

Annual Report

1 April 1994-31 March 1995

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Radiation Effects Research Foundation

A Cooperative Japan-United States Research Organization

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放射研 Radiation Effects Research Foundation
RERF A Cooperative Japan-United States Research Organization

Publication date: December 1995
Publisher: Radiation Effects Research Foundation

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Printing company: Seikosha, Inc

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Introduction

A message from the chairman

by **Itsuzo Shigematsu, MD**



Itsuzo Shigematsu

In publishing the RERF annual report for Fiscal Year 1994, I wish to express my profound appreciation to the atomic-bomb survivors and those concerned in the US and Japan for their support and cooperation in the research program of the foundation.

The year 1995 is not only a monumental milestone marking the 50th anniversary of the atomic bombings,

but also a memorable year for RERF, which marks the 20th anniversary of its establishment. If the relocation plan of the Hiroshima facilities had proceeded on schedule, relocation would have been expected to take place soon. But as reported in the Fiscal Year 1993 annual report, a sudden change occurred due to the financial retrenchment policy of the Clinton Administration inaugurated in 1993 and the appreciation of the yen against the dollar.

Since the first budgetary meeting in August 1993 requested by the US Department of Energy (DOE), six binational meetings of DOE and Japanese Ministry of Health and Welfare representatives have occurred up through March 1995. Those meetings are summarized in this annual report.

At the 28th Board of Directors meeting, the most important issues deliberated were streamlining of operations and reducing expenditures while minimizing the effects of budget reduction on RERF's major research program.

In parallel with the continued financial stringency of the US government, appreciation of the yen has accelerated, further reducing the yen contribution of the US for RERF operations. In view of the present situation, the US government has requested a review for changing the US-Japan equal cost-sharing system that is based on the official notes exchanged between the two governments and also has proposed discontinuation of the contract with the US National Academy of Sciences and transfer of the contract to an appropriate university in the US.

I sincerely hope that these problems will be resolved as soon as possible so that the foundation can devote itself to research. Your continued support will be appreciated.

In conclusion, I, together with the entire staff of RERF, pray for the repose of the many atomic-bomb survivors who died during the year.

A message from the vice chairman

by **Mortimer L Mendelsohn, MD, PhD**

This has been a year of continuing retrenchment and uncertainty. Following the departure of Chief of Research Seymour Abrahamson and Chief of the Secretariat Tomoyuki Kono on 30 June 1994, we were reduced from six to four directors. Similar reductions in all phases of RERF have taken place, driven by tight budgets and nonreplacement of retirees. With the retirement of Radiobiology Chief Takeo Honda as this fiscal year ends, his cytogenetics laboratory in Nagasaki also will close.



Mortimer L Mendelsohn

In spite of this, RERF should look little changed to the casual observer. Granted, the buildings need paint, the landscaping is not as fine as before, and there is no longer any meal service in Hijiyama Hall. However, the rooms and corridors bustle with activity, new results follow one after the other, and the flow of publications is remarkably constant. To this point, the vital forces driving RERF clearly have weathered the declining circumstances.

Then in January 1995, the US Department of Energy (DOE) announced a major administrative change to accompany the ongoing fiscal reductions. It was DOE's intention to discontinue the 48-year-old management role of the US National Academy of Sciences (NAS) and replace it with a new style of management as prescribed in an unsolicited proposal from an American university. The news had an immediate effect, outraging the staff and electrifying them into a direct confrontation with DOE. As this played out in the newspapers and science-oriented publications, DOE was forced to withdraw the unsolicited proposal and extend the NAS contract for another 6 months. It is still their intention to select a university contractor by competitive bidding, but the public process has yet to start.

This turn of events was more than we could absorb, and we were left with a negative effect on morale and operations that still continues. In recent months, the DOE made strong efforts to calm the waters and repair the damage, but not to change their position on elimination of the NAS. Time will tell how all this will play out. Meanwhile, the staff are doing their best to maintain creativity and quality science, while trying to convince our sponsors and the rest of the world that the core of our studies not only must survive, but must do so with minimal governmental interference.

Fiscal Year 1994 Research Activities Report

There were many distractions at RERF during Fiscal Year 1994 (FY94) and most of them will continue into Fiscal Year 1995 (FY95). Uncertainties about funding, both current and future, and the implementation of an inflexible and stringent downsizing plan based upon nonreplacement of both mandatory and voluntary retirements are without doubt the most serious problems facing RERF. The Nagasaki Laboratory has been most immediately affected by this downsizing through closure of its Cytogenetics Laboratory at the end of FY94 and the planned closure of the Cell Biology Laboratory and the Radioisotope Facility at the end of FY95. Most distracting in terms of staff time, energy and emotions, however, has been the announced plan of the US Department of Energy (DOE) to replace the National Academy of Sciences (NAS) as its RERF contractor with a university.

Both because of this possible removal of NAS as contractor and because this is the 50th year since the bombings of Hiroshima and Nagasaki, the news and television media have been interested in RERF and ABCC. Many individuals have contacted us with requests for information and more have come to visit RERF to interview members of the staff and to videotape the facilities. These visitors were, of course, in addition to the usual plethora of visiting scientists and other visitors to RERF.

One must add to this mix the great effort and anxiety involved with preparing for, and finally accomplishing, the removal of the mainframe computer. Members of the Research Information Center organized this effort and were, in large part, responsible for successfully achieving the goal by December 31, but they did so with considerable effort and the full cooperation of persons from all departments.

During FY94 because of the uncertainties surrounding the budget, research expenditures were cut back by 30% until fall, and no research equipment was ordered until the end of August. Purchase of computer hardware and software to make possible the removal of the mainframe computer was given the highest priority. The savings from a negotiated reduction in cost of the lease for the mainframe computer and the ¥15 million in leasing fees saved by its removal before December 31 also were used primarily for computer-related purchases.

In the fall, the DOE agreed to transfer sufficient funds to enable RERF to operate at the level of its original working budget for FY94. Because of the diminished rate of spending by all departments up until that time, surpluses were available. Knowing that the recent DOE commitment meant that DOE would run out of funds for RERF in June 1995 unless other monies were identified, it was decided to use much of the surplus to purchase equipment. We were able to purchase all remaining high-priority items of research equipment requested for FY94 and nearly all priority 1 and priority 2 items that had been requested for FY95 before the start of FY95 (1 Apr 1995). It was also possible to buy a considerable amount of additional computer hardware.

Faced with continued concerns over a tight budget, loss of manpower, and the threatened removal of NAS, staff anxiety levels have been high and morale low. It is hard to conduct productive investigations under such conditions. Furthermore, the uncertainty regarding future funding stifles innovation and creativity without which a research program will most assuredly decline.

Following are the FY94 research activities reports prepared by the department chiefs. Lists of research papers published during FY94 begin on p 51 and p 62.

