichi Human Service Center

Takeshi Matsuo, chief, Department of Pathology, Nagasaki Medical Health Center

Hiroo Matsuura, chief, Department of Pathology, Hiroshima Citizens' Hospital

Elaine Ron, chief, Radiation Epidemiology Branch, National Cancer Institute

Osamu Takahara, chief, First Department of Clinical Laboratories, Nagasaki Red Cross A-bomb Hospital

Masayoshi Tokunaga, psychiatrist, Kodama Clinic

Nobuo Tsuda, medical doctor of pathology, Department of Pathology, Nagasaki Medical Health Center

Shuji Yonehara, senior chief, Division of Pathologic Research Laboratory, Onomichi General Hospital

Department of Statistics

The Department of Statistics plays an important role in virtually all RERF research activities, collaborating and providing guidance to researchers on statistical analyses and data management. Methodological research is aimed at improving understanding of statistical questions raised by RERF data and developing and implementing improved statistical methods to analyze the broad range of data. The Department of Statistics also assists in designing modern data bases to make RERF data more accessible to all RERF researchers. Department members are also responsible for managing dosimetry data and computation of individual dose estimates.

A significant portion of the work of RERF statisticians is concerned with ongoing analyses of Life Span Study (LSS) (RP 1-75) follow-up data in collaboration with the Department of Epidemiology. During the last year, we published the final part of *LSS Report 12* dealing with noncancer mortality between 1950 and 1990. In addition, new papers dealing with the direct evidence for excess solid cancer risks at low doses (based on updated cancer incidence data) and lifetime risks were prepared and are now in press. We have begun work (with the Department of Epidemiology) on *LSS Report 13* that extend analyses of cancer and noncancer mortality data through 1997. We are also working on a new general report on the tumor registry-based cancer incidence with follow-up through 1995. This adds eight years of additional follow-up since the previous general report. We hope to complete the analyses and report writing within the next 18 months.

Members of the *in utero* and F_1 (RP 4-75) cohorts are now reaching ages at which mortality and cancer incidence rates increase markedly. A series of reports on mortality and cancer morbidity among the *in utero*-exposed are nearing completion. Work on similar reports for the F_1 is under way. It is likely that the *in utero* findings will be updated during the coming five years since the number of deaths and cancer cases can be expected to increase rapidly with the lengthening follow-up.

RERF statisticians are also taking a leading role in the analysis and preparation of reports on cancer risks based on detailed site-specific pathology reviews, including those of central nervous system (CNS) tumors (RP 4-92), liver cancer (RP 5-90), and thyroid cancer (RP 6-91). The liver cancer incidence study was published during the past year and a companion report on pathological findings is nearing completion. Follow-up for the CNS and thyroid studies has been extended to 1994. The analyses of the CNS data have been completed and a paper will be submitted for publication in early 2001. Department members continue to work with members of the Department of Epidemiology and Tumor registry staff to develop standards for managing data arising from these studies to ensure that findings are reflected in the tumor registry and are available for future use.

The Department of Statistics is currently involved in developing a general class of statistical models that can describe and suggest patterns in the excess relative risks and excess absolute risks associated with radiation exposure; methods for the joint analysis of site-specific risk

data; procedures to adjust for biases in risk estimates caused by random errors in individual dose estimates; methods to determine the impact of death certificate misclassification on cancer and noncancer risk estimates; methods to adjust for the impact of migration in analyses of LSS cancer incidence data; and statistical issues related to relative biological effectiveness (RBE) estimation for the LSS data; and in the development and application of new "mechanistic" models for radiation carcinogenesis. The work on low dose risks noted above has led to an increased interest in the development of non-parametric smoothing methods that can be used as an alternative to the usual parametric (generally linear and linear-quadratic) models used to describe the dose response functions for cancer and non-cancer risks.

To better utilize RERF's clinical data, the Department of Statistics is applying recent developments in the analysis of complex longitudinal data sets to RERF data and developing more effective ways to store and access the information. Studies in the next few years that integrate epidemiological and clinical data related to the observed association between radiation exposure and noncancer mortality will be of particular importance and will undoubtedly lead to challenging statistical problems.

In conjunction with the Departments of Genetics and Radiobiology, statisticians are engaged in comprehensive final analyses of conventional chromosome aberration data, assessment of data on various somatic mutation assays, and provision of advice and support for a broad range of fairly routine statistical analyses carried out by laboratory researchers. These analyses present a number of statistical challenges, including issues related to overdispersion (due to dosimetry error or unmeasured covariates) and correlated data. These data provide important insights into systematic errors in dose estimates for Nagasaki factory workers. Over the next few years, we anticipate that significant additional statistical support will be needed for analyzing two-dimensional electrophoresis (2-DE) DNA study data (pattern recognition) (RP 7-85), planning and analysis of molecular epidemiological studies (RPs 2-94, 7-93, 3-93, and 7-92), and comparing various potential biodosimeters (RP 1-92).

Work on the development of a family pedigree data base, which had languished for several years, was renewed in the past year. A basic pedigree database structure was developed and data obtained from clinical records are being entered. Continued development of this resource, which will be important in future genetic epidemiology studies, will require the development of acceptable methods for obtaining pedigree information from other sources (including sources outside of RERF).

While the Department of Information Technology is responsible for the actual implementation of RERF's new research data base, the Department of Statistics has been extensively involved in its design and documentation. Areas of statistical concern include: clarification of study population definitions, specification of contents and relationships between individual database tables, identification of appropriate data sources, and, in some cases, development of new coding schemes for specific items. The RERF data base currently includes most of the epidemiological follow-up data and basic dosimetry data for the major cohorts, and efforts are focused primarily on further integration of mail survey, clinical

follow-up, laboratory, and detailed dosimetric data (including shielding history and acute effects data). As data from various mail surveys are incorporated into the data base, the information may be more effectively employed in analyses of confounding and effect modification in RERF's epidemiological studies.

The Department of Statistics manages basic dosimetry data and computes dose estimates for individual survivors. The department has developed an expanded roster of people whose exposure status is of particular interest to RERF (i.e., LSS cohort members, mothers of *in utero* cohort members, and parents of F₁ cohort members) and restructured shielding history and acute effects data. This includes updated cohort definitions and dose estimation procedures. During this year the dosimetry and shielding tables in the research data base were updated and modified in order to take advantage of the new comprehensive roster. We have also developed new guidelines for the use of individual RERF survivor dose estimates and designed database access tools that make it easy for researchers throughout RERF to obtain doses that are computed in accordance with these guidelines. We continue to work on a special version of the basic DS86 software that can be used by anyone interested to compute individual dose estimates. These efforts have two goals. The first is to develop the interface between the dosimetry software and the RERF data base in order to facilitate the computation of new dose estimates once a revised dosimetry system is provided to RERF and to develop an easy-to-use tool that will enable researchers inside and outside RERF to compute DS86 estimates for selected (hypothetical) exposure scenarios.

RERF has been asked to develop and maintain a data base related to physical measurements made as a part of the ongoing DS86 reassessment. At the request of the NAS dosimetry committee we are working on an assessment of the uncertainties and possible biases that could affect the interpretation of the physical measurement data. In March 2000, RERF hosted an international workshop that allowed Japanese, US, and European researchers involved in the dose reassessment to meet to review outstanding issues and develop concrete plans for the dose reassessment activities. It appears that a new survivor dosimetry system will be introduced in the next two to three years. (*Dosimetry work is described in RP 18-59, Atomic-bomb dosimetry.*)

The Department of Statistics currently has primary responsibility for only one regular research protocol-based project (*See RP 4-86, Special Clinical Studies*) and one outside contract. (*See International Collaborative Activities, page 43*)

Overall, Department of Statistics researchers collaborated on 30 research protocols during the fiscal year and were primary authors on 11 publications and secondary authors on six.

Department of Statistics

Dale L Preston, PhD, department chief

Shoichiro Fujita, DMSc, assistant department chief (senior scientist)

Donald A Pierce, PhD, senior scientist (retired 31 December 1999); research scientist (employed 1 January 2000)

John B Cologne, PhD, senior scientist

Fumiyoshi Kasagi, DMSc, senior scientist

Eiji Nakashima, DMSc, research scientist

Harry M Cullings, PhD, research scientist (employed 18 October 1999)

Shizue Izumi, laboratory chief

Ritsuko Sato, group leader

Sachiyo Funamoto, research assistant

Sachiko Tomita, research assistant

Sonoko Ishii, clerk (concurrent assignment)

Nanayo Irifune, clerk (concurrent assignment)

Consultants

Robert Delongchamp, researcher, National Center for Toxicological Research

Yasunori Fujikoshi, professor, Department of Mathematics, Hiroshima University Faculty of Science

George D Kerr, senior research physicist, Oak Ridge National Laboratory

Megu Ohtaki, professor, Department of Environment and Biometrics, Research Institute for Radiation Biology and Medicine, Hiroshima University

Masanori Otake, professor, Faculty of Environmental Science and Technology, Okayama University

Michael Væth, professor, University of Århus

Takashi Yanagawa, professor, Department of Mathematics, Kyushu University Faculty of Science

Expert Advisors

Mieko Koda, former assistant section chief, Department of Information Technology, RERF

Richard Spoto, associate professor, University of Southern California

Daniel O Stram, assistant professor, University of Southern California

Department of Statistics

Department of Information Technology (ITD)

Network

The network environment utilizing a narrow bandwidth based on 10Base-2, which had been a bottleneck at RERF, was replaced with a wide-bandwidth network based on a gigabit ethernet during FY1999. It was a tremendous undertaking to introduce the new network while maintaining the current system. The gigabit switches that were installed on both first and second floors of each building were connected to the central main gigabit switch by fiber optic cables. Outlets for network connection were also installed in each room. As a result, the main gigabit ethernet switch installed in ITD is connected to the secondary gigabit ethernet switches in each building with a speed of 1 Gigabit/second and the secondary switches are connected to personal computers that employees use with a speed of 100 Megabits/second thereby allowing transmission of large files, such as image data files, without affecting other network activities. The new network environment also allows in-house distribution of image data using the Web as well as TV conferences.

Presently the Nagasaki Laboratory is wired with two lines with a connection speed of 192 Kbps and 128 Kbps. This is to prevent access to the two subnetworks—one for the Department of Epidemiology and the Secretariat located on the fourth floor and the other for the Department of Clinical Studies located on the first, second, and third floors—from interfering with each other because accesses to data bases are frequent.

This fiscal year, the network on the fourth floor was changed from the old one based on the 10Base-2 backbone to a new one based on the 100Base-TX backbone with a speed of 100 Megabits/second. This new network is fully capable of transmission of image data, which is to begin in the future after development of an optic filing system, and is unlikely to affect other network activities.

However, the backbone speed in the Department of Clinical Studies is still 10 Megabits/second. This will be upgraded to 100 Megabits/second as soon as possible next fiscal year. This will be done to prevent problems in constructing chest X-ray image filing system (data base). In addition, considering the requirement at the Nagasaki Laboratory for data bases and Internet connection with outside sources, the line speed should be increased at least three times compared with the present speed. We improved the network connectivity by using a communication method such as Asynchronous Transfer Mode (ATM) connection.

Data Base

As for hardware, two new high performance database servers were installed to create a clear distinction between the management data base and the research data base. The entire system was reconstructed. The management data base manages all data ITD handles. Included are data needed exclusively for management purposes. Some data comes directly from departments via the network, and others come through media such as floppy disks. Data in the management data base are frequently added and upgraded. The research data base has been

constructed in accordance with research purposes, and thus the tables therein are likely to be changed depending on studies. However, even when the necessity arises to change the research database table structures, because the original data are stored in the management data base, users can retrieve data from the management database table and easily create tables they want to use. Installation of the above-mentioned two database servers for different purposes has significantly improved the operation of data base and tables from the perspectives of both research and management.

In the previous database system, the basic software packages used as user interfaces for master file, tumor registry and tissue diagnosis data bases have been used over eight years, and cannot keep up with the new operation systems. Therefore the appropriateness of the software used and other options for basic software were reviewed. As a result, a decision was made to shift from the user interfaces running on Unix to the user interfaces running on Windows, and the programs are now being converted to achieve the transition. In this conversion work, efforts are being made to make what was difficult or impossible in the previous software possible. There is now some prospect for the solution to the long pending problem of extended Chinese character (*kanji*) set.

The construction of data bases (mainly for image data) was requested this fiscal year by the Nagasaki Department of Epidemiology as part of an optical filing system, and by the Departments of Clinical Studies in both cities as part of a chest X-ray filing system. The construction of data bases for the Departments of Clinical Studies is to begin next fiscal year. Thus, connection of image information with the conventional data bases has become increasingly important. Therefore, a project was undertaken to develop new user interfaces that allow image processing using the conventional text-based user interfaces. We intend to make standardized modules, whenever possible, which will be shared for image data processing by various programs, and allow use of other similar parts in the existing user interfaces without developing new ones.

Adult Health Study Management System

Previously database servers were installed in Hiroshima and Nagasaki separately for the Adult Health Study management data base (AHS data base). When the network line connecting Hiroshima and Nagasaki was increased from one to two, the servers in Nagasaki were removed, and presently only the servers in Hiroshima are being used to serve the system in both cities. As a result, maintenance and management of the system and development of new programs have become easier; however, the accessibility to data bases from the Nagasaki Laboratory has deteriorated because it largely depends on the line speed. To minimize the deterioration of accessibility caused by the unified database system, the conventional programs were reviewed, and changes were made so that as much processing as possible is done on the servers and personal computers are used to receive the results of the processing only.

There are more than 50 AHS-related programs, and requests for development of new programs are still being made by mainly the Departments of Clinical Studies in

both cities. Some requests require not only development of new programs but also creation of new database tables. Because most of the AHS-related programs involve complicated tables and cards, they were developed using the MS-Access. This makes it necessary for us to check and review the applications we developed each time the software is upgraded. We tried various software packages to solve this problem; however, no software package that is worth changing all applications developed using the MS-Access has been found yet.

Accounting and Payroll Systems

In FY1999 the MS-Access used for personnel management, accounting processing, and payroll processing was replaced with the Sybase database systems in order to efficiently link items in different tables and avoid duplication. As a result, processing speed increased and development of new applications became easier.

The use of MS-Access and customized user interfaces has allowed the avoidance of drastic changes in applications. But review and upgrading were inevitable.

The Sybase systems have made it easier to transfer data between systems and guaranteed smoother operation even with multiply operators simultaneously using a single system.

Areas for Development

There are only ten employees in the ITD Systems Technology Section. Two employees are assigned to network and hardware applications and the remaining eight employees work on applications development and database management. The workload is demanding hence ITD can not afford to allocate time nor employees to the construction of new data bases. ITD has to maintain and manage not only existing data bases but also newly developed ones. With the ever increasing workload an increase in staff size is vital. We strongly recommend the addition of two staff members to meet the needs in the areas of networks and application development-database management.

ITD also has in its charge the RERF Library. A long-standing objective for the Library is computerization. For modernization to take place careful planning and the placement of appropriate personnel is essential.

Department of Information Technology

Tsuneaki Isaka, administrative assistant department chief (retired 30 June 1999)

Hiroaki Katayama, administrative assistant department chief

Michael K Morimoto, research scientist (resigned 21 October 1999)

Akemi Wakamoto, unit supervisor

Systems Technology Section

Hiroaki Katayama, acting section chief (concurrent assignment)

Michio Sunamoto, unit supervisor

Nobuaki Harachi, unit supervisor

Hideaki Murata, unit supervisor

Kazunari Yamanaka, group leader

Masahiko Hasunaka, assistant group leader

Mayumi Tatenishiki, assistant group leader

Keiko Sugita, assistant group leader

Atsushi Miura, computer specialist

Yoko Osaki, computer specialist

Library Section

Ai Yokoyama, assistant section chief

Teruo Matsukawa, unit supervisor

Part-time Professional

Kaori Maeda, lecturer, Information Processing Center, Hiroshima City University

Consultants

Harvard H Holmes, deputy head, Computing Science Research Programs, Computing Services Department, Lawrence Berkeley Laboratory

Jill L Ohara, vice president of operations, Sunhawk.com

Thomas R Slezak, computer scientist, Human Genome Center, Lawrence Livermore National Laboratory

Expert Advisor

Reiji Aibara, assistant professor, Information Processing Center, Hiroshima University

Department of Information Technology

Publication and Documentation Center

The Publication and Documentation Center (PDC) is responsible for disseminating various information, including RERF research findings, to the local, national, and international radiation research community as well as to RERF's current and former employees. PDC accomplishes this task through six primary tools, *RERF Reports*, the *RERF Commentary and Review Series*, *RERF Update*, *RERF Newsletter*, the *RERF Annual Report*, and RERF's English and Japanese parallel web sites. In addition, RERF purchases pages in the *Journal of the Hiroshima Medical Association* to publish research results, bibliographic information, and special reports.