Department of Epidemiology and the Department of Epidemiologic Pathology

The epidemiology program covers a wide range of research and activities undertaken by two departments in Hiroshima (Epidemiology and Epidemiologic Pathology) and two in Nagasaki (Epidemiology and Biometrics, and Epidemiologic Pathology). This report covers activities in both Hiroshima and Nagasaki. The major objectives are (1) to manage the long-term follow-up of the Life Span Study (LSS), in-utero and F₁ cohorts; (2) to manage the Hiroshima and Nagasaki tumor registries, including the tissue registries; (3) to analyze and publish updated mortality and incidence data in the major cohorts; (4) to design and conduct a series of site-specific cancer incidence studies involving pathology experts; and (5) to design and conduct mail surveys and case-control studies to obtain information on factors. Recently, we also have been involved in collaborative research with radiobiologists at RERF and other institutions for developing and conducting molecular epidemiologic studies and for developing a genetic epidemiology program. We also have initiated and participated in various international collaborative studies.

One of the most important achievements in epidemiology in recent years is the restructuring of the Hiroshima and Nagasaki tumor registries, which was made possible by the deliberate joint effort undertaken by the tumor registry staff in both cities. This has led to the landmark publication of a series of LSS cancer incidence reports, including both solid and hematological cancers. The analyses of incidence and mortality data generated interest in various specific cancer sites where risk is elevated but which require further, more-detailed investigations. As a result, a series of site-specific cancer incidence studies were initiated, including skin, salivary glands, nervous system, liver, thyroid, ovary, lung and lymphoid system (Tokuoka, Tokunaga, Soda, Fujita, Mabuchi et al). Soon, another paper on the incidence of benign tumors in the LSS, using the tumor and tissue registry data, will be published [Editor's note: Ron et al, *Amer J Epidemiol* 142:68-75, 1995.] Analysis of second primary tumors as related to radiation exposure, started a few years ago, is now in progress (Rose, Mabuchi, Preston et al).

The preparation of *LSS Report 12* on cancer mortality through 1990, currently is being undertaken in collaboration with the Department of Statistics (Pierce, Shimizu, Preston, Væth and Mabuchi) and is in its final stages. Some analyses of LSS noncancer mortality also were performed, and preliminary results will be presented at the 1995 Scientific Council meeting. The most recent cancer risk data for the in-utero cohort (through 1989) was published last year (Yoshimoto et al, *Lancet* 344:345-6, 1994). Updating of the in-utero cancer data for an expanded cohort is now underway. Also underway is the analysis of updated mortality data for the F₁ cohort.

Over the years, a series of mail surveys have been conducted among members of the LSS cohort, with the most recent one being completed in 1990. The objective was to obtain information on nonradiation risk factors, such as tobacco smoking and alcohol consumption habits, socioeconomic variables, and reproductive variables in the LSS sample. These mail-survey data provide an opportunity for examining possible confounding and interactive effects of nonradiation factors on radiation risk. As an initial effort to analyze the mail-survey data, we examined factors for liver and breast cancers (Goodman, Mabuchi et al). We then began to systematically examine a variety of factors related to overall mortality, cancer mortality, and cardiovascular mortality. Preliminary results from the latter analysis (Cologne, Goodman, Mabuchi et al) indicate that smoking is a major factor for cancer and cardiovascular disease, as has been demonstrated by many other epidemiological studies, but that this and other factors, including socioeconomic factors, have little confounding effect on radiation risks.

New areas of research include molecular epidemiologic studies, genetic epidemiology, and international collaborations. Molecular epidemiologic studies are now underway in collaboration with the Department of Radiobiology and include such sites as the skin (*p53* and other oncogenes), liver (hepatitis B and possibly C viruses, *p53*), thyroid (*ret*), breast (*p53* and *BRCA* genes). Preliminary results from the skin and liver studies will be presented at the 1995 Scientific Council meeting.

Efforts to construct a family pedigree database for the LSS sample also are underway (Cologne, Mabuchi, Shibata et al). In a pilot study using breast cancer, much progress was made in designing the database and developing basic methods and procedures for identifying relatives based on information available from various RERF sources.

International collaborations include the preparation of the US National Cancer Institute/RERF project on epidemiologic support for various populations with chronic radiation exposure in the southern Urals such as the Techa River cohort and Mayak worker cohort (Preston and Mabuchi). We also have participated in international pooled analyses, including a recently published analysis of thyroid cancer incidence involving seven major studies (Ron and Mabuchi). [Editor's note: Ron et al, *Radiat Res* 141:259-77, 1995.]

Another collaborative project is a joint study of the atomic-bomb survivor populations and dose estimates (RERF DS86 and Hiroshima University ABS93D) in both Hiroshima and Nagasaki (Mabuchi, Shibata, Preston et al). The RERF and university populations differ in various ways, and the joint analysis is expected to provide better insights into comparability and limitations of dose estimates and differences in population coverage.

The tumor registries in Hiroshima and Nagasaki, operated by the Epidemiologic Pathology departments in the two cities, continue to provide high-quality population-based cancer incidence data for both the local community population and the RERF cohorts (Mabuchi, Soda, Fujita). The most recent incidence data for Hiroshima and Nagasaki have been included in the most recent volume of *Cancer Incidence in Five Continents* (published by the International Association/International Agency on Cancer Research), and childhood cancer incidence data are to be published in an upcoming volume on worldwide childhood cancer incidence.

The departments of Epidemiology and Epidemiologic Pathology, with technical support from the Research Information Center, have pursued actively restructuring the Master File/Tumor Registry database. The new relational database system will provide improved data quality, as well as provide better access to researchers and support personnel and should serve as the prototype for managing other important RERF data sets.

Given the mission imposed and the nature and size of research involved, the RERF epidemiology program is grossly understaffed. Last year, the Scientific Council emphasized the need for sufficient numbers of high-quality professional staff to be maintained in both epidemiology and statistics. While Japanese epidemiologists are extremely difficult to recruit, US epidemiologists are more attracted and easier to recruit. However, the effort to develop a collaborative program with the University of Southern California failed due to RERF's financial problem and the recent decision by the US Department of Energy to change the US administrator. Collaboration with university-based groups, both in the United States and Japan, may provide a solution to the recruitment problem, but RERF's research needs must be carefully assessed. Recruitment of qualified epidemiologists, both Japanese and American, will be most critical for maintaining and improving the productivity of the epidemiology program at RERF.

Department of Statistics

Currently eight professional staff members work in the Department of Statistics. The work of the professional staff is supported by three research assistants and two secretaries. At the beginning of 1995 Fumiyoshi Kasagi received a Doctor of Medical Science degree from Hiroshima University. In August 1994 Shizue Izumi, one of the department's research assistants, returned to RERF after 2 years of study in the Department of Biostatistics, University of Washington, having earned a master's

degree. Since her return Ms Izumi was promoted to group leader and, in addition to her own research activities, has taken a greater role in the management of the activities of the statistics research assistants. As a result of budget cutbacks and the inability to recruit statisticians (or other professional staff) caused by uncertainties about the future management of RERF, the number of statisticians at RERF has decreased by two over the past few years. This includes the loss, without replacement, of David Pawel in the summer of 1994. Dr Pawel worked on analyses of the chromosome aberration data and several other projects with the departments of Genetics and Clinical Studies. Because of the continuing inability to recruit much-needed epidemiologists, RERF statisticians have been taking a greater role in some activities of the Department of Epidemiology. To better serve the needs of the Department of Epidemiology, Donald Pierce is jointly working with the Department of Epidemiology.

Collaborating and providing of statistical guidance and assistance to other investigators at RERF continues to be a major function of this department. It is generally understood by researchers throughout RERF that nearly all investigations require statistical support in both the design and analysis stages. This support is needed not only for specific studies based on research protocols but also in a number of increasingly important ongoing activities, such as management of the Adult Health Study (AHS) and the Life Span Study (LSS) data, development of improved data-handling and quality-control procedures for the tumor registries and other major RERF databases, and the formulation of general plans for the use of the LSS data for analyses of radiation effects on cancer and noncancer mortality and cancer incidence. Members of the Statistics Department continue to take leading roles in a number of projects related to the reorganization of the RERF databases. These projects, which also involve members of the Research Information Center (RIC) and the Department of Epidemiology, include developing comprehensive master lists of members of the F₁ and in-utero cohorts, examining the nature of the dosimetric data for members of these cohorts, and restructuring of the tumor registry and mortality follow-up data to simplify access and improve the quality of these data.

Our close collaboration with members of the Department of Epidemiology on analyses of the LSS mortality and incidence data is continuing. Following publication of a series of comprehensive reports on cancer incidence about 18 months ago, the emphasis of our cancer incidence work has been on a number of site-specific incidence studies. Statisticians are currently actively involved in a number of site-specific incidence studies, including cancers of the lung, liver, skin, and salivary gland, tumors of the brain and central nervous system, and lymphomas. Work on *LSS Report 12*, which deals with mortality for the period from 1950 through 1990 will be completed in the summer of 1995. Part one of this report, which deals with cancer mortality, focuses on the nature of the dependence of the radiation-induced cancer risks on factors such as sex, age at exposure, and attained age. In preparing this report, we have been especially interested in the development of simple tabular and graphical summaries that we hope

will help readers develop a better understanding of the nature of the excess risks in the LSS data and make the RERF results more directly usable by the various groups that rely on the RERF data as the basic source of quantitative summaries of radiation risk.

While the collaborative work described above is important, methodological research carried out by RERF statisticians is also a major component of the department's contribution to the Foundation. This research includes both basic research aimed at improving our understanding of important statistical questions raised by the RERF data and the implementation of improved statistical methods for use with the types of data considered here.

Current research areas in which statisticians have taken a leading role include methods for the joint analyses of data for several endpoints as a means of assessing the potential magnitude of dosimetry errors or radiation sensitivity; general procedures to improve the approximations involved in the methods routinely used in analyses of the RERF data; the design and implementation of various methods for analyses of longitudinal or cluster-correlated data; statistical issues in biological radiation dosimetry, as a companion to laboratory studies currently underway in the departments of Genetics and Radiobiology; an investigation of issues related to the interpretation and estimation of relative biological effectiveness in RERF studies; and examination of the way in which so-called mechanistic or biologically-based models might be applied to the LSS cancer data. General work is continuing on statistical methods and software development for the analysis of large cohorts that has had a major impact on analyses of radiation effects data in the LSS and other populations.

To provide a better picture of the range of activities being carried out by members of the Statistics Department, activities of current members will be summarized briefly.

Department Chief Dale Preston is involved with a number of projects including *LSS Report 12* and several of the site-specific incidence studies. For several years, he has been working on a meta-analysis of radiation effects on breast cancer in several cohorts. Completion of this was delayed by the addition of data on a cohort of Swedish women treated for benign breast disease and the acquisition of updated information on several other cohorts. The first draft of the manuscript on the incidence analyses currently is being revised. During this past year, he also completed his term as a consultant for the preparation of the 1994 cancer epidemiology report by the United Nations Scientific Committee on the Effects of Atomic Radiation. Dr Preston has continued to work on the development of statistical methods and software for use in the analysis epidemiologic data of interest to RERF. He is also actively involved in the reorganization of the major RERF databases.

Over the past year, Assistant Department Chief Masanori Otake continued his work on the effects of prenatal radiation exposure on various measures of brain damage including severe mental retardation, IQ scores, and neuromuscular test scores. He also has made some progress in his work on radiation effects on growth and development at menarche in prenatally exposed A-bomb survivors. Dr Otake also has continued his

work on several other projects including studies of senile changes of the brain in A-bomb survivors and joint analysis of data on cataract and epilation.

Shoichiro Fujita continues his work on the documentation and development of the Dosimetry System 1986 (DS86). He continues to serve as the primary liaison between RERF and the Japanese Senior Dosimetry Committee. During the past year, Drs Fujita and Kasagi have been working with staff of Hiroshima University and Nagasaki University on comparing DS86 and the so-called ABS86 dosimetry system created by the university groups. Dr Fujita also continues to provide statistical support for studies of physiologic aging and some immunology and radiation cell biology research projects.

Eiji Nakashima's current work includes collaborations with members of the Nagasaki Laboratory's Department of Clinical Studies on studies of systolic blood pressure in persons exposed in utero, changes in cholesterol level among women at the time of menopause, and the prevalence of HTLV-I. Mr Nakashima's statistical research interests include methods for handling over-dispersed binomial data and the analysis of growth curve data. He also is doing some exploratory work on the use of mechanistic models for the LSS cancer data.

John Cologne's major collaborative projects are with members of the departments of Epidemiology (liver and breast cancer incidence, risk factors for cardiovascular and cancer mortality, radiation effects on onset of menopause, and interaction of radiation with other risk factors) and Radiobiology (consulting on issues of dose-response calibration and dosimetry with somatic mutation assays). Over the past year, with the support of staff from the RIC, Dr Cologne and Yoshiko Nakamura have made significant progress in the development of a family pedigree database. Dr Cologne is continuing his investigations of statistical issues in biological dosimetry and is involved in the development of a database of biological marker data.

Fumiyoshi Kasagi is working on a number of collaborative projects with members of the Department of Clinical Studies, including work on characterizing and predicting AHS participation rates, as well as several studies related to cardiovascular diseases. He also is involved in the study of senile dementia among AHS participants. Dr Kasagi continues to play a major role in organizing visits to Hiroshima by scientists from Russia and other countries under the auspices of the HICARE program. He also is active in a number of groups that are involved with studies of the epidemiology of cardiovascular disease in Japan.