RERF Reports

To replace the in-house Technical Report series, in 1992, RERF began to produce *RERF Reports*. Reprints of journal articles are purchased and bound in *RERF Report* covers with Japanese summaries, and Japanese translation is available for reports on major epidemiological and clinical studies. The series is intended to convey the results of original research carried out at the foundation. Distribution varies according to subject matter, but about 150 copies of each *Report* are sent to Japanese and American governmental ministries and agencies, local hospitals, libraries, and RERF directors and consultants. Twenty research papers were approved for journal publication during this fiscal year, and 14 papers were published in journals. As shown in the table on the next page, requests for 233 *RERF Reports* were received from 29 countries during the fiscal year.

RERF Commentary and Review Series

Reports in the *Commentary and Review Series* are published to rapidly disseminate ideas, discussions, comments, and recommendations on research carried out by RERF scientists. This series also includes working papers prepared for national and international organizations, discussion of research concerning atomic-bomb survivors carried out elsewhere, and, in general, materials of lasting importance to RERF and atomic-bomb-survivor research. Reprints from journals are bound in covers with Japanese summaries and distributed just as are *RERF Reports*. During this fiscal year, an in-house workshop report was approved for publication and is currently in press.

RERF Update

RERF Update is an English-language newsletter, begun in 1989, to inform international radiation researchers of RERF's recent journal publications, institutional news, and ongoing scientific projects. Two issues of *Update* were published in this fiscal year and distributed to more than 1000 persons and institutions free of charge.

RERF Newsletter

Since 1975, the Japanese-language *RERF Newsletter* has been published to disseminate institutional, scientific, and research news. During this fiscal year, six issues were published in the odd-numbered months. Each issue

was sent to about 350 individuals and local media free of charge.

RERF Annual Report

Two hundred and eighty copies of the Japanese-language version and 240 copies of the English-language version of *RERF Annual Report* for the 1998–1999 fiscal year were distributed free of charge to individuals and institutions, including about 110 libraries.

RERF's World Wide Web Site

RERF's new web site was inaugurated in November 1996 and is managed by PDC under the Public Relations Committee and the WWW Editorial Subcommittee. It is intended to communicate research findings to the scientific community and inform the public about radiation effects. Outside researchers can download publicly available data, order RERF publications, and read scientific briefs from *RERF Update*, all on-line over the Internet. For the public, information on radiation effects written by RERF researchers has been edited to a non-technical level.

About ten e-mailings per week are received, mostly from the general public with specific questions about radiation effects or from students seeking information for school reports on the effects of the atomic-bombs, as well as requests for detailed information, data, or collaboration from outside scientists. Six of the data bases used for major study reports, such as the Life Span Study reports, are downloadable. Especially after the criticality accident in Tokai-mura, Ibaraki Prefecture in September, about 20 questions were received partly from the anxious local residents.

Future plans include a searchable on-line data base of all RERF publications and downloadable data. Although there are no specific plans at the moment, Internet publication may eventually replace older forms of publication, such as *Update*, the *Japanese Newsletter*, or various brochures currently produced.

Archive Office

As of 1 October 1999, Margaret A Irwin arrived from the USA as an information specialist and the Archive Office was launched. The major objectives of the office are to establish a sound repository, to write and implement a strategic plan focused on archival record management, preservation, and access in the electronic age for the unique scientific documents of ABCC-RERF.

Journal of the Hiroshima Medical Association

Since 1960, the monthly *Journal of the Hiroshima Medical Association* (*Hiroshima Igaku*) has made available a section for ABCC-RERF research findings. RERF pays for these journal pages, which include research results and bibliographic materials as well as information concerning news of special interest, such as Scientific Council activities. The journal is distributed to about 6400 members of the Hiroshima Prefectural Medical Association, medical libraries, and medical institutions throughout Japan. RERF purchases an additional 70 reprints of journal articles for mailings to individuals, local media, and medical institutions.

PDC's Additional Supporting Role

In addition to the above publication and web activities, PDC supports the whole foundation by assisting in slide production for scientific meetings, taking pictures for major events, such as board of directors meetings and personal certifications, editing manuscripts, providing translation and interpretation services, providing clerical support for the internal review of manuscripts for journal submission, and constructing and maintaining publication data bases to update and disseminate information through the English and Japanese WWW and newsletters on *RERF Reports*, the *RERF Commentary and Review Series*, and other journal publications.

Requests for RERF scientific publications and reprints by country, April 1999–March 2000

Countries	Requests
Japan	97
USA	53
Germany	13
Poland	11
Canada, France, India	6 each
Cuba	5
Spain	4
Belgium, Lithuania, Russia	3 each
Columbia, Czech Republic, Finland, Slovakia, United Kingdom, Yugoslavia	2 each
Argentina, Bulgaria, Chile, Israel, Morocco, The Netherlands, New Zealand, Norway, Portugal, Slovenia, Switzerland	1 each
Total 29 countries	233 requests

PDC

Reiko Sasaki, assistant center chief

Administration and Support Section

Reiko Sasaki, acting section chief and unit supervisor (concurrent assignment)

Tokiko Himori, assistant section chief

Eiko Ishizaki, assistant section chief

Fumie Maruyama, unit supervisor

Naomi Umehara, unit supervisor

Miyuki Hosoya, group leader

Nagi Saito, group leader

Kosaku Okine, group leader

Mutsumi Tanizawa, translator

Margaret A Irwin, information specialist (employed 1 October 1999)

Tomoe Sugiyama, clerk

Editorial and Publications Section

Reiko Sasaki, acting section chief (concurrent assignment)

Kiyoko Yamayoshi, assistant section chief

Yoko Shimokawa, office chief

Yuko Ikawa, office chief

Rosalyn A Vu, chief editor

Kikue Mukae, unit supervisor

Kozue Kaneoka, group leader
Setsumi Harachi, group leader
Hiroshi Haba, clerk

Publication and Documentation Center

Section Three: Report from the Secretariat

Organization of the Secretariat

Hiroshima

Nagasaki

Report from the Secretariat

Personnel

RERF employees totaled 278 as of 31 March 2000, a decrease of 6 compared to a year ago. Eight employees reached mandatory retirement age during fiscal year 1999, but employment of new general employees is being kept to a minimum because of the policy of gradually reducing budgeted positions. (See Tables 1 and 2.)

Table 1a. Full-time personnel as of 31 March 2000

Full-time personnel	Hiroshima	Nagasaki	Total
Directors, Chief of Secretariat	4 (1)	—	4 (1)
Professional Staff	36 (8)	5	41 (8)
General	179 (3)	54	233 (3)
Total	219 (12)	59	278 (12)

Numbers in parentheses are personnel recruited by US National Academy of Sciences.

Table 1b. Other RERF personnel as of 31 March 2000

Department/Division	Consultants	Expert advisors	Part-time professionals	Total
Clinical Studies	32	5	25	62
Genetics	6	1	1	8
Radiobiology	7	0	0	7
Epidemiology	13	16	2	31
Statistics	7	3	0	10
Information Technology	3	1	1	5
Secretariat	2	0	2	4
Total	70	26	31	127

Table 2. Personnel composition as of 31 March 2000

Department/Section	Directors, Chief of Secretariat	Research scientists	Administrative	Manual/general technical	¹ Medical and technical (I)	² Medical and technical (II)	Total
Hiroshima							
Directors	3	—	—	—	—	—	3
Chief of Secretariat	1	—	—	—	—	—	1
Associate Chief of Research	—	—	—	—	—	—	—
Clinical Studies	—	6	16	1	9	11	43
Genetics	—	9	3	2	15	—	29
Radiobiology	—	7	3	2	13	—	25
Epidemiology	—	7	28	—	2	—	37
Statistics	—	7	4	—	—	—	11
Information Technology	—	—	13	—	—	—	13
Publication and Documentation Center	—	—	19	—	—	—	19
Radioisotope Facility	—	—	—	—	1	—	1
Consultant	—	—	—	—	—	—	—
Secretariat	—	—	37	—	—	—	37
Total	4	36	123	5	40	11	219
Nagasaki							
Clinical Studies	—	3	10	1	8	8	30
Epidemiology	—	2	15	—	2	—	19
Secretariat	—	—	10	—	—	—	10
Total	—	5	35	1	10	8	59
Grand Total	4	41	158	6	50	19	278

Note: Of the 158 administrative and clerical staff, 111 are in research units, and 47 are in the Secretariat.

¹Medical and technical (I) includes pharmacists, radiology technicians, and medical technologists.

²Medical and technical (II) includes public health nurses, nurses, and assistant nurses.

Fiscal and Property Report

The total RERF budget for operations was 4,149,645,000 yen, a decrease of 117,516,000 yen over the previous year. The major decreases were 102,327,000 yen in personnel expenses and 15,189,000 yen in operational expenses (Table 3).

The RERF settlement of accounts and balance sheets for FY99 are shown in Tables 4 to 6.

Secretariat, Hiroshima

Kazumasa Kunitoshi, chief of Secretariat

Jun-ichi Nakamura, attached to the Secretariat

Hiroyuki Tominaga, advisor (resigned 31 December 1999)

Richard D Sperry, advisor

General Affairs Section

Toshikazu Ohmori, section chief and unit supervisor (concurrent assignment)

Akiko Enami, chief, Director's Office (resigned 31 March 2000)

Sachiko Nagatani, assistant section chief and unit supervisor (concurrent assignment) (retired 31 December 1999)

Junko Houta, assistant office chief

Yutaka Ogasawara, assistant section chief

Toshiko Takata, assistant section chief and unit supervisor (concurrent assignment)

Yukiko Watanabe, assistant section chief

Sumiko Kumano, unit supervisor

Yutaka Nakamori, unit supervisor

Kimiko Konami, unit supervisor

Ayako Ishibe, group leader

Naohiro Hayakawa, assistant group leader

Rumi Tsuchioka, assistant group leader

Nobuko Shiba, clerk

Hiromi Makino, clerk

Mariko Ogura, clerk (employed 1 January 2000)

Kunie Matsuoka, health supervisor (concurrent assignment)

Table 3. Operating costs (in yen), 1997–1999

Category	Fiscal year		
	1997	1998	1999
Personnel expenses	3,271,083,000	3,367,118,000	3,264,791,000
Operational expenses	803,507,000	900,043,000	884,854,000
Total	4,074,590,000	4,267,161,000	4,149,645,000

Table 4. Settlement of accounts, summary sheet, 1 April 1999–31 March 2000 (All amounts are given in yen.)

Category	Total	Regular account	*Cancer case Life Span Study	*Termination trust fund	*National Academy of Sciences housing
Income					
Subsidy	3,916,726,304	3,916,726,304	0	0	0
Operational income (interest, etc.)	53,098,084	49,420,500	5,306	1,620,708	680,172
Transferred from special account	1,032,226	0	1,032,226	0	0
Entrustment fund	113,425,561	0	50,266,366	0	1,384,117
Carried over from previous year	187,431,613	0	0	184,857,675	1,267,590
Total income	4,271,713,788	3,966,146,804	51,303,898	186,478,383	3,331,879
Expenditures					
Personnel expenses	3,151,018,813	3,054,616,304	15,756,753	74,109,007	0
Operational expenses	1,002,146,977	911,530,500	31,636,762	0	2,768,230
Total expenses	4,153,165,790	3,966,146,804	47,393,515	74,109,007	2,768,230
Balance, income minus expenses	118,547,998	0	3,910,383	112,369,376	563,649

*indicates special account, Δ indicates expenditures in excess of income.

Personnel Section*Hideo Shinoda*, section chief*Fujiko Naito*, assistant section chief and unit supervisor
(concurrent assignment)*Hiroshi Sugino*, unit supervisor*Shoko Ogawa*, group leader**Accounting Section***Akio Ihara*, section chief*Hiroshi Moriwaki*, unit supervisor*Hiroshi Naito*, unit supervisor*Mikio Funaoka*, unit supervisor*Reiko Horimukai*, group leader*Keiichi Tenma*, group leader**Supply and Property Section***Tetsuji Kurihara*, section chief*Kayoko Arakawa*, assistant section chief*Hiroyuki Yamane*, assistant section chief*Kazuyoshi Uchiyama*, unit supervisor*Hiroyuki Ueoka*, unit supervisor*Kenji Nagasawa*, unit supervisor*Tomiko Sasaki*, unit supervisor (resigned 31 December 1999)*Kenji Onishi*, group leader*Yukimitsu Muraoka*, group leader*Masumi Yamada*, group leader*Masamichi Shiraga*, assistant group leader and driver
(concurrent assignment)*Katsusuke Sasaki*, maintenance staff (retired 31 December 1999)

Secretariat, Hiroshima

Secretariat, Nagasaki

Continued from the left page.

*Nagasaki Prefectural Cancer Registry	*Nonsubsidy expenses	*Epidemiologic Study: Mayak/Techa River	*International exchange program	*Liver and Breast Cancers and Adult T-cell Leukemia Study
0	0	0	0	0
0	1,582,370	Δ210,972	0	0
0	0	0	0	0
7,500,000	0	38,930,078	14,695,000	650,000
0	0	1,306,348	0	0
7,500,000	1,582,370	40,025,454	14,695,000	650,000
6,286,255	0	0	0	250,494
1,213,745	1,582,370	38,320,864	14,695,000	399,506
7,500,000	1,582,370	38,320,864	14,695,000	650,000
0	0	1,704,590	0	0

Table 5. Statement of income and expenditures, regular account, 1 April 1999–31 March 2000
(All amounts are given in yen.)

Category	Budget (a)	Settlement (b)	Balance (a) – (b)
Income			
Subsidy income	4,126,901,000	3,916,726,304	210,174,696
Japanese government treasury	2,525,890,000	2,525,890,000	0
US government treasury	1,601,011,000	1,390,836,304	210,174,696
Independent income	22,744,000	49,420,500	Δ26,676,500
Medical exams*	22,744,000	25,612,979	Δ2,868,979
Miscellaneous	0	23,807,521	Δ23,807,521
Total income (A)	4,149,645,000	3,966,146,804	183,498,196
Expenditures			
Personnel expenses	3,264,791,000	3,054,616,304	210,174,696
Salary	3,046,498,000	2,791,724,624	254,773,376
Termination allowance	218,293,000	262,891,680	Δ44,598,680
Operational expenses	884,854,000	911,530,500	Δ26,676,500
Fees and gratuities	79,194,000	34,852,282	44,341,718
Travel, directors and staff	12,775,000	20,594,030	Δ7,819,030
Travel, committee	9,315,000	9,360,539	Δ45,539
Travel, relocation	17,546,000	10,586,963	6,959,037
Travel, overseas	8,946,000	15,508,605	Δ6,562,605
Office and laboratory expenses	690,157,000	748,733,318	Δ58,576,318
Rent, land and buildings	57,667,000	63,044,863	Δ5,377,863
Maintenance and repair	8,461,000	7,665,000	796,000
Taxes	793,000	1,184,900	Δ391,900
Total expenditures (B)	4,149,645,000	3,966,146,804	183,498,196
Balance (A) – (B)	0	0	

*RERF receives a fee for every medical examination of an atomic-bomb survivor, as specified in the Atomic Bomb Survivors' Relief Law.

Δ indicates income or expenditures in excess of budget.

Table 6. Regular account balance sheet as of 31 March 2000 (All amounts are given in yen.)