Donald Pierce is working on general issues related to more-useful descriptions and inferences pertaining to the LSS cancer mortality and incidence data. Currently this involves two primary activities: (i) comparing site-specific risks for solid cancers in the LSS incidence data and (ii) preparing *LSS Report 12* on excess cancer mortality. These are part of more general and longer-term aims to clarify the generalizations that can be made from the LSS cancer research program and the major uncertainties that remain. The Statistics Department is placing greater emphasis on the need for RERF to play a

major role in this type of work. A "joint analysis" approach developed by Drs Pierce and Preston has led to progress in item (i). This approach involves fitting comprehensive models to the combined data on various cancer sites, so that some parameters may be taken as common to sites and others as site-specific, and it provides for clearer statistical inferences regarding site-specific differences in patterns of excess risks. Dr Pierce also is active in basic statistical research on the practical application of higher order asymptotics in parameter estimation and testing.

Robert Delongchamp's primary activities over the past year have focused on work with Drs Mabuchi, Yoshimoto, and Preston on evaluating health risks from in-utero exposure to radiation as observed in the survival data and cancer incidence data. In addition to carefully examining the mortality and incidence data within the in-utero cohort, this analysis includes an explicit comparison to data on cancer mortality and incidence among LSS members exposed in childhood. A similar approach will be undertaken in the development of a new database for analyses of cancer morbidity in the F₁ cohort. Dr Delongchamp also is working with members of the Department of Clinical Studies on a number of projects.

The Department of Statistics research assistants (RAs) make a major contribution to the work of the department. We continue to encourage them to take more active roles in analyses and general support. Yoshiko Nakamura and Sachiyo Funamoto work closely with department members on a variety of projects, including analyses of the AHS measurement data and of the LSS data on cancer incidence and mortality. Ms Nakamura's contributions to the family pedigree and liver cancer studies are particularly noteworthy. Ms Funamoto continues to play a central role in database development. Ms Izumi has begun an analysis of the AHS and F₁ blood group data. In addition to their primary responsibilities, the Department of Statistics RAs provide support for statistical computing and database access to members of all RERF research departments.

Department of Clinical Studies, Hiroshima

Introduction

The Adult Health Study (AHS) biennial examinations initiated in 1958 have continued in the Department of Clinical Studies. The primary purpose of this study is to determine by means of physiologically or biochemically determined values the types of diseases and abnormalities that might occur as a consequence of exposure to ionizing radiation, and to collate this information with other life experiences and death. However, if these examinations are to continue to be useful, more efficient examination methods and newer technologies must be introduced to obtain the kind of clinical information that will be needed to offset the steady attrition of the study population through death.

The following is an outline of research activities for FY94 in Hiroshima.

Adult Health Study platform protocol

AHS database

Since the decision was made to remove the mainframe computer, it became necessary to create a new AHS database for the workstation system. The AHS database working group, headed by Department of Statistics research scientist Fumiyoshi Kasagi, started work in July 1994 and has created the database design for AHS diagnoses and measurements. The actual work of creating these databases is in progress, and will require several more months to complete.

AHS Report 7

The AHS data accumulated during examinations from the first cycle to the 14th cycle have been analyzed. The results are being summarized as *AHS Report 7*. The content of this report includes three major topics: the characteristics of the AHS cohort, its morbidity status, and abnormalities in laboratory measurements. A manuscript on *AHS Report 7* is nearing completion.

In the first part, demographic changes of the population and projections for the future are analyzed. The population size of the original AHS cohort excluding the not-in-city (NIC) group was 13,846 (5,380 males and 8,466 females) in the first-cycle examination conducted from 1958 to 1960. The population has decreased significantly over the following 30 years by approximately 40% to 8,502 (2,844 males and 5,658 females) in the 16th cycle examination. By analyzing the temporal change in participation rate by birth cohorts, it became obvious that the participation rate tends to drop sharply after age 70 years. This brought to our attention the need to introduce new methods to supplement the loss of important information by introducing either annual examinations or a surveillance program.

The morbidity analysis includes studies of noncancer disease incidence even though only prevalence studies have been reported in previous AHS reports. Among the noncancer diseases studied, a significant dose response was observed in the incidence of myoma uteri and chronic liver diseases (chronic hepatitis and liver cirrhosis). This triggered new studies of these diseases to confirm their association with radiation exposure and to derive more accurate risk estimates. A manuscript on the incidence of noncancerous diseases was published in 1993 (Wong et al, *Radiat Res* 135:418-30, 1993).

Physiological or biochemical determinants such as serum cholesterol and blood pressure also were analyzed longitudinally over time rather than cross-sectionally using a growth curve analytical method to clarify the interaction of radiation on the aging process. The results for serum cholesterol have been submitted for journal publication. A manuscript on blood pressure is now nearing completion.

AHS health surveillance

Since the information on disease morbidity mainly has been dependent on the findings obtained at the time of examination, maintaining the participation rate has been an essential factor in the quality control of the AHS program. However, because of aging of the population, it is anticipated that the participation rate will fall significantly in the near future, resulting in less complete data collection on morbidity.

In response to the recommendations of the 1994 Scientific Council, a pilot mail survey followed by telephone contacting for nonresponders was conducted in Hiroshima and Nagasaki to assess the feasibility of using this method in the AHS program.

The response rate to the pilot survey was 92.5% in total; 70.9% by mail and 21.5% by telephone contacting. To implement this program for all AHS participants, the annual cost estimate for postage is about 1,760,000 yen for both Hiroshima and Nagasaki. In addition to the mail survey, additional information from medical records of clinics and hospitals will be collected. The implementation of the mail survey and medical record review will substantially improve health information retrieval on AHS participants. Since the feasibility of this method has been confirmed, we plan to introduce this method in July 1995.

Consent for blood storage

Storage of serum and other biological materials has been a high priority of the AHS. Routine collection and storage of lymphocytes from AHS participants was initiated in June 1990 in collaboration with the Department of Radiobiology.

A pilot study was conducted to investigate whether consent for storage of blood and its future use can be obtained from AHS participants without any problems. In both cities, a total of 156 patients had been approached for approval as of 20 January 1995. Only 3 patients refused in Nagasaki and none in Hiroshima. As of February 1995, the use of the form became a part of routine AHS operation in both cities.

Special clinical studies

Hyperparathyroidism

Saeko Fujiwara and others have been studying the prevalence and incidence of hyperparathyroidism among the AHS participants in Hiroshima and Nagasaki. An analysis showed that hyperparathyroidism is significantly increased in the exposed population. A molecular biology study of parathyroid adenoma has been initiated with the cooperation of the Department of Radiobiology.

Cardiovascular disease

Department Chief Kazunori Kodama, research scientist Hironori Ueda, and others are evaluating the AHS population from the standpoint of radiation-related cardiovascular disease including myocardial infarction, stroke, calcification of the

aortic arch and the abdominal aorta, systolic hypertension, retinal arteriosclerosis, blood coagulation, and peripheral vascular disease. These studies are particularly important to determine not only the presence or absence of an association between radiation and cardiovascular diseases but also whether any effect is direct.

The measurements of pulse wave velocity, which is known to reflect stiffness of the aorta caused by atherosclerosis, was initiated in April 1994 in Hiroshima, and the data were analyzed for radiation effect. The prevalence of abnormal pulse wave velocity (≥ 9.0 m/s) was significantly higher among heavily exposed subjects and the odds ratio at 1 Gy was 1.31 ($p = 0.02$). However, the effect became marginal when adjustment was made for age, body mass index, and systolic blood pressure. This result was consistent with the previous reports on various other endpoints of atherosclerosis.

In July 1993 measurement of ankle/arm blood pressure using a doppler device was introduced to detect latent peripheral vascular disease. The data collection is expected to be completed in June 1995.

Osteoporosis

Saeko Fujiwara and others started to examine bone mineral content by means of a new dual X-ray bone densitometer (HOLOGIC QDR2000) in December 1993. The data collection will be completed in 1995, and we hope the relationship between radiation and bone mineral density will be clarified by this study.

Dementia

In September 1992, Michiko Yamada and others initiated a senile dementia study to determine if an association exists between exposure to ionizing radiation and subsequent impairment of cognitive function and the occurrence of senile dementia. Data collection is expected to be completed in 2 years.

Menopause

Thanne Rose, Michiko Yamada, Midori Soda, and others have initiated a new prospective menopause study using the measurement of hormones, such as follicle-stimulating hormone (FSH) and estradiol (E_2), among the cohort that was young at the time of the bombings. This issue is important for understanding the biological changes induced in ovarian function by radiation. The hormone measurements were initiated in January 1994 in both Hiroshima and Nagasaki. Quality-control procedures using serum donated by volunteers also are underway in Hiroshima.

Liver disease

Shizuyo Kusumi and others began a liver study related to hepatitis B and C virus using serum measurements initiated in Hiroshima in May 1993 and in Nagasaki in September 1993. The measurements will be completed in 1995, and the analysis will follow.

Benign tumor study

Detection of various benign tumors such as myoma uteri, ovarian tumor, prostatic tumor, and liver hemangioma are being undertaken using abdominal ultrasonographic techniques in Hiroshima. Since an increase in the incidence of myoma uteri among heavily exposed subjects, which was reported in *AHS Report 7*, might have been caused by bias, it was necessary to conduct a new study using a uniformly applied diagnostic method.

An ultrasonographic study to detect tumors of the uterus was initiated in Hiroshima in March 1992, and data collection for one cycle has been completed. During the study period from December 1991 through December 1993, 2,031 women underwent ultrasonographic examinations. The prevalence of myoma nodules detected by ultrasonography revealed a significant dose response ($p < 0.05$), even after adjustment of examination condition (empty bladder vs full bladder) and uterine volume. The odds ratio at 1 Gy was 1.61.

Although the result indicated a strong association between the prevalence of myoma uteri and radiation exposure, the pathogenesis remains unclear. The results of this study will be presented at the 1995 Scientific Council meeting by Sachiko Kawamura.

Monoclonal gammopathy

Kazuo Neriishi and others are monitoring the occurrence of both benign and malignant monoclonal gammopathy in relationship to radiation exposure in the entire AHS population using serum protein electrophoresis as the screening test.

A new research proposal (RP 2-95, Masaharu Nobuyoshi) to study molecular biological events within the plasma cell during transformation may shed light on the pathophysiology of this malignant conversion and suggest earlier ways for its detection.

Psychosocial studies

A study to assess the frequency and nature of the social and psychological problems experienced by the survivors using accumulated data has been in progress.

The frequency of physical symptoms and the number of symptoms which fit the diagnostic criteria of somatization disorder, anxiety disorder, and depression by DSM 3R were analyzed based on a self-administered medical questionnaire survey conducted from 1962 to 1965.

Results suggested that the frequency of both physical and mental symptoms was higher among those exposed to the atomic bombs. Not only radiation dose, but also factors not related to radiation dose, such as death of family member due to the atomic bombing, affected this tendency.

Others

A medication survey on all AHS participants has been in progress in Hiroshima since January 1991.

Department of Clinical Studies, Nagasaki

Hepatitis C virus positivity study

A study on the relationship between radiation exposure and hepatitis C virus antibody positivity is continuing for all AHS participants in Nagasaki to obtain basic data concerning the mechanisms by which the incidence of hepatitis and other liver diseases are increased among the survivors.

Senile dementia study

The AHS subjects over 60 years of age are being studied to determine the prevalence of senile dementia. After the CASI questionnaire and the P-300 test are administered for screening, a neurologist examines the patient and makes a final diagnosis. The studies are being performed using the same methods for Japanese-Americans residing in Seattle, San Francisco, and Honolulu. We will analyze the various factors that may be involved in geographical differences in the prevalence of dementia.

Menopause study

We found in an earlier study that female survivors in Nagasaki who were exposed to at least a 2-Gy radiation dose had experienced the onset of menopause more than 1 year earlier. In a prospective study, we have now started to measure FSH and E₂ regularly in study participants who have yet to experience menopause to elucidate the effects of radiation exposure on the onset of menopause as determined by changes in serum hormonal levels.

Menopause and cholesterol study

The incidence of ischemic heart diseases increases after menopause. Based on the results of a previous menopause study in Nagasaki, we analyzed changes in coronary risk factors in the perimenopausal period and found that only the cholesterol level increased due to menopause. By using the study population for RP 5-93, we are conducting a joint follow-up study with the Third Department of Internal Medicine, Nagasaki University School of Medicine, on the trends of blood apoprotein, lipoprotein, FSH, and E₂ throughout the premenopausal and postmenopausal periods.

Department of Genetics

Laboratory of Biochemical Genetics

The following three projects are being carried out: 1) establishment of cell lines as samples for mutation screening, 2) development of techniques to detect mutations at

the DNA level, and 3) the undertaking of a pilot study to detect mutations in DNA sequences.

Establishment of cell lines

Our goal is to establish cell lines from B lymphocytes from 1000 families composed of a father-mother-child trio. In half of the families, one or both parents were exposed to A-bomb radiation of more than 0.01 Sv gonadal dose calculated using the relative biological effectiveness (RBE) of 20; the remaining half were the controls. Intact lymphocytes and granulocytes also are stored in liquid nitrogen for confirmation of mutations. In 1985, we selected 1525 families with an expected cooperation rate of 70%. At the time of selection, the Dosimetry System 1986 (DS86) was not available, and samples were selected using the revised tentative 1965 dosimetry (T65DR). In each of the selected families, a T65DR dose was available for both parents or one of the parents was not in city (NIC) at the time of the bombings (ATB).