Category		Amount
Assets		
Current assets:	Cash, deposits	262,587,871
	Accounts receivable	6,822,527
	Accounts prepaid	5,754,241
	Interfund receivable	5,662,686
	Prepayment	1,000,000
	Total current assets	281,827,325
Fixed assets:	Buildings	183,929,460
	Equipment	853,022,486
	Total fixed assets	1,036,951,946
Total assets:		1,318,779,271
Liabilities		
Current liabilities:	Accounts payable (regular account)	32,479,785
	Salary deductions on hand	15,545,176
	Balance of subsidy to be returned to the Japanese government	116,744,723
	Balance of subsidy to be returned to the US government	117,057,641
	Total current liabilities	281,827,325
Fixed liabilities:	Termination allowance reserve fund	0
	Total fixed liabilities	0
Total liabilities:		281,827,325
Property funds	Basic property (buildings)	183,929,460
	Operating property (equipment)	853,022,486
	Total property funds	1,036,951,946
Total liabilities and property funds		1,318,779,271

Employee Health Doctor (part-time)

Keiko Hiyama, assistant, Second Department of Internal Medicine, Hiroshima University School of Medicine

Secretariat, Nagasaki

Yasutaka Ohgushi, assistant chief of Secretariat (retired 31 December 1999)

Hiroshi Ichoda, assistant chief of Secretariat

General Affairs Section

Yasutaka Ohgushi, acting section chief (concurrent assignment) (retired 31 December 1999)

Hiroshi Ichoda, acting section chief (concurrent assignment)

Kayoko Hirano, assistant section chief and unit supervisor (concurrent assignment)

Nami Sakata, unit supervisor

Shigetoshi Hayashi, unit supervisor

Yasuaki Nakamichi, group leader

Sumiko Inada, assistant group leader

Accounting Section

Yasuyuki Takeda, section chief

Tomoko Nishiyama, assistant section chief and unit supervisor (concurrent assignment)

Tomoko Yamaguchi, unit supervisor

Kengo Hosoi, group leader

Yasuaki Nakamichi, guard (concurrent assignment)

Employee Health Doctor (part-time)

Ryuji Hazama, director, Hazama Internal Medicine Clinic

Consultants, Hiroshima and Nagasaki

Hisashi Kodama, director, Kodama Hospital

Shoji Tokuoka, former senior consulting scientist, RERF

Standing Committees as of 31 March 2000

Research Protocol Review Committee

Sheldon Wolff, chairman, vice chairman and chief of research

Nori Nakamura, deputy chairman, chief, Department of Genetics

Shoji Tokuoka, consultant

Saeko Fujiwara, assistant chief, Department of Clinical Studies

Jun-ichi Asakawa, senior scientist, Biochemical Genetics Laboratory, Department of Genetics

Donald G MacPhee, chief, Department of Radiobiology

Seishi Kyoizumi, chief, Immunology Laboratory, Department of Radiobiology

Kiyohiko Mabuchi, chief, Department of Epidemiology

Dale L Preston, chief, Department of Statistics

Masazumi Akahoshi, chief, Department of Clinical Studies, Nagasaki Laboratory

Akihiko Suyama, chief, Department of Epidemiology, Nagasaki Laboratory

Akiko Enami, executive secretary, chief, Director's Office, General Affairs Section, Secretariat

Scientific Reports Review Committee

Sheldon Wolff, chairman, vice chairman and chief of research

Shoji Tokuoka, consultant

Norio Takahashi, chief, Biochemical Genetics Laboratory, Department of Genetics

Seishi Kyoizumi, chief, Immunology Laboratory, Department of Radiobiology

John B Cologne, senior scientist, Department of Statistics

Junko Houta, executive secretary, assistant office chief, Director's Office, General Affairs Section, Secretariat

Human Investigation Committee

Senjun Taira, chairman, permanent director

Kiyohiko Mabuchi, deputy chairman, chief, Department of Epidemiology

Toshio Hisayuki, lawyer

Fumio Kanazawa, professor, Law and Economic Faculty, Okayama College of Commerce

Saeko Fujiwara, assistant chief, Department of Clinical Studies

Mimako Nakano, associate senior scientist, Cytogenetics Laboratory, Department of Genetics

Yuko Hirai, senior scientist, Immunology Laboratory, Department of Radiobiology

Hiroyuki Tominaga, former assistant chief, Secretariat

Kanjuro Hidaka, executive secretary, administrative assistant department chief, Department of Clinical Studies

Library Committee

Nori Nakamura, chairman, chief, Department of Genetics

Saeko Fujiwara, assistant chief, Department of Clinical Studies

Norio Takahashi, chief, Biochemical Genetics Laboratory, Department of Genetics

Yukiko Shimizu, assistant chief, Department of Epidemiology

Donald A Pierce, research scientist, Department of Statistics

Hiroaki Katayama, administrative assistant department chief, Department of Information Technology

Fumie Maruyama, unit supervisor, Administration and Support Section, Publication and Documentation Center

Hideo Shinoda, chief, Personnel Section, Secretariat

Richard D Sperry, advisor, Secretariat

Public Relations Committee

Senjun Taira, chairman, permanent director

Yoichiro Kusunoki, associate senior scientist, Immunology Laboratory, Department of Radiobiology

Shoichiro Fujita, assistant chief, Department of Statistics

Hiroaki Katayama, administrative assistant department chief, Department of Information Technology

Fumie Maruyama, unit supervisor, Administration and Support Section, Publication and Documentation Center

Yutaka Ogasawara, executive secretary, assistant section chief, Director's Office, General Affairs Section, Secretariat

Section Four: Appendices

Scientific Council Meeting

Board of Directors Meeting

Multinational Peer Review

Workshop

Appendix One
Twenty-Sixth Scientific Council Meeting

Recommendations of the 26th Scientific Council Meeting

April 7–9, 1999, Hiroshima

Scientific Councilors: Maurice S Fox (co-chairman), Hiromichi Matsudaira (co-chairman), J Martin Brown, Joe W Gray, Tomio Hirohata, Susan Preston-Martin, Masao Sasaki, Shin-ichiro Ushigome, Yusuke Nakamura (absent), Theodore L Phillips (absent)

Overview

The 26th Scientific Council, chaired by Drs. Matsudaira and Fox, met April 7–9, 1999 in Hiroshima to review the scientific program of the Radiation Effects Research Foundation. During the review, Drs. Fujiwara and Akahoshi presented the Adult Health Study (AHS). Dr. Preston reviewed the current status of the Statistics program. Drs. Kyoizumi and Iwamoto summarized plans for the Department of Radiobiology. Dr. Nakamura reported on two aspects of the Genetics program. Drs. Takahashi and Kusunoki summarized recommendations from recent workshops in clinical genetics and immunology, respectively. Dr. Mabuchi and staff presented their responses to the Epidemiology Peer Review. In addition, Dr. Taira summarized progress and plans for dealing with ethical and tissue acquisition issues associated with the proposed progeny (F_1) study and the ongoing AHS. Finally, Drs. Nagataki and Wolff briefed the council on efforts to develop a 5-year plan to be presented to the Department of Energy (DOE) and the National Academy of Sciences and on efforts to recruit individuals to fill several senior leadership positions at the RERF.

The Scientific Council continues to support the strong focus on characterization of the effects of radiation on exposed individuals and their progeny. It also encourages general scientific investigations of health related issues that take advantage of the unique tissue and epidemiological resources at the RERF; especially those that may contribute in the long term to the well being of participants in the AHS and F_1 studies.

The Scientific Council commends Drs. Heath and Wolff on their efforts to develop a 5-year plan for the RERF. They suggest that developing several specific research themes that take advantage of resources or expertise that are uniquely available at the RERF would strengthen the proposal. Specific studies that might be included (after careful and critical scientific evaluation—both internal and external) are:

- A focussed commitment to the generation and use of biological dosimetric efforts to revise the DS86 dosimetry.
- A definitive test of the hypothesis that early onset breast cancers occurred in individuals who were genetically predisposed to cancer (i.e. were putative carriers of BRCA1, BRCA2, RAD51 mutations or other genetic characteristics that predisposed them to cancer). Candidate genes identified in rodent cancer susceptibility studies might be included in these studies as they are discovered.
- Identification of genetic or epigenetic events that may be associated with clearly defined disease phenotypes that are revealed in the AHS and F_1 populations (even those that may not be associated with radiation). Asthma and

hypertension are examples of possible targets.

The Scientific Council strongly encourages the plan to increase interaction between RERF scientists and the international scientific community. This will strengthen the RERF scientific program within RERF and will provide needed scientific and political visibility. This might be accomplished in several ways.

- Establishing collaborations to analyze the rich tissue and epidemiological resources available at RERF. This should include making tissue samples available to collaborating investigators.
- Encouraging RERF scientists to visit or work in laboratories: 1) to establish collaborations, 2) to gain experience with technologies that may be useful for RERF studies (e.g. array technologies), 3) to make tissue available to collaborating institutions, and/or 4) to perform feasibility studies.
- Funding external researchers to perform analyses that are not possible at RERF.
- Continuing efforts to establish collaborative programs with Japanese universities. Interaction with RERF alumni now at these universities might facilitate this process. The council encourages attempts to attract university graduate students to RERF studies but does not think that establishment of an independent Ph.D. program at RERF is necessary to achieve this objective.

The Scientific Council encourages efforts to strengthen the scientific program within the RERF. Specific measures might include:

- Frequent, RERF-wide critical evaluation of long-term scientific objectives.
- Establishment of an internal competitive granting program with funds going to groups or departments judged by external review to be most meritorious.
- Increased interdepartmental interaction (e.g. through joint seminars or interdepartmental retreats).
- Open recruitment of senior program leaders.
- More extensive and effective use of expert consultants to advise on technical and scientific aspects of the RERF program (e.g. through week-long interactions).

The Scientific Council strongly supports the development of advanced molecular analysis technologies within the RERF. However, it cautions that these technologies are currently evolving rapidly and that investment in any one at this time may be premature. Thus, the council suggests that experience with all relevant technologies be gained by establishing collaborations with expert laboratories and/or by extended visits to expert laboratories to make prototype measurements.

The Scientific Council commends Dr. Taira and colleagues on their efforts to secure access to tissue samples from the pathology communities at Hiroshima and Nagasaki. However, the council views this as an issue of

critical importance and encourages a redoubling of effort in this area. Focus during the next year should be on obtaining samples of breast and thyroid cancers for which the probability of causation by radiation is greater than 50%.

The Scientific Council encourages the continued accumulation and evaluation of molecular and epidemiological information from the AHS and F₁ populations. However, it is concerned about pursuing mechanisms to explain apparently statistically significant but biologically insignificant correlations. Such studies should be critically evaluated before they are initiated to insure that the biological studies have a clear, attainable and biologically reasonable endpoint. The council encourages RERF scientists to investigate the feasibility of using existing data from other studies to validate hypotheses generated from molecular epidemiological studies (e.g. use of data from mouse and dog irradiation experiments or from other exposed populations).

The Scientific Council supports continued development of the F₁ study. However, it recognizes that RERF has received considerable input from previous Scientific Councils and the Clinical Genetics Workshop relating to the initiation and conduct of these studies. All recommendations urge that RERF take steps to conduct active follow-up of F₁ cohort. During the course of the Scientific Council meeting, questions were raised about whether the subjects used for the pilot study to test the mailed questionnaire should be members of the F₁ cohort or should be a sample of non-F₁ individuals drawn from another source. Another issue relates to whether or not health questions should be included in the mailed questionnaire. Solutions to these and other outstanding issues are beyond the charter of the Scientific Council and will have to be resolved by the investigators, consultants and other parties involved. The council does encourage the formation of a small local ethics committee, perhaps including representatives of the F₁ population, to aid in the resolution of these issues.

In conclusion, the Scientific Council commends the RERF directorate and staff on their efforts to strengthen the RERF program. The 5-year plan now under development is a critically important part of this process. The council recognizes that this is a formidable task and urges that its development be a collaborative effort between the directorate, staff and expert consultants. The council also sees this as an opportunity to identify areas where vigorously recommended independent grant support might be obtained. Studies of health related issues in the AHS and progeny seem especially attractive in this regard.

Department of Clinical Studies

Current research and future plans of the department were presented by Drs. Fujiwara and Akahoshi, for Hiroshima and Nagasaki, respectively. The works of the department were also mentioned in the reports and recommendations by International Peer Review Panel of the Epidemiology Program, Clinical Genetics Workshop and Immunology Workshop. Details of the activities were also

presented and discussed during the informal meeting with the staff of the department.

The council was pleased with the progress of the work carried out in the department with their collaboration with almost all the departments within the RERF. It appreciates the results of the ongoing biennial examinations of more than 18,000 survivors drawn from Life Span Study (LSS) study samples including about 900 *in utero* exposed people. Since the AHS studies include many individuals in the high dose exposure group and are longitudinal in nature, they have an advantage of revealing earlier the trend of diseases related to radiation exposure. Despite attrition of the study samples (now about 9,500) due to aging and death AHS follow-up has been supplemented by mail and telephone surveys, initiated in 1995, and it shows a continued high participation rate of about 80%. The department is also conducting special studies on various malignant and non-malignant diseases, and age-related diseases and physiological changes. Another contribution of the department is the collection and storage of biological samples which are precious resources for studies undertaken in other departments. The council strongly recommends the continuation of these activities. (A small scale F₁ health study will be initiated when the program is finalized.)

Several topics and achievements were presented this year. 1) Special clinical and laboratory studies on liver diseases. Interdepartment liver studies initiated in 1998 have suggested an interaction between radiation, HCV, chronic hepatitis, and cirrhosis which may lead to liver cancer. No evidence was found for interaction of HBV with radiation exposure. 2) The prevalence of diabetes mellitus (DM) was studied in relation to radiation and age ATB. A higher prevalence of DM was found for people exposed to high doses (>2 Gy) at younger age. Since DM consists of two types with different pathogenesis, further studies are planned to differentiate the types of the disease together with studies on possible target genes. 3) Recently an increased risk of cardiovascular diseases, particularly of myocardial infarction, was found by Epidemiology and Statistics studies. This finding has been expanded to other adult onset diseases. Now a question has arisen about the validity of radiation induction or acceleration of non-cancer diseases as a general concept. Efforts are being made in both Hiroshima and Nagasaki laboratories to understand the mechanisms of the apparent increase of non-cancer diseases such as cardiovascular diseases, hypertension, and thyroiditis. Various indications are being studied including fatty liver. The possible role of infection and immunity also are being explored. 4) The collection and proper storage of biological materials, particularly of sera (in frozen or freeze-dried form) are necessary and already done for 16,000 subjects. An improvement in storage of these materials was made recently. This is greatly assisting the analysis of target gene products and virus, etc. to understand the mechanism of malignant and non-malignant diseases.

Department of Epidemiology

The activities of the Department of Epidemiology,

which are evaluated every year by the Scientific Council, were also reviewed by the Blue Ribbon Panel and, in November last year, by the Multinational Epidemiology Peer Review Panel (Epidemiology Panel). The Scientific Council basically endorses all the recommendations of the Epidemiology Panel. The Department of Epidemiology is conducting various research activities, with its core projects being studies on the increase of risks of detrimental health effects due to exposure to A-bomb radiation. These are also the central projects of the entire RERF. Although about half a century has passed since exposure, further follow-up is necessary to estimate the lifetime risks of those who were unfortunately exposed to the A-bombs. Since those exposed at younger ages, especially those exposed under 10 years of age and exposed *in utero*, are reaching ages when the risks of cancer and chronic diseases are high, further follow-up is essential. Follow-up of this younger cohort is vital in differentiating between the relative and absolute risk models. Which of these models is correct can have a major impact on projections of lifetime risk for radiation exposure of children. Risk assessment by the Department of Epidemiology is important and serves as a basis for estimation of risks due to radiation exposure by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the International Commission on Radiological Protection (ICRP).

Molecular epidemiology studies have become increasingly important. It is expected that studies in this area will develop by conducting collaborative studies with other departments at RERF as well as with universities and research institutes in Japan and abroad.

Life Span Study sample

The LSS sample consists of about 120,000 people including 93,000 exposed and 27,000 unexposed individuals. The follow-up of this population should be continued. Because of the use of *koseki* information, the mortality from cancer and other diseases has been followed up almost completely. Use of the cancer registries in Hiroshima and Nagasaki has enabled analysis of cancer incidence, and the results of the analysis have been published by the Department of Epidemiology. Analyses of both mortality from cancer and other diseases and of cancer incidence should be continued. Mail surveys have also been conducted on the life style of this population. However, their results have not been fully utilized. Recently case-control studies on bladder and breast cancers were conducted using the results of the mail surveys. These nutritional epidemiology studies on bladder and breast cancers were conducted in collaboration with researchers at Kyushu University and the Imperial Cancer Research Fund (ICRF) in Oxford, respectively. Such studies should be performed more actively.

The Scientific Council recommends that the follow-up of the LSS sample should be continued. With the recent decrease of the case fatality rate of cancer in Japan in mind, more emphasis should be placed on the analysis of cancer incidence based on the cancer registry. The life-style of the LSS sample has been grasped through mail surveys.

The results of these surveys should be further utilized.

In utero cohort

This cohort is, like the LSS sample, unique in the world, and consists of about 3,300 individuals who were exposed *in utero*. These individuals are now in their mid-fifties, and their cancer risk will increase in the years to come. We support the Epidemiology Panel in its recommendation that the follow-up of this cohort should be continued for at least another 20 years. We also support the panel's recommendation that more active follow-up of this cohort should be considered. Health examinations are now being conducted on about 1,000 of the 3,300 individuals of the cohort. If possible, all individuals in this cohort should be examined.

The Scientific Council supports the Epidemiology Panel's recommendations that the follow-up of the subjects exposed *in utero* should be continued for at least another 20 years and that more active follow-up of the cohort should be considered.

F₁ cohort

Mortality studies have been conducted on about 88,000 individuals of the F₁ cohort. No increase has been observed in the mortality risk of this cohort. A mail survey has been planned for the F₁ cohort, and health examinations of a limited number of the cohort subjects have also been planned. Since the previous meetings of the Scientific Council, Epidemiology Panel, and Clinical Genetics Workshop reviewed and made recommendations on the F₁ study plan, it would not be necessary to dwell on the matter in detail here. We hope that the F₁ study, which will be conducted mainly by the Departments of Epidemiology and Clinical Studies, will be carried out based on the recommendations of the said review groups, with due consideration for not only scientific credibility, but also ethical aspects.

Molecular epidemiology studies and other epidemiological studies using biological samples

The rapid progress of molecular biology has enabled molecular epidemiology studies. RERF has long been maintaining tissue registries, which provide valuable resources. It is desirable to conduct studies in this area in collaboration with other departments at RERF as well as universities and research institutes in Japan, the US, and other countries. Such studies are expected to lead to new developments in radiation effects research.

RERF has cryopreserved serum samples of the AHS sample. The Department of Epidemiology should promote serum epidemiology studies using those sera in collaboration with the Department of Clinical Studies. Availability of only one vial of serum per person (although the situation has improved) seems to have prevented active use of the samples. However, the number of samples to be used in nested case-control studies is limited. Also, the effects of thawing serum samples should be reviewed carefully. Many other cohort studies using stored sera have been conducted around the world, and further progress at RERF is expected in this area. Possible

research areas include HCV and HBV infection, *Helicobacter Pylori* infection, pepsinogen, and micro-nutrients, etc.

Molecular epidemiology studies will be an extremely important research area of the Department of Epidemiology in the future. In conducting these studies, collaboration with other departments at RERF, universities and research institutes in Japan and abroad is desired. In collaboration with the Department of Clinical Studies, the Department of Epidemiology should further promote studies using serum samples, which have long been stored at RERF.

Personnel problems

All studies depend on human resources. Advancement of scientific research cannot be expected without competent researchers. The Department of Epidemiology has traditionally suffered from a shortage of senior scientists. Last year, Dr. Shibata moved to Nagasaki University, which made the situation much worse. Out of concern over this problem, the Epidemiology Panel recommended the establishment of closer linkage with universities. The change in the policy of the Ministry of Education has enabled the research department chiefs to concurrently assume professorship at universities. We hope that further efforts by the RERF administration and the Department of Epidemiology will bring about closer linkage with universities and enable the establishment of a system by which graduate and post-graduate students can engage in studies at the said department.

The Scientific Council considers that the shortage of senior scientists in the Department of Epidemiology is a serious problem. Solution of this problem is essential. Taking advantage of the change in policy of the Ministry of Education, efforts should be made to establish formal linkage with universities and accept graduate and post-graduate students.

Pathology

The former Department of Pathology has become part of the Department of Epidemiology. Many paraffin blocks of tumors resected are stored in community hospitals in Hiroshima and Nagasaki and those of autopsied cases (from the late 1940's to the mid 1970's) are stored at RERF. However, these paraffin blocks in community hospitals are not always easy to utilize by scientists at RERF at the present time. Further, there are limitations for molecular study using paraffin blocks. It may be necessary therefore for some studies of tumors to use fresh tissue samples. For this purpose, the council recommends that the RERF should establish better official contact and stronger cooperation with local community hospitals and their pathologists in Hiroshima and Nagasaki. These materials should become available to interested scientists at RERF.

We have thus reviewed the activities of the Department of Epidemiology. This department has provided important information concerning the risks of cancer and other diseases in A-bomb survivors. We hope that the department will continue to play a central part in the RERF program.

Genetics Program

Dr. Nakamura reviewed the cytogenetic and molecular biology components of the Genetics program. The council supports the program's efforts to develop and apply new generation analytical techniques (e.g. ESR, microarray technology, 2-D gel DNA analysis) to increase the sensitivity with which genetic damage can be detected in the AHS and F₁ populations. However, the council urges a critical assessment of the questions to be asked using these technologies and whether the technologies have the power to answer these questions. The council also supports evaluation of the utility of these and other technologies to provide information about the health of the AHS and F₁ populations including non-radiation related disease. Technologies that might be evaluated include array-based laser desorption mass spectrometry to identify serum or urine proteins that might be early disease markers or single nucleotide polymorphism analysis arrays to identify genetic polymorphisms associated with disease. The council cautions that these technologies are currently evolving rapidly and that investment in any one at this time may be premature. Thus, the council suggests that experience with all relevant technologies be gained by establishing collaborations with expert laboratories and/or by extended visits to expert laboratories to perform feasibility studies.

The council notes that the new generation technologies planned for the future are information intensive. Effective use of these approaches will require a substantial expansion of the RERF informatics capabilities as well as addition of personnel with expertise in large-scale statistical analysis. A significant challenge to this group will be to deal with the problem of false correlations that will result from correlative studies using these "megavariate" analysis technologies in the AHS and F₁ populations. Extensive interactions between the Statistics and Genetics department members will be needed to insure that statistically significant but biologically insignificant correlation are recognized and eliminated from further study.

The council strongly supports the proposed use of multi-color FISH to assess chromosome aberrations in individuals exposed at an early age from Hiroshima and Nagasaki. The council believes that this will correct analysis biases that may have resulted in differences in aberration frequencies between Hiroshima and Nagasaki populations. However, they note that multi-color FISH is labor intensive and expensive at present and urges participants in the process to visit or establish collaborations with laboratories experienced in the technology. The council strongly urges that this cytogenetic effort be closely coupled to efforts to revise and correct the DS86 dosimetry program. Without this, the value of the expanded study is questionable. The council also supports previous suggestions that the cytogenetics program evaluate the feasibility of identifying the specific genes that when mutated by translocation lead to clonal expansion. This is an example of a project that might be best accomplished in collaboration with a laboratory involved in genome research.

Department of Radiobiology

Research in the Department of Radiobiology was evaluated one year ago by a Multinational Peer Review Committee. The primary focus of the recommendation was to develop a tighter focus for the research. Some progress has been made in this, though, it has been clearly hampered by the lack of a chief for the department after Dr. Seyama's departure. Following the recommendation of the committee an open search for the chief was conducted and two finalists are presently being considered. This is a very important position. Because of the increasing need for a modern molecular basis for the research questions to be addressed by the Department of Radiobiology, as well as RERF as a whole, a major criterion for the successful candidate should be one with strength in molecular biology.

One of the main recommendations of the Peer Review Committee was to concentrate on common tumors that have a high probability of being radiation induced. The plans for the study of BRCA1 and 2 mutations in early onset breast cancer that were presented seemed appropriate. These plans need to be put into action as soon as possible. In particular, locating and obtaining material from the 100 or so early onset cases with substantial DS86 doses should be a priority.

The department needs to develop a coherent research strategy to use its expertise and the unique resources available to it at RERF. This will be an important priority for the new department chief. Since the mandate of RERF includes studies to benefit the health of those exposed to the A-bomb, research in the department can be broader than simply focused on radiation effects. For example, possibilities could include molecular epidemiological studies of serum samples collected over many years to ask questions relating to risk factors for cancers and other diseases irrespective of radiation.

Increasingly, modern biomedical research is interdisciplinary and collaborative. No one laboratory, department or even an institute of the size of RERF can have all the expertise, techniques and instrumentation to answer many of today's important biological questions. The Scientific Council therefore strongly supports the collaborations presently underway and encourages new ones. RERF, with its huge collection of biological material and epidemiological data base, has a lot to offer to such collaborations. But it also needs to position itself for the new genomic and post-genomic eras. This is where the Department of Radiobiology can, and should, play an important leadership role. The Scientific Council recommends that an interdepartmental task group be formed, possibly headed by the new chief of the Department of Radiobiology, to plan for how RERF can develop expertise and resources in genomics and bioinformatics. Already members of the Departments of Radiobiology and Genetics are interested in investing in chip technology to study mutations and global gene expression. This is a rapidly emerging technology and it is far from clear which systems will emerge as optimum for various studies. However, irrespective of the outcome, expertise in statistics, management of large data bases as well as molecular biology knowledge will be required. RERF has

much that is needed to be a player in this new world. Its infrastructure and resources of people, equipment and samples can be leveraged to open up new collaborative ventures. However, much of the expertise needs to be acquired. It will require several of the present personnel to spend time in laboratories currently working with new technologies. RERF's resources should be used to stimulate such interactions and collaborations. Possible projects could include studies of disease predisposing genes and prognostic significance of global gene expression in cancers. For example can one predict which cancers are likely to be metastatic and/or resistant to radiotherapy or chemotherapy from gene expression levels? Whether this can be done from archival material is an important question that needs immediate attention. If fresh material is required collaborators will be forthcoming if RERF has the necessary expertise in genomics and bioinformatics. As a first step, collaboration with the US National Cancer Institute (NCI) should be explored in this area. The NCI Fellowship program recently set up is another possibility for RERF personnel to gain expertise in this area as well as bring scientists knowledgeable in this area to RERF.

The Scientific Council recommends that the above initiative to develop expertise in genomics/proteinomics and bioinformatics, so as to make maximum use of the data and samples that have been collected over the past 40 years, be a major focus of the molecular biological section of the Future Plans document to be presented to the DOE.

The Scientific Council is concerned about some of the conclusions and directions of the immunology program in the Department of Radiobiology. The theory that radiation upsets the balance between the Th1 and Th2 products of the helper T cell is interesting, but it is based on very small differences of cytokine levels (5–10% in some cases) between the low and high radiation dose groups. Although these appear significant by conventional statistical tests, their biological significance is questionable. Careful examinations with statistical help of these data is required and, if possible, a test of the hypothesis with other exposed individuals (the high dose Chernobyl workers for example). Also the significance for disease development of an imbalance of Th1 and Th2 with genetically altered mice should be considered, possibly as a collaborative investigation with groups outside RERF.

Department of Statistics

The Department of Statistics remains strong. They have collegial collaborative interactions with investigators in all other departments. In addition to taking a leadership role on a number of major projects, they provide statistical support to investigators in all departments. Their publication record continues to be strong and includes timely periodic updates on cancer mortality and cancer incidence. We expect that in future these periodic published updates will also include reports on non-cancer outcomes among the various survivor cohorts.

Issues of particular concern to the Scientific Council relate to data access, family pedigree studies, further

exploration of age/time relationships and development of analytic techniques for handling the huge numbers of variables that are likely to be available on individuals in future genetic epidemiological studies. Statisticians in the department are making efforts to create data bases that will make various of the RERF data sets more readily available to investigators outside the department, and presumably outside RERF. The council encourages the group to work with other interested parties at RERF (e.g., heads of other departments and the directors) to develop a policy for granting access to these primary data sets for non-RERF investigators. This policy should aim to allow for an increase in sharing of RERF data with outside investigators.

Although the Scientific Council reports from a number of previous years have encouraged this group to develop family pedigrees for survivors, fairly little progress in this appears to have been made to date. The present council encourages investigators involved in this effort to sharpen their aims with respect to family pedigree studies. This should involve focused discussion of what will be done with family pedigree data and what they hope can be learned from these studies. If the consensus after such discussions is that work on establishing family pedigrees should proceed, investigators need to sit down together with all interested parties and decide how this can be done.

The department is encouraged to continue their further investigation of age/time effects on associations between exposure and various health outcomes. For some cancers, for example, it now seems that what initially appeared to be age at exposure effects may at least partially be an effect of attained age. Further clarification of these associations is important not only for cancer outcomes, but for non-cancer outcomes as well.

Although the department has long experience with multivariate analyses, the new array technology and other similar technologies that are likely to become standard in genetic epidemiological studies at RERF will provide data on hundreds to tens of thousands of variables on each study subject. RERF statisticians need to give serious thought as to how such megavariable correlative analyses are to be conducted and interpreted.

The continued vacancies in a number of professional staff slots in the department remain an issue of concern. Steps need to be taken to fill these slots with qualified statisticians so that the important work of this department can continue without interruption.

Appendix Two
Thirty-Third Board of Directors Meeting

The 33rd Board of Directors Meeting Minutes

23-24 June 1999

Nagasaki Laboratory, Radiation Effects Research Foundation

Agenda

I. Minutes of the 32nd Meeting of the Board of Directors

II. Items for Information

1. Status report of RERF
2. Present personnel status
3. FY98 salary revision, etc.
4. Labor Union's FY99 demands for improvement of working conditions, etc.
5. Others
 - (1) International collaboration
 - (2) Health effects study for the children of A-bomb survivors (F_1)
 - (3) Others

III. Items for Deliberation and Action

1. Recommendations of the Multinational Peer Review of the Epidemiology Program
2. Recommendations of the 26th meeting of the Scientific Council
3. FY98 research activities report and audit report, etc.
4. FY98 settlement of accounts and audit report
5. FY99 research activities plans
 - (1) Responses to recommendations of the Multinational Peer Review and the Scientific Council
 - (2) FY99 research plans
6. FY99 working budget
7. FY2000 provisional budget plan
8. Revision of the Act of Endowment
9. Revision of rules and regulations
10. Election/Appointment of directors and others
11. Schedule of the next board meeting

Participants

Permanent Directors

Dr. Shigenobu Nagataki, chairman
Dr. Sheldon Wolff, vice chairman and chief of research
Dr. Senjun Taira, permanent director

Visiting Directors

Dr. Toshiyuki Kumatori, consultant, Radiation Effects Association (submitted a letter of attorney)
Dr. Masumi Oike, chairman, Japan Anti-Tuberculosis Association (submitted a letter of attorney for June 24 meeting)
Mr. Kazuaki Arichi, permanent director, Japan Institute of International Affairs
Dr. Richard B. Setlow, senior biophysicist, Biology Department, Brookhaven National Laboratory, adjunct professor of Biochemistry and Cell Biology Department, State University of New York at Stony Brook
Dr. Patricia A. Buffler, professor of epidemiology, Division of Public Health Biology and Epidemiology, School of Public Health, University of California, Berkeley

Dr. Jonathan M. Samet, professor and chairman, Department of Epidemiology, Johns Hopkins University School of Hygiene and Public Health (submitted a letter of attorney)

Absent: *Dr. William J. Schull*

Supervisor

Mr. David Williams, senior financial officer, National Academy of Sciences

Scientific Councilors

Dr. Hiromichi Matsudaira, chairman, Radiation Effects Association
Dr. Tomio Hirohata, professor emeritus, Kyushu University Faculty of Medicine

Observers

Dr. Toshinobu Sato, assistant director, Planning Division, Health Service Bureau, Ministry of Health and Welfare
Mr. Hiromasa Kuroki, chief, Medical Care Activities Unit, Planning Division, Health Service Bureau, Ministry of Health and Welfare
Dr. James H. Hall, minister-counselor (science), Embassy of the United States of America
Dr. Evan Douple, director, Board on Radiation Effects Research, Commission on Life Sciences, National Research Council, National Academy of Sciences
Ms. Catherine S. Berkley, administrative associate, Commission on Life Sciences, National Research Council, National Academy of Sciences

Dr. Itsuzo Shigematsu, consultant emeritus
Dr. Clark W. Heath, Jr., associate chief of research
Mr. Kazumasa Kunitoshi, chief of secretariat
Mr. Richard D. Sperry, administrative advisor

Proceedings

The board of directors meeting began at the appointed time with *Dr. Nagataki* acting as Chair. As the first order of business, *Mr. Kunitoshi* reported that two directors had submitted a letter of attorney and that seven were present. This satisfied the quorum requirements, under Article 21 of the Act of Endowment, for a properly constituted board meeting.

First, *Dr. Nagataki* expressed his gratitude to the directors, supervisor, scientific councilors, and representatives of the US and the Japanese agencies who attended the meeting. He brought up three issues to which he wanted to call the participants' attention; 1) That this was the first board meeting to be held in Nagasaki in seven years; 2) That the 5-year financial commitment of the US government, which was made in accordance with the recommendations of the Blue Ribbon Panel, will expire in 2001; and 3) That an agreement on future

clinical studies was signed by RERF and the second-generation A-bomb survivors.

Since 1975, when the official documents which established RERF were exchanged between the US and Japanese governments, RERF has been a US-Japan joint research institute in terms of finance, personnel, and research. Recently, however, the financial support from the US government has become unstable due to various circumstances. At present, there is no guarantee for US financial support beyond 2001. Dr. Nagataki said that RERF has requested that the two governments negotiate about the future status of the organization. In conclusion, he asked for those who are interested to lend their support.

The board appointed Drs. Wolff and Taira as signatories to the minutes of this meeting. Dr. Nagataki presided over the meeting, as provided in the Act of Endowment, and the board proceeded with the agenda.

A new director, Dr. Richard B Setlow (senior biophysicist, Biology Department, Brookhaven National Laboratory), was introduced. He is the successor to Dr. Warren K. Sinclair, who retired as of June 30 last year.

I. Minutes of the 32nd Meeting of the Board of Directors (presented by Dr. Nagataki)

The minutes of the 32nd meeting of the board of directors were presented together with a summary explanation of their contents. The minutes were unanimously approved.

II. Items for Information

1. Status Report of RERF (presented by Dr. Nagataki)

Dr. Nagataki reported on the future financial condition, the future research direction, and the relationship with A-bomb survivors and concerned local organizations. Concerning the financial condition, the Department of Energy's (DOE's) 5-year financial commitment (No. 5 of the record of discussion between DOE and Ministry of Health and Welfare [MHW]) will end in October 2001. Although the future financial problems have been discussed with the National Academy of Sciences (NAS) and DOE, the outlook is "uncertain" at present. A US-Japan meeting was scheduled for June this year. However, the meeting was postponed until October or later due to DOE's budgetary problems. It was reported that a governmental negotiation would be held next year.