The number of families for which cell lines have been established reached 914 during FY94. Among them, at least 711 families can be used in our future study, in which a DS86 dose is available for both parents or is available for one parent with the other parent being NIC. In addition, cell lines seem to be usable for 91 families among whom a DS86 dose is available for one parent with the other parent having been exposed at 4000 m or more from the hypocenter ATB, according to the master sample questionnaire. Thus, cell lines from approximately 800 families are usable.

Development of techniques to detect mutations

We have concentrated on introducing and improving two techniques to detect deletion/insertion/rearrangement (D/I/R) type mutations that removed or duplicated the totality of single alleles in single copy sequences. One method is the quantitative analysis searching for a 50% decrease or increase in band intensity on a Southern filter. This is because a fresh mutation would usually be detected in heterozygotes for one normal and one mutated allele. We have optimized conditions in Southern blotting and chemiluminescence staining of bands for image analysis and have examined the accuracy and repeatability of the analysis. Using the optimized conditions, we have started a pilot study to detect D/I/R events.

The other is a new two-dimensional gel electrophoresis (2-DE) approach, termed restriction landmark genome scanning, reported by Izuho Hatada et al, which provides over 2000 DNA fragments (spots) from a genomic DNA digest without using any probes. We had optimized experimental conditions for obtaining good 2-DE gels. Intensity and position of the spots are being analyzed by an image analyzer equipped with computer algorithms developed by James V Neel's group at the University of Michigan. We have examined the repeatability and accuracy of the technique with DNA samples from three mother/father/child trios. For characterization of variant or mutant fragments, we have prepared a genomic DNA library and developed methods

that permit target cloning of DNA spots on the 2-DE gels. The cloned DNA spots have been used as probes in the screening of the DNA library and Southern blot analysis of 2-DE gels. We have applied for funding from the US National Cancer Institute (NCI) for a program titled "The study of human mutation" comprised of four projects, each of which is based on examination using this technique. Collaborative studies with Drs Neel and Samir M Hanash of the University of Michigan will be carried out if the application is accepted.

The pilot study

We examined 100 families, a subsample of the 800 cell-line families, composed of 50 exposed families with 64 children and 50 control families with 60 children to detect mutations in microsatellites. Among the 128 gametes that produced the 64 children from the exposed families, 65 gametes were derived from exposed parents and the mean parental gonadal dose for these gametes was 1.9 Sv, and 63 gametes were derived from unexposed parents. Microsatellites consist of around 10-50 copies of motifs from 2-6 bp in length and are highly polymorphic in copy number of motifs, are randomly distributed in human DNAs, and occur frequently. We examined two tetranucleotide repeat sequences in the gene on chromosome 5 encoding the macrophage colony-stimulating factor 1 receptor in parents and children of the 100 families. The first tetranucleotide repeat sequence is composed of CCTT repeats and CTTT repeats, and the second is composed of TAGA repeats. The number of these repeats is genetically determined.

We detected two mutations in each of the two repeat sequences. All of them were derived from the unexposed parents. The mutation rate was 1.1% per gamete in the unexposed parents and 0% in the exposed parents for each of the tetranucleotide repeat sequences. Previously, we did not detect any mutations in three types of trinucleotide (CGG, CTG, CAG) repeat sequences in three genes controlling fragile X syndrome, myotonic dystrophy, and spinobulbar muscular atrophy, respectively, of 124 children. Thus, in total, we examined 307 alleles of the microsatellites derived from the exposed parents and detected no mutations, the mutation rate being 0% per locus per gamete. Four mutations were detected in 809 alleles from the unexposed parents, the mutation rate being 0.5% per locus per gamete. The mutation rates of the exposed and the unexposed gametes did not differ significantly.

These children and parents also were examined to detect mutations in the DNA fingerprints using multilocus minisatellite probes of 15.1.11.4 and 6.3 kindly provided by Alec Jeffreys. The average number of bands detected by the former and the latter probes were 17.4 and 16.6 per individual, respectively. We detected 25 and 16 mutations, respectively, at the loci detectable by the 15.1.11.4 probe and the 6.3 probe. However, it was impossible to determine the parental origins of the mutations. In the fingerprint examined with the 15.1.11.4 probe, 12 mutations were detected in the children of the exposed families and 13 in the children of the control families. By using

the 6.3 probe, 6 and 10 mutations were detected in the exposed and the control families, respectively. The mutation rate in the DNA fingerprints of the two groups did not differ significantly. These preliminary results suggest that A-bomb radiation did not heavily affect the germline instability at these minisatellite loci.

As a pilot study to detect *D/I/R* type mutations by using quantitative analysis of the intensity of chemiluminescent bands on a Southern filter, we examined type I procollagen α -2 chain genes and β -globin genes of 109 children from the 100 families after their DNAs were digested by *HindIII*. A total of 1.24×10^7 bp was examined but no *D/I/R* events were detected. Because no *HindIII* restriction fragment length polymorphism is reported in the two DNA regions examined, and the frequency of the *D/I/R* events seems to be very low, we did not examine parents. Parents should be examined when *D/I/R* events or candidates of the events are detected in the children. The efficiency of these examinations will increase as a result of this exclusion of parental examinations. It would be expected that 7×10^8 bp could be examined per year with this method.

Cytogenetics Laboratory

FISH examinations

Cytogenetic examination of Hiroshima survivors using the fluorescence in situ hybridization (FISH) method started in April 1994 on a routine basis. From April 1994 to the end of March 1995, 173 survivors were scheduled for examination and 129 blood samples actually were obtained. This participation rate of about 75% is close to what we had anticipated.

As for Nagasaki survivors, we confirmed no adverse effect of shipping blood samples to the Hiroshima Laboratory. However, we have not started routine examinations yet because of insufficient staffing in the laboratory.

FISH versus conventional staining data

From January to March, 18 Hiroshima survivors were examined by FISH to complete the pilot study RP 10-89. They consisted of the remaining samples from about 100 survivors who were to be examined by both FISH and conventional methods, but on different occasions. Preliminary analysis of the data showed that the aberrant cell frequency determined by conventional methods was on the average about 80% that of the genomic translocation frequency revealed by FISH (correlation coefficient $r = 0.90$). This means that the simpler Giemsa staining method will detect approximately 80% of stable aberrations provided that the observers are well trained.

Deletion analysis of G-banding data

G-banding data for 114 proximally exposed (average dose of 1.72 Gy) and 24 survivors of the control group have been summarized. Among the 27,000 cells examined, 1672 deletions were identified (1343 terminal deletions and 329 interstitial

deletions). The distribution of terminal deletion was positively associated with chromosome length, though weakly. In contrast, 115 interstitial deletions (35%) clustered on the long arm of chromosome 5 (5q).

Interstitial deletion of 5q is frequently observed in myelodysplastic syndrome (MDS) and in patients with acute myelogenous leukemia (AML). Several tumor suppressor genes appear to reside in the commonly deleted region, 5q14-5q33. Thus, it is possible that lymphocytes bearing the 5q deletion among the survivors are a result of positive selection of such aberrant cells. In fact, 5q deletions observed in each survivor tended to be identical although the deleted portion differed among survivors, which is in favor of the hypothesis. Compared with the size of the deletion observed in MDS and AML, it was considerably smaller in the A-bomb survivors. No common hematologic abnormality was found among six survivors bearing lymphocytes with 5q deletions at a frequency of about 2% or more.

Estimation of minimum detectable size of translocated chromosome segment by FISH

The FISH method allows easy detection of reciprocal translocations as a pair of bicolored chromosomes. However, not infrequently we encounter cases of apparent nonreciprocal translocations, ie, the presence of only one bicolored chromosome. We hypothesized that such translocations are, in fact, reciprocal as a result of two breaks, but one break occurred near the terminal end of the chromosome so that the translocated fragment is too small to be detected.

Among 2441 aberrations involving one of the painted chromosomes 1, 2, or 4, it was found that 2295 could be classified as reciprocal (type 1), nonpainted distal fragment is missing (nonreciprocal: type 2), or painted distal fragment missing (nonreciprocal: type 3). The ratio of the three types was 1629:501:165, respectively. Mathematical equations assuming a random distribution of chromosome breaks indicated that the minimum detectable sizes of painted and nonpainted chromosome tips are 11.1 Mb and 14.4 Mb, respectively. These values are close to the previous estimates of 5-10 Mb using the G-banding method.

Clonal aberration derived from bone marrow stem cells

We have previously identified one A-bomb survivor who carries an identical aberration (2 translocations) in about 10% of the T lymphocytes. The same aberration was found in about 10% of B-cell colonies established by EB virus transformation (collaborative work with the Immunology Lab). Because lymphoid-specific stem cells are not known, the results strongly suggested that the origin of these cells is a multipotent stem cell in bone marrow.

To confirm this, we examined BFU-E (erythroid) and CD34⁺ (a marker of multipotent stem cells) cell cultures from mononuclear cells in peripheral blood and found the same aberration at a similar frequency (ie, ~10%). Because these cells were cultured in vitro, there is no guarantee that they grew equally, and thus the frequency

does not necessarily represent the in vivo frequency. Nevertheless, the occurrence of identical aberrations consisting of two translocations within a cell is unlikely to occur independently, and therefore this is taken as confirmation of our hypothesis.

This is a new area of collaborative work between the Cytogenetics and Immunology laboratories.

Biodosimetry using tooth enamel by electron spin resonance

In April 1992, 100 tooth samples were sent to Midori Iwasaki of Katsumi Niwa's laboratory at Ohu University School of Dentistry for enamel separation and electron spin resonance (ESR) measurement. Because of limited staffing, ESR measurement proceeded slowly. Only 11 samples could be measured by the end of 1994.

In January 1995, ESR equipment was installed in the Cytogenetics Laboratory. Isolated enamels were returned to RERF, and ESR measurement was initiated. By the end of April 1995, 25 samples were measured, and the correlation between ESR signal intensity and the chromosome aberration frequency of the tooth donors was reasonably good. Cytogenetic outliers vis-à-vis DS86 dose disappeared when plotted against the ESR signal of tooth enamel.

International collaboration

About 40 blood samples (30 exposed and 10 controls) from the Urals Research Center for Radiation Medicine in Chelyabinsk, Russia, were examined by FISH. No significant dose effect was observed. Several explanations are possible. Firstly, the estimated doses of about 1 Gy were found to be bone marrow doses, mostly attributable to incorporated ^{90}Sr . Consequently, lymphocyte doses would be expected to be considerably smaller. Secondly, low dose-rate exposure is known to allow cells to repair DNA damage. Thus 1 Gy of chronic exposure may not be sufficiently large to detect as a dose effect by examining 500 cells per sample. Thirdly, the background frequency of stable aberrations may increase to several percent in the elderly, and this would have seriously confounded the dose effect.

Another collaborative study, though preliminary, concerns the Taiwanese living in a condominium containing ^{60}Co -contaminated iron in ferroconcrete. Physical dose reconstruction is still in progress, but it probably ranges between 0.5 and 1 Gy during the past 10 years. A total of 40 people (20 exposed and 20 controls), all below the age of 20 years, were examined by conventional staining methods. Only 39 aberrations were found in total, and the two groups did not differ statistically in any significant way.

These results suggest that the cytogenetic approach may not be useful for dose reconstruction after chronic exposures. Even if we detect a significant increase in the aberration frequency, conversion of the cytogenetic data to dose is not simple. For example, the dose-rate factor for stable aberration induction is not known. One may use the linear coefficient after fitting the in vitro dose-response data to the linear-quadratic

model. However, the model needs to be supported by actual data. Second, there are some indications that individual variation in radiosensitivity may be greater as the dose rate is reduced. Therefore, we now feel it is better to adopt ESR measurements on tooth enamel as a first approach to estimating radiation dose.

Department of Radiobiology, Hiroshima

Somatic mutation studies

We have been conducting various somatic mutation assays, and the major objectives of the studies are 1) to quantitatively evaluate the effects of A-bomb radiation on the genes of human somatic cells and 2) to test the applicability of this information to biological dosimetry and the risk of cancer development.

The erythrocyte glycophorin A mutation assay

We have measured the frequency of hemizygous mutant erythrocytes at the glycophorin A (GPA) locus by flow cytometry for 1226 heterozygous A-bomb survivors in Hiroshima and Nagasaki. In summary, GPA mutant frequency (Mf) slightly but significantly increases with age and the number of cigarettes smoked. Also, Mf is significantly higher in males than in females even after adjustment for smoking, and it was higher in Hiroshima than in Nagasaki. All these characteristics of background GPA Mf correspond to those of background solid cancer incidence obtained from a previous epidemiological study of survivors. The analysis of the dose response of Mf shows that the doubling dose is about 1.20 Sv, whereas the minimum dose for detecting a significant increase in Mf is about 0.24 Sv. No significant effects of sex, city, or age at the time of exposure on the dose response were detected. Interestingly, the doubling dose of GPA Mf was close to that for solid-cancer incidence in A-bomb survivors. This observation is in line with the hypothesis that radiation-induced somatic cell mutations are the major cause of excess cancer risk after radiation exposure. Furthermore, the dose response is significantly higher in persons previously or subsequently diagnosed with cancer than in cancer-free individuals. This may suggest an earlier onset of cancer due to elevated Mf or a higher radiation sensitivity in the cancer group, although the possibility of dosimetry errors should be taken into account. Based on these results, we propose that the GPA Mf can be used as a biomarker for the assessment of cancer risk among radiation-exposed persons.