A report was also made on the direction of future research. Scientific significance and social effects are to be extensively explained. The support of individuals and organizations that are associated with RERF is to be gained through their understanding of the achievements and the present financial situation of RERF. RERF is going to make its utmost efforts to obtain research funds within the scope of its mission. Since the last Board of Directors meeting, a second multinational peer-review conference, two workshops, and the 26th Scientific Council meeting have been held.

Lastly, the relationship with A-bomb survivors and concerned local organizations was touched upon. For the

first time, RERF organized the 40th Meeting for the Late Effects Research of A-bomb Radiation. Thanks to this initiative, we think that RERF is now officially regarded as a local research institute. RERF has also participated in events organized by concerned local organizations and committees, and attended seminars sponsored by the government. Also, RERF has strengthened its ties with the government agencies concerned. Negotiations with the A-bomb survivors' organizations are continuing. In late March this year, an agreement was reached on the booklet whose publication had been held in abeyance due to a disagreement with a group of survivors over the extent to which atomic bomb radiation may have been underestimated. The booklet was published in June. On May 19, a letter of confirmation concerning the conduct of the F₁ health effect study was signed by RERF and the All Japan Second Generation A-bomb Victims Liaison Council (*Niseikyo*), after a series of discussions on the purpose and method of the study. Specific preparations to implement the study will be made after establishing a scientific committee and an ethics committee.

2. Present Personnel Status (presented by Mr. Kunitoshi)

Mr. Kunitoshi reported on personnel status as of May 1, 1999. The total personnel strength in Hiroshima and Nagasaki combined was 284; three directors, one Chief of Secretariat, 38 research scientists, and 242 general staff members. Although efforts have been made to secure the target of 48 research scientists—budgeted personnel slots—there have been four retirements since the last meeting. However, one research scientist has been hired at the Department of Clinical Studies in Nagasaki in April this year, and another employed at the Department of Clinical Studies in Hiroshima in June. One more research scientist will be employed for the Department of Genetics in August. The chief of the Department of Radiobiology will assume his post in September. As for the chiefs' positions, which are now vacant, at the Department of Clinical Studies in Hiroshima and the Department of Epidemiology in Nagasaki, efforts are being made to select suitable persons. It is expected that these posts will be filled by the end of this year. In addition, one research scientist will be employed for the Department of Clinical Studies in Nagasaki by the end of this year. Efforts to employ research scientists are now beginning to come to fruition. Further efforts will be made to recruit competent research scientists.

The 242 general employees break down into 174 in research departments and 68 in administrative departments. The number of general employees has decreased by four over the year, which reflects the efforts to minimize the employment of replacements for mandatory age retirees. Since around 1995, both the numbers of budgetary personnel slots and the actual personnel have been drastically reduced to cope with the financial difficulties. Mr. Kunitoshi expressed his concern that continued reduction in the number of personnel was liable to have adverse effects on the research level, and he said that he intended to employ replacements for some retirees, and increase the number of personnel for departments which

need strengthening, while making efforts to employ more research scientists and bearing in mind the national government's policy of reducing the number of budgetary slots.

3. FY98 Salary Revision, etc. (presented by Mr. Kunitoshi)

RERF revises its salary scales every year following the recommendations of the National Personnel Authority and the national government employee law and the salary law revision which has been based on the National Personnel Authority's recommendation. Mr. Kunitoshi reported that RERF revised its salary scales this year following the recommendations of the National Personnel Authority. The rate of increase was 0.61% and 0.72% for research scientists and general employees, respectively. The most noteworthy event for the FY98 salary revision was the discontinuation of salary increases for employees who had reached the age of 57. This had been established by RERF following the intensified national government policy by which salary increases for national government employees aged 55 and above were discontinued.

Mr. Kunitoshi explained that the salaries of the directors and the chief of secretariat were revised using as a guide the revision of the "National Government Payscale for Designated Positions." Mr. Arichi asked why there were two amounts listed for the chief of secretariat. In response to this question, Mr. Kunitoshi explained how these two amounts were decided. Dr. Wolff said that the salary amount should be decided in accordance with the RERF regulations and not the regulations for employees of the national government. Dr. Shigematsu, after explaining the financial situation of RERF at the time, said that the salary amount for the chief of secretariat had been negotiated and approved between MHW and the Ministry of Finance.

4. Labor Union's FY99 Demands for Improvement of Working Conditions, etc. (presented by Mr. Kunitoshi)

The Labor Union submitted its FY99 demands for improvement of working conditions, etc. dated March 5 this year. Although a wide range of demands were listed, they were basically not very much different from the previous ones. The main demands were 1) revision of the Japan-US equal-sharing system and the reorganization of operations, 2) strengthening of the research system at the Nagasaki Laboratory, and 3) salary raise and improvement of working conditions. RERF responded to these demands, observing the principle of being fair and just. Mr. Kunitoshi stated that RERF had maintained and would continue to maintain a good management-labor relationship.

It was also reported that the Labor Union recently assisted RERF in the F₁ health study issue by acting as an intermediary between the second-generation A-bomb survivors' organization and RERF.

5. Others (presented by Dr. Taira)

(1) International Collaboration

Dr. Taira reported on international collaborations,

now a social demand. RERF has been participating in international collaborations since the Chernobyl accident. He addressed the following three points:

1) Participation in International Collaborative Activities

For Chernobyl-related collaborative activities, RERF has given guidance for collaborative studies in relation to medical collaborative activities in Chernobyl; also, at the request of the Sasakawa Memorial Health Foundation, RERF has dispatched Dr. Shibata to Belarus twice for on-site collaborations. Other international collaborative activities have included the dispatch of research scientists to a Chelyabinsk-related project. For Semipalatinsk-related collaborative activities, Dr. Taira has attended an international meeting. He also conducted an on-site inspection and engaged in public relations activities for the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE) projects. In addition, Dr. Wolff organized and participated in the symposium of the Atomic Energy Council in Taiwan. He and a few others gave lectures.

2) Acceptance of Visitors from Overseas for Briefing and Training

RERF accepted 194 trainees from abroad, including 24 persons related to Chernobyl, one related to Chelyabinsk, two related to Semipalatinsk, and 26 related to the Japan International Cooperation Agency (JICA).

3) International Collaborative Research Activities

With MHW's international collaboration fund of ¥14,700,000, (a) Japanese specialists were dispatched, (b) trainees were accepted from abroad, and (c) two workshops were held.

Lastly, Dr. Taira used slides to report on the "Second International Meeting on Radiation, Ecology and Health" held in Kazakhstan and to report on the present situation in Semipalatinsk.

(2) Health Effects Study for the Children of A-bomb Survivors (F₁) (presented by Dr. Taira)

Dr. Taira reported on the progress of nearly two years of negotiations over the F₁ health effects study. In 1996, in order to conduct a mail survey, RERF obtained *koseki* (family registry) attachments for Hiroshima and Nagasaki without first consulting second-generation A-bomb survivors. This action met with a strong protest from *Niseikyo*. Upon subsequent negotiations, RERF and *Niseikyo* signed a letter of confirmation on May 19 this year. The letter confirms that a plan will be developed for examination procedures and examination items, based on the results of thorough discussions between the two parties. RERF will establish third-party committees; a scientific committee and an ethics committee, which will review the details and duration of the study. In addition, he touched upon the F₁ health effect study plan (draft). Taking heed of the reviews by both the scientific and ethical committees, 20,000–25,000 people will be asked whether they are interested in participating in the health study via a mail survey. One year and six months will be

necessary for mailing, analysis, and a report of the results. After that, 500–600 people will undergo health examinations as a preliminary study. Subsequently, the study subjects will be increased to include about 10,000 people in order to conduct the full-scale study.

In response to Dr. Arichi's question about the F_2 study, Dr. Taira said that RERF could not consider the F_2 study before conducting the F_1 study first.

III. Items for Deliberation and Action

1. Recommendations of the Multinational Peer Review Panel (presented by Dr. Hirohata)

The multinational peer review of the Department of Epidemiology was held in November 1998 at RERF with Dr. Richard Monson (Harvard University) as chair. The following recommendations were given:

Recommendations

Life Span Study (LSS) Sample

- (1) Studies of radiation carcinogenesis based on LSS and Adult Health Study (AHS) populations have produced new findings with the passage of time. Further continued surveillance on LSS and AHS populations are essential. Inclusion of cancer incidence data should be a priority.
- (2) Factors other than radiation, including socioeconomic factors, smoking, alcohol intake, dietary habits, viral and bacterial infections, and genetic susceptibility should be considered in the future study. The primary focus should be the interaction of these factors with radiation exposure.
- (3) Diseases other than cancer, particularly a possible increase of cardiovascular disease, should be evaluated further. A workshop with experts on relevant diseases should be planned.
- (4) Interdepartmental approaches, as exemplified in the study on primary liver cancer, should be pursued further.
- (5) Genetic and molecular epidemiologic approaches should be used to evaluate the finding of an increased risk of early onset breast cancer among females exposed to radiation at <20 years of age, including a search for markers of genetic susceptibility among these cases.

In Utero Cohort

- (6) Follow-up of the *in utero* cohort should be continued at least 20 more years. Active follow-up should be considered.

F_1 Cohort

- (7) Follow-up of the F_1 cohort should be conducted, and all available cohort members should be included to strengthen the statistical power and to maximize the potential for evaluation of sub-populations.
- (8) The ethical advisory committee should include a member with epidemiologic expertise.
- (9) Membership of the scientific advisory committee for the F_1 cohort study should include epidemiologic expertise in relevant areas, including nutrition.

- (10) If evaluation of psychological health is intended to be included in assessment of the F_1 cohort, a strong scientific justification must be developed and appropriate expertise should be consulted. A workshop on psychological aspects of A-bomb survivors would be advisable to assess any scientific justification.
- (11) A strategy must be developed at the onset of the F_1 study to communicate to the participants and to other interested parties the issues that will be involved in the interpretation of the initial cross-sectional data.
- (12) In advance of the F_1 study, there must be a determination of which data may be used to assess causal hypotheses in the cross-sectional data, and to assess which causal hypotheses can be assessed only in the follow-up data.
- (13) Attempts should be made to obtain risk estimates for radiation induced hereditary effects, especially for multifactorial diseases and late occurring dominant mutations.

Molecular Epidemiology

- (14) A strategic plan for research in molecular epidemiology should be developed that includes a list of priorities, types of cancer, selection of biomarkers, and study subjects. An external expert committee should assist in developing this plan.

Risk Assessment

- (15) Future risk assessments should include estimates based on cancer incidence as well as on cancer mortality. The inherent limitation of the cancer incidence data should be part of the assessment. Risk assessment of other diseases also should be conducted.
- (16) The use of mathematical models should continue to be an adjunct to the basic analyses that are conducted on the epidemiologic data. Rigorous testing of the assumptions used in the models is needed to assess the utility of the models.

Organization and Performance

- (17) RERF should develop affiliations with universities, including those at Hiroshima and Nagasaki.
- (18) The training of doctoral students and postdoctoral fellows should become an important part of the mission of RERF.
- (19) Sufficient resources should continue to be provided to insure that as new data are collected, they will be added to the current database without delay. Collaboration of all RERF programs in this resource is essential. Also, there must be careful attention paid to off site duplication of the RERF data and the management system in the event of a catastrophic loss of computer resources.
- (20) The Epidemiology program should be involved in all epidemiologic studies conducted by RERF. Interdisciplinary collaboration within RERF must receive a high priority.
- (21) The present organization in Nagasaki should be maintained to address the data management issues

related to follow-up of the Nagasaki cohort.

- (22) Staffing levels should be increased to enable optimum use of the existing data at RERF.
- (23) A grant program should be developed by RERF to enable universities to work with RERF data. Priority should be given to Japanese universities.

Dr. Wolff said that the recommendations of the Multinational Peer Review Panel were submitted to the Scientific Council, which endorsed those recommendations.

The recommendations of the Multinational Peer Review Panel were approved after deliberation.

2. Recommendations of the 26th Meeting of the Scientific Council (presented by Dr. Matsudaira)

Dr. Matsudaira stated that in summary the Scientific Council recommended RERF to continue its studies focusing on the effects of radiation on exposed individuals and their progeny and to conduct a study relating to fundamental general health using molecular biological technique.

Recommendations to each department

Department of Clinical Studies

The Council appreciates the results of the ongoing biennial examinations of more than 18,000 survivors drawn from LSS study samples including about 900 in utero exposed people. Since the AHS studies include many individuals in the high dose exposure group and are longitudinal in nature, they have an advantage of revealing earlier the trend of diseases related to radiation exposure. Despite attrition of the study samples due to aging and death AHS follow-up has been supplemented by mail and telephone surveys, initiated in 1995, and it shows a continued high participation rate of about 80%. Another contribution of the Department is the collection and storage of biological samples which are precious resources for studies undertaken in other departments. The Council strongly recommends the continuation of these activities.

Department of Epidemiology

The Scientific Council basically endorses all the recommendations of the Multinational Peer Review Panel. The Department of Epidemiology is conducting various research activities, with its core projects being studies on the increase of risks of detrimental health effects due to exposure to A-bomb radiation. These are also the central projects of the entire RERF. Although about half a century has passed since exposure, further follow-up is necessary to estimate the lifetime risks of those who were unfortunately exposed to the A-bombs. Since those exposed at younger ages, especially those exposed under 10 years of age and exposed *in utero*, are reaching ages when the risks of cancer and chronic diseases are high, further follow-up is essential. Follow-up of this younger cohort is vital in differentiating between the relative and absolute risk models.

Molecular epidemiology studies have become increas-

ingly important. It is expected that studies in this area will develop by conducting collaborative studies with other departments at RERF as well as with universities and research institutes in Japan and abroad.

Department of Genetics

The Council supports the program's efforts to develop and apply new generation analytical techniques (e.g. ESR, microarray technology, 2-D gel DNA analysis) to increase the sensitivity with which genetic damage can be detected in the AHS and F₁ populations. However, the Council urges a critical assessment of the questions to be asked using these technologies and whether the technologies have the power to answer these questions. The council also supports evaluation of the utility of these and other technologies to provide information about the health of the AHS and progeny populations including non-radiation related disease.

Department of Radiobiology

One of the main recommendations of the Multinational Peer Review Committee was to concentrate on common tumors that have a high probability of being radiation induced. The plans for the study of BRCA 1 and 2 mutations in early onset breast cancer that were presented seemed appropriate. These plans need to be put into action as soon as possible. In particular, locating and obtaining material from the 100 or so early onset cases with substantial DS86 doses should be a priority. The Scientific Council recommends that the above initiative to develop expertise in genomics/proteinomics and bioinformatics, so as to make maximum use of the data and samples that have been collected over the past 40 years, be a major focus of the molecular biological section of the Future Plans document to be presented to the DOE.

Department of Statistics

This department has collegial collaborative interactions with investigators in all other departments. In addition to taking a leadership role on a number of major projects, they provide statistical support to investigators in all departments. Their publication record continues to be strong and includes timely periodic updates on cancer mortality and cancer incidence. We expect that in future these periodic published updates will also include reports on non-cancer outcomes among the various survivor cohorts. Issues of particular concern to the Scientific Council relate to data access, family pedigree studies, further exploration of age/time relationships and development of analytic techniques for handling the huge numbers of variables that are likely to be available on individuals in future genetic epidemiological studies.

In conclusion, Dr. Matsudaira commended the RERF directors and staff on their efforts. It was recommended that the RERF program (including the 5-year plan) be carried forward since it was very good.

The recommendations of the Scientific Council were approved after deliberation.

Dr. Setlow asked whether it was possible for an RERF research scientist to concurrently serve as a professor or an assistant professor at a university. Dr. Nagataki expressed his view that even if one is a public employee, one can be concurrently assigned as a consultant to RERF. Dr. Wolff explained that many RERF research scientists had already been teaching at universities and that Ph.D. students were conducting studies at RERF. Furthermore, the following opinions were raised by other directors and scientific councilors.

Ties with universities in Japan as well as abroad should be strengthened. Senior research scientists should be recruited. It is equally important for RERF to prevent senior research scientists from leaving. While the mandatory retirement age at RERF is 60, that for Japanese universities is 65. Can RERF do something to improve this situation? How about making a plan to foresee the situation at RERF 20 years from now?

In response, Dr. Nagataki explained that the financial uncertainty beyond 2001 had caused anxiety about RERF's future, which was the main reason for RERF's difficulty in recruiting competent research scientists. For the past seven or eight years RERF has been subjected to constant worry about the US financial support. Dr. Nagataki requested the understanding of the directors and the participants.

Dr. Buffler said that she could understand the problem of the DOE's internal budget management; however, it was hard to believe that the US government was looking at RERF in such an unstable way. RERF is regarded by the US agencies other than DOE as an important research institute for studying the health effects of radiation. DOE is not necessarily an appropriate funding agency for RERF. It may be easier to receive funds from other US agencies. She suggested that RERF think about this possibility.

Dr. Wolff supplemented Dr. Buffler's opinion by saying the following. It is not possible to say that it is the overall policy of the US government to reduce the budget for RERF or to withdraw from RERF. The present situation is triggered, rather, by the DOE's internal financial problems.

Dr. Nagataki explained the present understanding as follows: It is impossible to recruit competent research scientists without reassurance about the future of RERF. It is necessary to have a clear financial commitment from the US. A request to hold a governmental meeting was made last year. Although the meeting was scheduled for June this year, it was cancelled for the convenience of DOE. Although meetings with NAS-related people were held last year and this year, there is no clear picture about the future of RERF at present. He does not necessarily think that the US budget will solve all the problems; and he thinks that it is still important for RERF to think about how to function as a US-Japan joint research institute.

Dr. Taira proposed to listen to the opinions of MHW, the US directors, and others concerned on the following day since this issue was very important. It was agreed to discuss this issue again on the following day.

Second Day (June 24)

Before starting discussions, Mr. Kunitoshi reported that Dr. Oike, who was present on the previous day, was absent for personal reasons. Concerning the items for deliberation and action, it was necessary to have a satisfactory quorum for each agenda item. Dr. Oike submitted a letter of attorney. Therefore, of the 10 directors, three directors had submitted a letter of attorney, and six were present, which satisfied the quorum requirements under Article 21 of the Act of Endowment for a properly constituted board meeting.

3. FY98 research activities report and audit report, etc. (presented by Dr. Wolff)

The following were reported as the activities of the past one year.

- (1) Two significant workshops, one on clinical genetics and the other on immunology, were held. Negotiations were being carried out with *Niseikyo*, who objected to certain aspects of the proposed F_1 study. It became appropriate to obtain expert advice on the controversial scientific aspects of the study. A superb international group of geneticists came together for two days of extensive discussions of the issues. A consensus was reached, and they recommended that RERF proceed with the F_1 study. The immunology workshop brought together a distinguished group of immunologists particularly expert in T-cell phenomena. They endorsed the plans for the immunologists in the Department of Radiobiology to study the role of different types of T cells in the etiology of radiation-related diseases in the survivors.
- (2) Personnel problems regarding staffing were touched upon. Dr. Donald MacPhee of La Trobe University in Australia has been selected via an international search to fill the vacant position of chief of the Department of Radiobiology, and he will assume his post in September. The chiefs of the Department of Epidemiology in Nagasaki and the Department of Clinical Studies in Hiroshima have resigned. Although RERF has been committed to the procedure of carrying out open searches for senior positions, it is our belief that the head of the Department of Clinical Studies should be a Japanese physician.
- (3) Although we have completed only two years of the five-year plan recommended by the Blue Ribbon Panel, we have begun an additional but different type of five- or more- year plan. The first point of the plan is a continuation of our traditional epidemiological studies that have been so important in quantifying the effects of radiation from the atomic bombs, and the second is comprised of new molecular biological studies on the basic mechanisms by which radiation causes its effects. The first of these is necessary, even though our current studies already provide the gold standard for establishing the risks of radiation worldwide, because the survivor cohorts on which they are based largely are still alive. The second will enable us to utilize our invaluable resource of stored biologic specimens to gain a fundamental understanding of radiation-in-

duced diseases and the mechanisms behind them.

Following Dr. Wolff's report, Dr. Buffler said that the mandatory retirement issue was a very serious problem for the Department of Epidemiology and asked what kind of measures could be taken by RERF to maintain important research scientists. In response to her question, Dr. Wolff explained about the possibility of re-employment and the possibility of delaying retirement, i.e., being extended. Dr. Taira said that the utmost efforts should be made to recruit new research scientists to activate the work place. Dr. Nagataki said that the financial instability beyond 2001 was hindering RERF from recruiting young research scientists. Replacements for mandatory retirees have not been employed due to the financial circumstances. Extending the mandatory retirement age for research scientists alone may pose a big problem.

On behalf of Dr. Yamazaki, who was absent, Mr. Williams read the supervisor's summary of the scientific activities report.

After the above reports were presented, the FY98 research activities and audit reports were approved.

4. FY98 Settlement of Accounts and Audit Report (presented by Mr. Kunitoshi)

Mr. Kunitoshi explained the settlement of account (summary sheet). The total income in the regular account was ¥4,356,988,035, of which US and Japanese government subsidies amounted to ¥4,311,279,651. Total expenditure was ¥4,148,396,939. As a result, there was a favorable balance of ¥208,591,096. The main reasons for this balance were that we did not have as many voluntary retirees as we had anticipated, we were not able to recruit as many new research scientists as we had expected, and the yen became weaker in relation to the dollar in FY98. Out of the balance of ¥208,591,096, ¥116,744,723 and ¥91,846,373 are to be returned to the Japanese and US governments, respectively, but it is hoped that RERF will keep the balance and use it properly under the supervision of the funding agencies of the two governments. The most noteworthy event in the execution of the FY98 budget was that there were two supplementary budgets, which were part of the measures to stimulate the Japanese economy. RERF obtained, as additional funds, a total of ¥217,309,000 (¥115,194,000 first and ¥102,115,000 later). In conjunction with this supplementary funding from the Japanese government, the US government provided ¥164,994,400 from the FY97 RERF budget surplus of ¥222,921,746. That led to a large amount (¥382,303,406) of total additional funds from the two governments. From these funds, about ¥240,000,000 was expended for partial renovation of antiquated facilities and ¥89,000,000 for facilities to separately store biological samples in Hiroshima and Nagasaki. In addition, ¥52,000,000 was used to purchase research equipment to improve the research environment.

Then, nine special accounts of RERF, which have been established, were explained. The LSS Cancer Case Special Account and the Termination Trust Fund Special Account were described. Although the records of some

special accounts show differences between income and expenditure, these are due to differences in the fiscal years between the two countries, and to delays in remittance and they will eventually be corrected.

This matter was followed by an explanation of the Settlement of Accounts (Summary Sheet). The total assets in the regular account were ¥1,472,506,496, whereas the total liabilities were ¥534,319,829. The balance of ¥938,186,667 represented net assets. The net assets included about ¥190,000,000 for buildings and about ¥747,000,000 for equipment. The ¥166,091,072 increase in net assets from the previous year was due to equipment purchases.

Dr. Buffler requested that the usage of the surplus be reported, because the board recommended last year that it be used for the renovation of the facilities in Hiroshima. In response, Mr. Kunitoshi reported that, out of the US surplus of ¥229,921,746 in FY98, ¥164,994,000 had been used for facility renovation. First, Hijiyama Hall was renovated, and air-conditioning, fire-fighting, and water-supply facilities were improved, and then facilities for dual storage of biological specimens in Hiroshima and Nagasaki were established. Currently ¥58,000,000 still remains from FY98, and the total US surplus still available amounts to ¥150,000,000, including the FY98 surplus of ¥91,000,000. As at least \$500,000 was available from the US, Dr. Buffler suggested that research facilities be renovated in stages, in order for RERF to pursue new research areas. Dr. Nagataki expressed his appreciation to Dr. Buffler for her constructive and useful advice.

This was followed by an audit report by Mr. Williams. Price Waterhouse conducted an audit of the RERF accounts and reported that the accounts were in good order. He expressed his concerns about the unfunded portion of the termination allowance liability. The RERF Secretariat conducted a separate internal audit and no adverse findings were contained in its report.

In relation to the report that the use of the surplus to pay termination allowances had been discontinued in FY97, Dr. Buffler asked if an approval of the board had been obtained for that measure. Mr. Kunitoshi answered that unlike organizations in the US, RERF (which operates with funds from taxes) does not have a system to accumulate funds for termination allowances. Dr. Nagataki suggested that the Secretariat review how the termination allowances should be covered by the funds from the two governments, and how RERF should cope with exchange rate fluctuations in order to have a stable financial basis.

With the above discussion, the FY98 settlement of accounts and the audit report were approved.

5. FY99 Research Activities Plans (presented by Dr. Wolff)

(1) Responses to Recommendations of the Scientific Council and (2) FY99 Research Plans

The Scientific Council made three major suggestions and several of less immediate importance of what might be included in the 5-year plan. Most, if not all, of the

suggestions of what might be included actually restate, and then support, what RERF is already doing.

Among the three major suggested inclusions was that RERF state a focused commitment to the generation and use of biologic dosimetric efforts to revise the DS86 dosimetry.

Since a National Academy committee is evaluating DS86, following which US, Japanese, and joint US-Japanese workshop groups will work on any revisions, which are anticipated to be completed in 2 to 3 years, it seemed inappropriate to add this to a 5-10 year plan. Also suggested was the inclusion of a definitive test that early onset breast cancers arose in individuals genetically susceptible to cancer induction. The council further suggested that candidate genes identified in rodent cancer susceptibility experiments might be included in these studies. RERF is already instituting such studies in a collaborative study with scientists from the British Radiological Protection Board. These will be added to the 5-10 year plan because the Scientific Council has also strongly recommended collaborative studies, which the foundation concurs with and actually had underway prior to the Council meeting.

The third possible inclusion deals with a major focus being made on the identification of genetic events associated with the AHS and F₁ populations. Because all previous experiments on genetic effects in the F₁ have been negative, it is premature to indicate that a major focus of RERF research in the next 5-10 years will deal with genetic events found in the AHS and F₁.

The Scientific Council then made several statements about RERF in general before making more specific comments about each department. In the main these comments encouraged increased collaboration with the international scientific community. They especially encouraged collaborative efforts in which RERF researchers are utilizing their tissue and epidemiological resources.

After endorsing RERF's efforts to attract graduate students to carry out their research at RERF, the Council also recommended that RERF not establish an independent Ph.D. degree awarding program within RERF. RERF staff were grateful for this recommendation for they never anticipated beginning such a program in the first place.

One recommendation that RERF establish an internal competitive granting program with funds going to groups or departments judged by external review to be the most meritorious needs serious evaluation before any attempted implementation. RERF has a limited budget that must be judiciously utilized to ensure that the entire mission is accomplished. Any investigator specific competition for the available funds could compromise the commitment to fulfill RERF's multifaceted program.

The Council endorsed all the recommendations made by the Multinational Peer Review of the Department of Epidemiology. Since RERF does not have the expertise, the Multinational Peer Review Panel recommended that a workshop with outside experts be held to determine research directions in molecular epidemiology. Holding such a workshop, with participants who would not be familiar with RERF studies, was expected to pose some difficulties. The Immunology Workshop endorsed a pro-

posal to study a possible imbalance of T-helper cells, but the Council expressed some skepticism. Since the views of the workshop participants and councilors were different, RERF will carefully weigh all the advice.

All in all, the Scientific Council addressed many policy issues and research approaches that were being carried out by RERF. Virtually without exception, they recommended approaches already being instituted by the RERF directors and department chiefs, which was very gratifying. That ended the report from Dr. Wolff.

Dr. Hirohata stated that the Scientific Council basically endorsed current RERF research activities. He also mentioned that the mandatory retirement age at RERF was 60, whereas the retirement age at many universities in Japan was 65, pointing out that this was disadvantageous for recruiting senior scientists. Dr. Wolff agreed with his comment, stating that, in addition to the need to employ young scientists (as had been emphasized the previous day), RERF should consider the possibility of raising the mandatory retirement age.

Dr. Douple asked why the retirement age had been set at 60, and whether that could easily be changed. Dr. Taira urged the board members to take into account the restrictions that RERF has in changing its regulations. The RERF Act of Endowment contains conditions which were attached when the Ministry of Foreign Affairs approved the establishment of RERF as a non-profit organization. Any change in the Act of Endowment must be discussed with the appropriate authorities. The RERF wage system should be in accord with the regulations for government employees, and RERF cannot change its system as freely as private companies can. Dr. Nagataki stated that one of the great restrictions that RERF has is that it must reduce the number of staff because of financial constraints. It will be a matter of importance to decide whether an increase in the mandatory retirement age should be applied only to the research scientists, or if it should be applied to the entire staff. He added that the key issue would be whether the general staff would agree to an increase in the mandatory retirement age which would apply only to research scientists.

With the above, the responses to the recommendations of the Scientific Council and FY99 research plans were approved.

6. FY99 Working Budget (presented by Mr. Kunitoshi)

In compiling the FY99 working budget, RERF intended to strengthen the research departments, while taking into account the need to reduce costs and make efficient use of the budget. The total budget is ¥3,960,939,000, and the number of budgeted personnel slots is 283. The budgeted number of research scientists is 48, whereas the actual number was 39 as of 1 June, and an increase in the number of research scientists is envisioned. Nine general employees are due to retire, and a minimum number of replacements are planned to reduce the general staff number. Personnel expenses have

been calculated based on a 1% salary revision and a 1.8% periodical salary increase. NAS expenses of ¥200,000,000 have been included in the personnel budget. The total operating budget is ¥819,842,000, which is the same as the amount unofficially announced by the government. The equipment budget is ¥173,575,000, about ¥130,000,000 less than the FY98 settlement of accounts. This is because of the unusually high equipment budget in FY98, which included the supplementary funding from the Japanese government and the "contribution from the new year postcards fund" from the Ministry of Posts and Telecommunications. The FY99 equipment budget is less than last year, but is about the same as other years. Similarly, the budget for supplies is about ¥25,000,000 less than the last year's settlement of accounts, which is due to the discontinuation of funding for supplies from HICARE. This year's budget for supplies is also about the same level as other years. The communications budget was increased because of the planned mail survey to the second generation of A-bomb survivors. The contract services budget was also increased, due to the F₁ study. The plant maintenance budget was decreased because of last year's renovation, which was done using supplementary funding.

In response to Dr. Nagataki's question as to why the US budget had decreased, Mr. Kunitoshi answered that it was not an actual decrease, but that one half of the portion to be borne by the two governments, calculated based on a fixed exchange rate, was only listed in the working budget.

The FY99 working budget was approved.

7. FY2000 Provisional Budget Plan (presented by Mr. Kunitoshi)

Personnel expenses were calculated by allowing for an FY2000 salary revision of 1% and a periodic salary increase of 1.8%. Due to an increase in the number of retirees (3), compared with FY99, the termination allowance was increased. The total personnel expenses are estimated to be ¥3,269,761,000, which is 3.9% more than the previous year. The FY2000 number of budgeted personnel slots has not been decided yet, so 283, the number as of the end of FY99, was used. The total operating expenses are estimated to be ¥832,140,000, which is 1.5% more than the previous year, because of increases in the equipment, contract services, and rent land/buildings budgets. The total FY2000 expenses are estimated to be ¥4,101,901,000, which is 3.6% more than the previous year. The presented budget is provisional and subject to change based on the unofficial budget allocation by MHW in December. At that time the FY2000 working budget will be compiled, and presented at the next board meeting. The FY2000 provisional budget plan was approved.

8. Revision of the Act of Endowment (presented by Mr. Kunitoshi)

The term of visiting directors will be staggered by one year for each director so that all of them will not retire at the same time and continuity of work will be allowed. The four-year term prescribed in Article 16 of the Act of

Endowment will not be changed, and a supplementary provision will be added. Of the visiting directors appointed to start on 1 July 1999, two will serve a term of two years (one Japanese and one American), and two will serve a term of three years (one Japanese and one American). It was explained that a similar revision had already been made for the term of scientific councilors. (Effective date: 1 July 1999)

The Board approved the revision of the Act of Endowment.

9. Revision of Rules and Regulations (presented by Mr. Kunitoshi)

(1) Revision of Employment Rules

(a) Partial Revision of Child Care Leave (Reference: Article 19-2)

As of 1 April 1999, it was decided to put into effect "The Law Concerning Welfare Benefits Such As Child Care Leave and Care Leave for Workers Engaged in the Care of Infants or Family Members" to make the care leave system a legal requirement, and restrict late night work by women. Accordingly, RERF revised a portion of its child care and care leave regulations. Change of leave period, restriction on midnight work and shortening of work hours will be made in accordance with the new law. (Effective date: 1 April 1999)

(b) Revision of Loan Regulations (Reference: Article 42)

The old loan system, which was based on the Agreement on Termination Allowance Trust Fund entered into by and between NAS and RERF in 1976, had been in use as part of the employees' welfare benefits. However, 23 years have passed since then and, due to the decreasing fund, we may not be able to maintain the loan system the way it is after the end of 2000. Under the revised loan system, internal funds mentioned above are not used, and an RERF employee enters into a loan contract with a financial institution, which, in turn, has a working contract with RERF and provides loan funds. (Effective date: 1 April 1999)

(2) Revision of Regulations Governing Salaries of Directors and Chief of Secretariat

The base pay of the directors and chief of secretariat was increased by 0.65% on average using as a guide the revision of the National Government Payscale for Designated positions. (Effective date: 1 April 1998)

(3) Revision of Wage Regulations

Base pay, dependents allowance and family separation allowance were revised using as a guide the FY98 revision of pay scales for national government employees. Also, a system of suspending salary increases based on age was introduced.

(a) Salaries: Increase by average of 0.72% for general employees, and by average of 0.61% for research scientists.

(b) Periodical salary increases: Periodical salary increases are discontinued for employees who reach age 57. (Effective dates: (a) 1 April 1998, (b) 1 April 1999)

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(b) Periodical salary increases: Periodical salary increases are discontinued for employees who reach age 57. (Effective dates: (a) 1 April 1998, (b) 1 April 1999)

The Board approved the above three items for revision of rules and regulations.

Before proceeding further with the agenda items, Dr. Nagataki asked Dr. Sato to state MHW's stance on financial support after 2001.

With regard to the financial support after 2001, Dr. Sato mentioned the following: If the subsidy from the US is reduced, there would be the following three options for the Japanese government? although we are not sure if all of them are possible.

- (a) MHW will compensate for the reduction of funds from the US.
- (b) Regardless of the reduction in the budget from the US, MHW will keep the same financial support level as in FY1999.
- (c) MHW will decrease its funding to the same level as the US funding based on the policy of equal sharing.

The Japanese government should notify the US government of its stance and views in various ways. Based on the discussion at this meeting, the Japanese government will formulate its stance. No matter which of the above three options MHW takes, it cannot make any commitment at this stage. Apart from financial measures, the following two possibilities can be considered in the worst scenario:

- (a) Cooperation and merger with another research institute. However, this is not a good time because the ministries and agencies in the Japanese government will be reorganized in 2001. This option can be considered after such reorganizations.
- (b) The last measure would be to lobby US congressmen. The Ministry of Finance will not accept any of the above three options at this stage. If the Japanese government is advised of the names of the key persons in the US, it may be able to work on them by some means.

Dr. Wolff asked if it would be possible for the representatives of MHW to go to the US to negotiate and if continued support could be obtained after Dr. Sato's transfer to another position. Dr. Sato mentioned that travel expenses to attend an important meeting would be covered and that his successor could deal with the matter in a similar manner after his transfer. Dr. Nagataki asked if the Board could do something useful for MHW, and if it would be useful to provide MHW with the plan for the future developed for DOE. Dr. Sato answered that any constructive opinion could be used to work on the Ministry of Finance and that the plan for the future would be useful. Dr. Taira stated that the Board hoped for continued support from DOE.

Then Mr. Hall from the US Embassy expressed his appreciation to the Board for inviting him as a representative of the US government and for having productive and useful discussions during the past two days. He added that, although the Embassy staff had to work under the instructions of the government, he would like to serve as a window of communication between RERF and the US government.

Dr. Nagataki expressed his gratitude to Mr. Hall.

Dr. Douple explained NAS's major arguments to be presented at a meeting with DOE in July in relation to the long-term plan developed by RERF.

- (1) RERF should be provided with the necessary financial support to continue its activities and accomplish its mission. NAS will refer to the number of A-bomb survivors who will be alive in 2020. NAS will request the US government to provide stable long-term support after 2001, and this issue has been discussed with Dr. Alberts, president of NAS.
- (2) It will be emphasized that the number of RERF staff is presently at the minimal level. The number of research scientists should be increased. The funding must be maintained at the present level or increased. Research needs will not be affected directly by the number of A-bomb survivors.
- (3) When DOE signed an agreement with MHW in 1996, DOE made three decisions. NAS hopes that these three decisions will be reconsidered and changed.
 - (a) Decrease in the number of US directors
 - (b) Severe budget reduction
 - (c) Decision to have the Japanese government cover all the expenses for AHS and the F₁ health study. Since the F₁ and AHS studies will continue to be very important, the US government should provide financial support as well.
- (4) There are three points of concern, which NAS hopes to resolve in cooperation with RERF.

(a) Dosimetry

The dosimetry committee at NAS (headed by Dr. Sinclair) is reviewing how the question of the existing discrepancy in DS86 can be settled.

(b) Facility

If NAS recommends continued support from the United States for RERF at least up to 2020, the current facility may not be good enough. Establishment of a committee to study the adequacy of the current facility should be considered.

(c) Surplus funds

Fortunately, during the past two years, surplus funds became available and were effectively used for facility repair and establishment of a specimen storage room. Some of the funds are still unexpended. It should be considered how the funds can be used most effectively for the future of RERF.

That ended a report by Dr. Douple. Dr. Sato stated that, in terms of DS86 reassessment, he was aware of the opinion that it was desirable for the Japanese side, including MHW, to reorganize the project so that it would move ahead. MHW hopes to review this matter within the ministry.

Dr. Nagataki asked what NAS was expecting from the negotiations with DOE on 12 July. He asked about the possibility that NAS could persuade DOE to change its three decisions, i.e., (a) decrease in the number of US directors, (b) severe budget reduction, and (c) decision to have the Japanese government cover all the expenses for AHS and the F₁ health study.

Dr. Douple replied that on 12 July they would probably discuss the level of funds that could be made available to RERF. As the new fiscal year starts on 1 October and travel funds will be available, DOE representatives might be able to visit Japan. Progress is unlikely earlier than that. NAS will make necessary proposals to DOE and emphasize the issues mentioned above.

Dr. Buffler prepared a draft letter of resolutions regarding the number of directors. The decrease in the number of permanent directors from six to three is a matter of concern. It is stipulated in the Act of Endowment that the number of American and Japanese directors be the same. Thus Dr. Buffler expressed her desire to have the Board of Directors unanimously adopt the following resolutions:

- (a) The Board of Directors supports the Act of Endowment which endorses an equal number of permanent directors to represent the United States and Japan.
- (b) The Board of Directors requests both governments that the number of permanent directors be returned to two from the United States and two from Japan.

Dr. Nagataki pointed out that these resolutions would constitute a request for a change of one of the nine items in the "Record of Discussion Concerning the Management of the Radiation Effects Research Foundation" exchanged between MHW and DOE in 1996. Dr. Shigematsu explained the background of the reduction in the number of US directors by one, and stated that an increase of American directors could not be considered until after the improvement of the financial state of the American side.

This was followed by active discussion among the directors. Dr. Buffler proposed that the American directors send a written request to the science advisor in the White House to ask for appropriate action to deal with the uncertainty in the availability of financial support to RERF beyond 2001. Before making such a request, a letter expressing the Board's resolutions should be prepared. In response to Dr. Buffler's comments, Dr. Nagataki said that caution should be taken at this stage because, although such resolutions might be effective when dealing with NAS and DOE, the potential effect of such resolutions on MHW and the Ministry of Finance was unclear.

Dr. Buffler then withdrew the proposal to send a letter expressing the Board's resolutions. As one of the American directors, she would like to think about different ways to approach the US government. Finally, Dr. Nagataki asked the board to leave the matter to the Executive Committee since this issue was of extreme importance and needed to be discussed further.

10. Election/Appointment of Directors and Others (presented by Dr. Nagataki)

(1) Election of Directors

A discussion was held on the reelection of the three Japanese directors (Dr. Kumatori, Mr. Arichi, and Dr. Oike) and the three US directors (Drs. Buffler, Samet, and Setlow), whose terms were set to expire as of 30 June this year. Dr. Nagataki explained that, although the term

of office for directors had previously been set at four years, the Act of Endowment had been revised so that two (one Japanese and one American) would serve two-year terms, and two (one Japanese and one American) would serve three-year terms for the appointments of this year. After deliberation, reelection of all the visiting directors was unanimously approved.

Toshiyuki Kumatori	Term: 1 July 1999–30 June 2001
Kazuaki Arichi	Term: 1 July 1999–30 June 2002
Masumi Oike	Term: 1 July 1999–30 June 2003
Patricia A. Buffler	Term: 1 July 1999–30 June 2001
Jonathan M. Samet	Term: 1 July 1999–30 June 2002
Richard B. Setlow	Term: 1 July 1999–30 June 2003

(2) Election of Supervisors

Reelection of Japanese Supervisor Yamazaki and US Supervisor Williams, whose terms were to expire as of 30 June this year, was discussed and unanimously approved.

Shudo Yamazaki	Term: 1 July 1999–30 June 2003
David Williams	Term: 1 July 1999–30 June 2003

(3) Election of Scientific Councilors

Reelection of Japanese Scientific Councilor Sasaki and US Scientific Councilor Phillips, whose terms were to expire as of 30 June this year, was discussed and unanimously approved.

Masao Sasaki	Term: 1 July 1999–30 June 2004
Theodore L. Phillips	Term: 1 July 1999–30 June 2004

(4) Appointment of Operating Committee Members

There were no new appointments. The current members will continue to serve.

11. Schedule of the Next Board Meeting (presented by Dr. Nagataki)

The Board decided to hold the next meeting in June 2000 in Washington, D.C., US. Dates will be decided later in consultation with the directors.

Upon completion of discussion of all items on the agenda, Dr. Nagataki declared the meeting closed at 5:50 p.m.

Appendix Three
Multinational Peer Review
Department of Genetics

Report of a Multinational Peer Review Committee on the Current and Future Genetics Programme of the Radiation Effects Research Foundation (RERF)

The Committee met at RERF Hiroshima on November 1–3, 1999 and consisted of:

- Dr. H. John Evans (chairman), professor, MRC Human Genetics Unit, Western General Hospital, Edinburgh University, UK
- Dr. Joe W. Gray, professor of Laboratory Medicine and Cancer Center, University of California, San Francisco
- Dr. Yusuke Nakamura, director of Human Genome Center, Laboratory of Molecular Medicine, Institute of Medical Science, The University of Tokyo
- Dr. A. T. Natarajan, professor of Department of Genetics, Radiation Genetics and Chemical Mutagenesis, Leiden University, The Netherlands
- Dr. Norio Niikawa, professor and chairman, Department of Human Genetics, Atomic Bomb Disease Institute, Nagasaki University School of Medicine
- Dr. Taisei Nomura, professor and chairman, Department of Radiation Biology and Medical Genetics, Graduate School of Medicine, Osaka University
- Dr. Akihiro Shima, professor, Department of Integrated Biosciences, Graduate School of Frontier Sciences and Department of Biological Sciences, The University of Tokyo

The Committee was indebted to the Chairman, Vice Chairman and Chief of Research, and staff of the Foundation for the excellent written summaries and oral presentations describing the achievements and future proposals relating to the Foundation's genetics programmes. The remit of the Committee was to review the genetics programme as a whole, both in terms of ongoing and proposed future work; to evaluate the performance of the staff; to assess the level of scientific management and involvement in collaborative studies; and to proffer advice from the Committee on what should constitute the possible future activities of the group.

General Comments

The quality of the work undertaken by RERF is acknowledged internationally and the results of its research form much of the basis on which governments base their legislation on radiation protection. The genetics group has made major contributions to this research, and the Committee complimented the group on its past and current achievements.

Much of the research undertaken by the genetics group was, and is, of necessity "mission orientated" and the Committee felt that the time had come to place a greater emphasis on more basic research along the lines identified below, but without compromising the emphasis on the effects of radiation on the individuals exposed to A-bomb radiation.

The Committee was impressed by the rapidity whereby staff had acquired and, in some cases developed and modified, sophisticated techniques in molecular ge-

netics and cytogenetics, and was impressed by the oral presentations of the staff and their participation in discussions. The programme of work has been well managed, but the Committee felt that collaborative programmes with other institutes/universities should be increased, and that this would help to promote some of the proposed more basic research activities.

The science of genetics has been expanding rapidly and advances in technology have, and will, enable major tracts of the human genome to be rapidly and accurately characterized so that any induced alterations in DNA sequence may be readily identified. In the meantime it is essential for the genetics group to define the level of significance that they should adopt in endeavouring to assess the genetic consequences of the radiation exposures of the A-bomb survivors.

Specific comments on the current and proposed future programmes are summarized below, together with a list of recommendations from the Committee.

Specific Comments

Following a welcoming address by Dr. Nagataki, Chairman of RERF and an introductory overview of the Foundation's research by Dr. Wolff, Vice Chairman and Chief of Research, Dr. Nakamura described the organization of the genetics group and the structure of its research programmes. During discussion comments were made on the recent finding by the Foundation's staff of a small, but significant, increase in non-cancer late effects in radiation survivors. Staff at RERF were also aware of a very recent publication by Parker et al. in the UK claiming that paternal low dose occupational radiation exposure was associated with an increased frequency of still births and neural tube defects. The possibility that this association is causal appears to be unlikely, but Dr. Preston indicated that RERF would be reexamining their own data in this area in some detail.

• DNA microarrays

Dr. Takahashi and colleagues have made excellent progress in the development of DNA microarrays for the detection of sub-microscopic microdeletions. The demonstration of the ability to detect a single copy number change at the HPRT locus using array CGH to a 10 kb plasmid clone was particularly impressive. Development of array technology within the RERF is highly appropriate since the technology is improving rapidly both in sensitivity and precision. It is likely that this technology, in the near future, can be used to screen a significant fraction of the genome for both mutations and deletions. This should allow definitive assessment of radiation effects transmitted to the F₁ population. In addition, the same technology can be applied to search for induced genomic changes in radiation-induced tumors. The challenge will be to select the most appropriate microarray analysis platform. Many possibilities are now being developed. These include genomic DNA, cDNA and

oligonucleotide based arrays. RERF scientists should carefully define their measurement objectives and requirements (e.g. an acceptable false positive rate) prior to selection of an analysis platform and then carefully check to make sure the system operates as desired. In addition, substantial effort must be deployed to development of computational techniques that will allow accumulation and analysis of the resulting data. The work in this field would benefit considerably by interaction with workers in other establishments and at national and international levels. The Committee was strongly supportive of collaborative studies.

• Two-dimensional DNA electrophoresis in mice and in the offspring of the survivors

Dr. Asakawa presented data on the frequency and spectrum of mutations detected by two-dimensional electrophoresis of restriction enzyme digested genomic DNA from the F_1 progeny of X-irradiated male mice, as well as preliminary data on DNA from the offspring of survivors.

The work was of very high quality and demanding in the search for rare events, and involved the use of computer analysis to detect variations in fragment ("gel spot") size as a result of existing polymorphisms or induced deletion/duplication. DNA analysis of mother/father/child trios had been undertaken in establishing the technique and, in collaboration with colleagues at the University of Michigan, deletions and some point mutations had been identified in the offspring of male mice having received 3 or 5 Gy of X-rays, although the numbers of mutations were small.

It was proposed to extend the use of this approach to examine 100 offspring of survivors exposed to a parental dose of >1 Sv, to continue the studies on the mouse, and to consider the use of the female guinea pig as an appropriate model system for the human female. The Committee raised doubts concerning the proposed guinea pig studies, but was more supportive of extending the mouse work, although emphasizing that other more efficient approaches to detecting induced deletions were becoming available.

• Microsatellite and minisatellite analysis

Dr. Kodaira presented the results of mutation analysis at microsatellite and minisatellite loci in F_1 individuals of A-bomb survivors.

No mutations were found in six microsatellite loci examined in 363 gametes (children) from survivors exposed to a mean dose of 1.9 Sv whereas they found 6 (0.6%) mutations in 939 gametes tested in controls, indicating that radiation effects in children of A-bomb survivors were not likely to be detectable using microsatellite mutational assays.

They have also examined mutations at minisatellite loci using multilocus fingerprint probes as well as single-locus minisatellite probes. Analysis of DNA's from exposed individuals using multilocus probes detected mutations at a frequency of 1.3% in 1,080 alleles, but this mutation rate was almost identical to that (1.4%) observed in the control population. This result also indicated no detectable effect on the mutation rate in the

F_1 individuals. However, the data obtained by Dubrova et al. from heavily-polluted individuals of the Chernobyl accident and their children suggested a doubling of the mutation rate at the children's minisatellite loci. Since a UK population was used as controls for this analysis, the difference in the mutation rate may reflect a difference between the different ethnic groups or of other factors in the environment. In fact, in as yet unpublished data from Estonia, in which the progeny of the Chernobyl "clean up" workers who had received around 25 rads were examined, also suggested no effect on the mutation rate at the same minisatellite loci examined in the UK report.

The work of Kodaira's group is of high quality so that their present conclusion that the mutation rate was not increased in F_1 individuals from the A-bomb survivors is probably acceptable, although they should estimate how confident their results are.

Taking account of this information, the Committee recommend that the group should not continue this type of analysis by simply expanding the number of the test materials. Although substantial progress has been made in developing sophisticated genome analysis tools, it may be that application of these tools will not reveal measurable genetic damage. Indeed, all of the data presented at the review (2D gels, DGGE and minisatellite analysis) suggest that comparisons of children of exposed and control populations now underway will not show statistically significant differences. Thus, it is critical that a "stop work" decision threshold be established for each project. For example, one possible criterion is that work should stop when control and highly exposed populations show no difference with 90% confidence.

It is expected that most projects will reach this threshold in the near future. Thus, it is important to develop long term plans for RERF research. One possibility is to initiate studies of basic aspects of mechanisms that influence susceptibility to propagation of genetic damage in F_1 populations with the goal of increasing the sensitivity with which damage can be detected. For example, investigations of mouse strains with varying sensitivity to propagation of such damage may reveal specific genetic polymorphisms that influence F_1 damage propagation. These polymorphisms might then be used to stratify highly exposed F_1 populations, so that damage assays search for differences between unexposed and the most susceptible subset of the exposed population.

• Biodosimetry

Dr. Nakamura presented data on the use of ESR of dental enamel to estimate dose, and demonstrated that accurate dose determinations could be made down to 0.3 Gy. A series of ESR analyses in relation to translocation frequency and DS86 skin and bone marrow doses suggest that DS86 underestimates dose at low exposure levels up to around 1 Gy, and overestimates dose at higher exposure levels. A similar conclusion was arrived at from the data on severe epilation.

Both ESR and chromosome aberration frequency clearly have utility for dose evaluation and the data from

these studies will be useful for any further studies envisaged to correct DS86. The Committee suggested therefore that future work in this area should be directed specifically at providing information for re-evaluating DS86, following which the work in this area should be de-emphasized. However, and in the context of potential nuclear accidents, it is essential that the capability for ESR and chromosome dosimetry should be retained within the Foundation.

• Clonal aberrations

Dr. Ohtaki presented convincing data demonstrating the presence of clonal aberrations in the blood of A-bomb survivors. Examining 158 survivors whose mean DS86 dose was 2.05 Sv, his group found chromosomal aberrations in more than one third of 50,000 cells. These included recurrent interstitial deletions involving the regions of 5q, to which MDS/AML deletions map, and the recurrent appearance of inv(14)(q11;q32) inversions. Both these types of aberration are frequently found in leukemias although there is no evidence of an increased risk for leukemia in these patients. However, the number of cases was small so it is important to follow these patients carefully. The frequent presence of these aberrations suggests that they encode genes that have a biological role in clonal expansion when deleted or rearranged. Efforts to precisely map these abnormalities and to eventually clone the involved genes are strongly encouraged. One possible approach is to isolate DNA from individual aberrant chromosomes, amplify it by degenerate PCR and hybridize the resulting material to microarrays being developed by Dr. Takahashi. This should allow efficient breakpoint/deletion analysis.

Dr. Nakano described the importance of clonal analysis in dose estimation. She clearly demonstrated that the incidence of clonal aberrations increases with dose. She also showed that failure to correct for the presence of clonal aberrations will cause doses to be slightly overestimated at higher doses.

Dr. Kodama presented impressive studies on the origin of these clonal aberrations within the lymphocyte lineage. Some appear to originate in the stem cell pool and others in the memory T-cell pool. Dr. Kodama also presented data on the association between clone frequency and size and radiation exposure that eventually may allow estimation of the numbers of human stem cells. These are the first data in humans that address these important questions and most likely could only be accomplished using material uniquely available at RERF. Further work on these topics is strongly encouraged.

• Neutron fingerprint F-value and S-value

Based on the track structure of low- and high-LET radiation, it was proposed that ratios of induced dicentric to rings (F-value) should be lower following neutron exposure in comparison to X-irradiation. Thus, lower F-values could be used as a fingerprint for exposure to high-LET radiation. Based on the F-value it has been proposed that the contribution of neutrons to dose is high in the atomic-bomb survivors in Hiroshima. Dr. Itoh pre-

sented both *in vitro* and *in vivo* data that showed no difference in F-values between neutrons and X-rays. Extensive data in the literature do not show a clear trend to suggest that F-values can be used as a fingerprint for exposure to high-LET radiation.

The low ratio between complete and incomplete translocations (S-value) has also been proposed as a fingerprint for exposure to high-LET radiation, assuming that high-LET radiation-induced breaks are difficult to be repaired. Dr. Itoh presented data that showed no difference between S-values for aberrations in atomic-bomb survivors and from those induced *in vitro* by X-irradiation. Since, it is now known that incomplete exchanges are indeed artifacts, the low S-value has no value as a fingerprint for exposure to high-LET radiation. It is therefore proposed that future studies in this area should be discontinued.

• Future plans

Dr. Kodama outlined possible future plans for the group under four headings: biodosimetry, genetics, clonal aberrations, and genetic instability.

The Committee considered that the proposal to extend the biodosimetry analysis by multicolor FISH to 1,500 survivors would require some 3,000–5,000 cells per person and was impracticable both in terms of labor and indeed cost. It was proposed that this work should be severely reduced, but that the capability for biodosimetry using chromosome and ESR analysis must be retained.

In searching for inherited induced chromosomal damage transmitted to F_1 progeny, the chromosomes from 16,000 children had been analyzed and only one mutational event was discovered in each the exposed and unexposed groups. It was proposed that 5 cells from each of 2,000 children born to parents with the highest exposures should be analyzed for chromosome rearrangements using multicolor FISH. It was recognized that the probability of detecting induced mutations in these children was very low, but that it was necessary to undertake this work on behalf of the offspring of those exposed.

The Committee considered the studies on the origin of clones and the structure and molecular nature of the rearrangements to be of high priority. A molecular analysis of breakpoints in the context of conferring selective advantage was very worthwhile.

The Committee considered the proposals on genetic instability, including *in vitro* studies on children born to high dose survivors, were not worth pursuing.

Recommendations

The Committee recognizes that the Foundation activities are somewhat constrained by the mission oriented nature of its research. The mission is very important and must not be lost sight of, but there should be an increase in emphasis on parallel and collaborative basic studies. A general expansion of current activities would not be an appropriate way to proceed for the future.

Specifically the Committee would recommend:

1. It is essential that every effort is made to expand the number of cells and cell lines derived from F_1 children and their parents, particularly those from parents ex-

posed at the highest dose levels. This is an unique and most valuable resource.

2. The work on mutations at microsatellite and minisatellite loci in radiation exposed individuals and their children is really completed and should be discontinued.

3. The group has established that S and F ratios do not define and distinguish between chromosome damage induced by radiations of different LET and there is no reason for further work in this area.

4. It is essential to establish microarray analysis for examining submicroscopic chromosomal deletions. For this effort, interaction with laboratories working on genome research is critical.

5. Rigorous "stop work" criteria should be established in all efforts to detect radiation effects (especially for F₁ studies) when it appears likely that effects will be small or undetectable (e.g. when "no effect" can be established with 90% probability). Once established, projects should be de-emphasized when they reach the stop work threshold.

6. The results of the origin of clonal chromosomal aberrations were biologically very interesting observations. Particularly the findings that some chromosomal clonal aberrations were of peripheral origin, and that conversion of memory T-cells to naïve cells was significant. Basic science studies related to these materials are strongly recommended.

7. Analysis of genetic instability needs extensive effort and significant findings would be unlikely to be obtained by the efforts available within the group. Hence the Committee does not recommend that the cytogenetics group spend their limited resources to pursue this approach.

8. Basic research should be initiated to identify subpopulations of F₁ individuals that will be more likely to harbor radiation-induced changes (e.g. children of exposed individuals that are susceptible to transmission of germ line defects). Genetic predisposing events may be detected from animal studies and/or by identification of individuals carrying predisposing polymorphisms involving genes involved in DNA repair, meiotic segregation, etc. Collaborative approaches to such research are strongly encouraged.

9. DGGE, minisatellite analysis, 2D gel DNA electrophoresis, and DNA microarray analysis techniques should be critically compared to identify the technique most suitable for large scale deletion analysis. That technique should then be put into routine use and the others de-emphasized.

10. Continued cytogenetic and ESR analyses of exposed individuals should be carried out only as needed to support DS86 modification efforts. However, the proposed multicolor FISH analysis of lymphocytes of children born to parents who had received high exposures should be supported.

11. In some clonal chromosomal aberrations, especially inv(14)(q11;q32), observed in A-bomb survivors, the region or breakpoints involved should be characterized at the molecular level. Microdissection and subsequent PCR-based cloning, and/or FISH using cosmid/BAC/PAC clones can be used for this approach.

12. The establishment of a genetics advisory group with

expertise in genomics, genetics, and haemopoiesis is strongly encouraged. This group should convene annually to review RERF work and to discuss research plans.

13. Research priorities must be established and resources redistributed accordingly.

Appendix Four

Workshop

International Dosimetry Reassessment Workshop

*by Shigenobu Nagataki, chairman, and
Shoichiro Fujita, assistant chief, Department of Statistics*

On 13 and 14 March 2000, more than 60 participants from Japan, the United States, and Germany, and including RERF Hiroshima and Nagasaki researchers, met at the ANA Hotel in downtown Hiroshima for the U.S.-Japan Joint Dosimetry Workshop, the largest meeting ever hosted by RERF. The workshop was co-chaired by Tatsuji Hamada, permanent director of Japan's Nuclear Safety Research Association, who headed the Japanese dosimetry group, and Warren K. Sinclair, former RERF director and president emeritus of the U.S. National Council on Radiation Protection and Measurements, who heads the National Academy of Sciences (NAS) Dosimetry Committee and who headed the U.S. working group.

RERF's mission is to conduct research to ascertain the human health effects of radiation and to disseminate research findings for use by the international community, including the numerous bodies that establish international radiation protection standards. The atomic-bomb dosimetry system we currently employ for our studies was adopted in 1986 and is referred to as the DS86 system. It replaced an earlier system—established in 1965—as better methods of calculating radiation dose were developed. In the almost 14 years since the 1986 methods were introduced, new published observations and calculations have led to a questioning of the usefulness of the DS86 system, but no consensus has been reached as to how to interpret the new information.

The National Academy of Sciences (NAS) Dosimetry Committee has been deliberating the issues surrounding DS86, and they are scheduled to make a final report in September 2000. This U.S.-Japan Dosimetry Workshop was convened to solicit the input of an international spectrum of scientists before the NAS report is finalized. The specific goals of the workshop were to provide a forum for Japanese, American, and European investigators to discuss openly the latest research results, any unresolved issues, and methods to solve any problems, to help decide the need for a revised dosimetry system and reach agreement between Japan and the U.S., to establish where future Japanese- and U.S.-funded work is going based on the observations of the Japanese and U.S. working groups and the NAS committee, and to provide a summary report of the conclusions and recommendations emanating from the two-day workshop.

For the greater part of the first day, the workshop participants reviewed the measurements of fast and thermal neutrons and of gamma rays, which had been obtained in Japan, the U.S., and Germany. In Hiroshima, there has been a discrepancy between DS86 calculations and actual measurements of the radioactivity induced by thermal neutrons in exposed rock, iron, and concrete (Eu-152, Co-60, and Cl-36). The measurements become greater than the DS86 calculations as the distance from the hypocenter increased. This issue of neutron discrepancy has been examined in the U.S. and Japan for about ten years. The tendency is clear, and it is considered that

we already have enough measurement data. With regard to the neutron activation measurements, some presentations and considerable discussion addressed the issue of background levels that might be produced by cosmic rays or other unidentified sources and the related issue of the depth profiles of measured values in core samples from massive bodies of material. Although it is generally thought that there is no such systematic discrepancy in Nagasaki, data suggest its presence. Therefore, measurements are still underway in Nagasaki.

Recently, it has become possible to measure very low radioactivity induced by fast neutrons in exposed copper samples (Ni-63), and several copper samples are being measured now. Since fast neutrons constitute a large portion of the neutron dose, it is expected that these measurements will be a key to solving the neutron problem. The number of available well-documented copper samples is quite small, and collection of more samples is urgent.

Gamma doses are measured by a method called thermoluminescence dosimetry (TLD). Measurements are slightly higher than DS86 calculations (by about 10%), but their correspondence is quite good. For the assessment of total radiation dose, the contribution of gamma dose is considered to be larger than that of neutrons. Thus, gamma doses are important. It is considered that we already have enough measurement data.

An RERF data base containing about 600 measurements of exposed materials was explained in outline form. The data base is elaborate and includes detailed information on the characteristics of each data set, and it is expected to be useful in a comprehensive assessment of measurement information and dose uncertainty.

Theoretical dose calculations were discussed towards the end of the first day, and examples of calculation aimed at achieving consistency with the existing measurements were presented. At this stage, it is extremely difficult to match calculations with measurements perfectly. Valuable data from the Tokaimura accident, which showed the credibility of the theoretical calculations of neutron dose, were also presented.

Workshop participants also considered how to achieve a more active exchange of information on survivor location and shielding as well as the role biological dosimetry should play in dose assessment.

Most of the second day was spent discussing current problems and their solutions, which were the key workshop issues. At the end of the workshop, the co-chairmen read a statement that not only emphasized the importance of the collection and measurement of exposed copper samples but also described the need to complete comprehensive assessment of radiation dose, including neutrons, within the next year. It was confirmed that DS86 would continue to be used until a new system was completed and approved jointly by senior dosimetry groups in the U.S. and Japan.

Workshop participants (non-RERF participants)

Masayori Ishikawa, assistant researcher, Research Institute for Radiation Biology and Medicine, Hiroshima University

Tetsuji Imanaka, assistant researcher, Research Reactor Institute, Kyoto University

Kazuo Iwatani, professor, Department of Radiation Technology and Science, Hiroshima Prefectural College of Health and Welfare

Satoru Endo, associate professor of applied nuclear physics, Faculty of Engineering, Hiroshima University

Takamitsu Oka, vice president, Kure University

Yutaka Okumura, professor, Department of Radiation Biophysics, Atomic Disease Institute, Nagasaki University School of Medicine

Kazuo Kato, assistant professor of home science, Suzugamine Women's Junior College

Toshisou Kosako, assistant professor, Nuclear Energy Research Center, University of Tokyo

Kazuhiisa Komura, chief, Low Level Radioactivity Laboratory, Faculty of Science, Kanazawa University

Masao Sasaki, professor, Radiation Biology Center, Kyoto University

Shozo Sawada, president, Hiroshima Prefectural College of Health and Welfare

Itsuzo Shigematsu, emeritus consultant, Radiation Effects Research Foundation

Kiyoshi Shizuma, professor, Common Lecture Course on Applied Atomic Nucleus, Faculty of Engineering, Hiroshima University

Seiichi Shibata, professor, Research Reactor Institute, Kyoto University

Tokushi Shibata, chief, Radiation Science Center, High-energy Accelerator Research Organization

Tatsuya Shimasaki, assistant researcher, Research Center for Isotope Science, Kumamoto University

Zhaksibay S. Zhumadilov, visiting professor, Research Institute for Radiation Biology and Medicine, Hiroshima University

Jun Takada, assistant professor, Research Institute for Radiation Biology and Medicine, Hiroshima University

Kouichi Takamiya, researcher, Research Reactor Institute, Kyoto University

Hiromi Hasai, professor, Department of Electric Engineering, Faculty of Engineering, Hiroshima Kokusai Gakuin University

Tatsuji Hamada, permanent director, Nuclear Safety Research Association

Norihiko Hayakawa, director, Research Institute for Radiation Biology and Medicine, Hiroshima University

Yasumasa Fukushima, assistant director, Planning Division, Health Service Bureau, Ministry of Health and Welfare

Masaharu Hoshi, professor, International Radiation Information Center, Research Institute for Radiation Biology and Medicine, Hiroshima University

Hiromichi Matsudaira, chairman, Radiation Effects Association

Takashi Maruyama, chief, Planning Department, Radiation Effects Association

Harold L. Beck, former scientist, Environmental Measurements Laboratory, U.S. Department of Energy

Robert F. Christy, professor emeritus of physics, California Institute of Technology

Sue B. Clark, assistant professor of chemistry, Department of Chemistry, Washington State University

Evan B. Douple, director, Board on Radiation Effects Research, Commission on Life Sciences, National Research Council, National Academy of Sciences

Stephen D. Egbert, Science Applications International Corporation (SAIC)

Naomi H. Harley, research professor in environmental medicine, Department of Environmental Medicine, New York University School of Medicine

Dean C. Kaul, Science Applications International Corporation (SAIC)

Albrecht M. Kellerer, director, Radiobiological Institute, Ludwig-Maximilians University (Germany)

Kenneth J. Kopecky, scientist, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center

Alfredo Marchetti, staff scientist, Lawrence Livermore National Laboratory

Jeffrey McAninch, staff scientist, Center for Accelerator Mass Spectrometry, Lawrence Livermore National Laboratory

Werner Ruehm, research scientist, Radiobiological Institute, Ludwig-Maximilians University (Germany)

Warren K. Sinclair, president emeritus, National Council on Radiation Protection and Measurements

Tore Straume, professor, Radiobiology Department, University of Utah

David Thomassen, program coordinator, Office of Biological and Environmental Research, U.S. Department of Energy

Joseph F. Weiss, Japan Program manager, Office of International Health Studies, U.S. Department of Energy

Robert W. Young, founding partner, INSIGHT

Marco Zaider, attending physicist, Department of Medical Physics, Memorial Sloan-Kettering Cancer Center