As for the molecular analysis of GPA mutants, we have developed a reverse transcription-polymerase chain reaction (RT-PCR) system to detect GPA messenger RNA (mRNA) in reticulocytes enriched from peripheral blood. Reticulocytes normally circulate in peripheral blood at a frequency of about 1-3% of total erythrocytes and contain various amounts of mRNA in their cytoplasm. GPA mRNA extracted from reticulocytes was detected by 2-step PCR after cDNA synthesis. GPA M- and N-type cDNA were identified by RFLP analysis using B γ -I and Dde-I restriction enzymes, respectively. GPA mRNA in mutant reticulocytes from survivors who have high

mutant frequencies ($> 100 \times 10^{-6}$) was analyzed, and mutant reticulocytes were found to express non-productive-type mutations in the GPA gene, most probably gene deletion.

The lymphocyte TCR mutation assay

We have completed the T-cell receptor (TCR) mutation study of measurements on about 600 A-bomb survivors. Briefly, the slope of the dose response of the mutant frequency on A-bomb survivors is shallow, probably due to a mutant half-life of 2-3 years. However, it has been demonstrated that the TCR mutation assay has potential value as a biological dosimeter for those with recent or chronic radiation exposure. However, there is one difficulty in using this method as a biological dosimeter immediately after radiation exposure. Because most peripheral lymphocytes are at the resting (G_0) stage, it takes several months for the mutants to lose the expression of pre-existing TCR/CD3 molecules from the cell surface. So, we cannot detect an increase of the mutant frequency (Mf) until several months after the radiation exposure. It is presumed that the mutant phenotype could be expressed soon after irradiation if the lymphocytes were stimulated with a mitogen in vitro. Currently, we are studying this possibility. We examined the lymphocytes from uterine cervical cancer patients who had undergone radiotherapy. The TCR Mf in lymphocytes cultured with phytohemagglutinin in vitro for 7 days significantly increased after 1 week of radiotherapy (total 10 Gy for 1 week), whereas their Mf in vivo (before culture) remained at almost constant levels. Both in vivo and in vitro cultured Mf in healthy donors showed no significant changes. On the basis of the in vitro dose-response curve, an average irradiation dose of lymphocytes for the patients was estimated to be about 1 Gy, which was very similar to that (1.2-1.3 Gy) previously estimated by unstable chromosome aberration frequency for uterine cancer patients who received radiotherapy with the same regimen as in the present study (Lloyd et al, *Int J Radiobiol* 28:75-90, 1975). These results suggest that the TCR Mf in PHA-stimulated lymphocytes can be used as a biological dosimeter for recent radiation exposure.

The granulocyte Fc γ RIII mutation assay

Using flow cytometry, we have recently established a granulocyte Fc γ RIII gene mutation assay that is suitable for studying heterozygotes for NA1 and NA2 antigen. We examined blood samples from 395 NA1/2 heterozygous A-bomb survivors and from 17 volunteers from among the laboratory staff. Preliminary analysis showed that the Mf in healthy adults was $1-5 \times 10^{-4}$ and that it increased significantly with age. No relationship between Mf and radiation dose was found in the A-bomb survivors. However, dose dependency was observed for the Mf among those who were in utero or under 10 years old at the time of the bombings ($p < 0.05$).

Furthermore, we have established a system to do a molecular analysis of the mutants from A-bomb survivors. Genetic alterations of mutant cells not expressing

NA1 were examined by means of the restriction enzyme (Sal I) digestion method after RT-PCR of single cells that had been sorted by flow cytometer. The results revealed that the genetic alterations of the FcγIII gene were responsible for the mutant cells detected by FACS.

The lymphocyte HPRT mutation assay

To study whether there are unique mutations or differences in mutation spectra for mutants caused by radiation exposures, we have analyzed mutational events at the *hprt* locus of TG^γ mutant T cells cloned from A-bomb survivors using multiplex RT-PCR and sequencing. Gross structural alterations, detected by multiplex PCR as a loss of, or shift in, exon fragments of genomic DNA, were found in 10-15% of both the control and heavily exposed groups. The altered sequences in the *hprt* cDNAs, eg, base substitutions, deletions or insertions, and exon skipping, were found in similar frequencies in both groups. Such gross structural changes may be one mechanism by which A-bomb-induced HPRT mutant T cells have been largely eliminated from the peripheral blood in the decades since exposure.

Immunological studies

The study objectives are to clarify 1) the effects of ionizing radiation on differentiation, maturation, and competence of the immune system, and 2) the relationship between epidemiological differences in the development of diseases and altered immune function.

Studies on the existence of gene abnormalities induced in long-lived multi-potential stem cells

Chromosomal aberration frequency in peripheral blood lymphocytes is elevated in radiation-exposed persons, and identical karyotypic changes are not infrequently encountered in one blood sample as well as in separate samples taken from the same donor. Such clonal propagation originates either from a single immature stem cell able to expand and differentiate into several cell types or from a single mature lymphocyte able to expand after antigen stimulation *in vivo*. We have studied and confirmed, for the first time, that a single stem cell of an adult is capable of generating long-lived myeloid and lymphoid progeny that constitute several percent of the total population of circulating lymphocytes and hematopoietic progenitors.

Studies on the number and the activity of hematopoietic stem cells in peripheral blood

Blood from about 1100 AHS participants has been examined for the frequency of CD34⁺ cells by using flow cytometry and monoclonal antibodies along with hematopoietic colony formation by BFU-E and CFU-GM. The results of preliminary analyses of the studies follow. First, the number of total hematopoietic stem cells in the peripheral blood was significantly higher in males than in females, and their number

decreased with age in both sexes. Second, the number of hematopoietic stem cells, particularly those for monocytes and granulocytes, significantly increased with radiation dose in females. This suggests that myelopoiesis is promoted in females in the high-dose group. It is possible that the production of myeloid cell growth factors such as G-CSF and GM-CSF is increased in this group. We are now preparing a new research protocol to study the levels of cytokines in the plasma of these persons. Finally, there is a significant negative correlation between GPA Mf in erythrocytes and the number of erythroid progenitor BFU-E. Therefore, it seems worthwhile to compare both somatic mutations and hematopoietic activity to clarify the details of the late effects of A-bomb radiation on the hematopoietic system.

Studies on the usage of the T-cell receptor repertoire

To determine whether population biases exist among A-bomb survivors, we have examined the variable region (V α and V β families) of their mature peripheral blood T cells by flow cytometry using monoclonal antibodies against the various *TCR V* gene products. The responsiveness to superantigen staphylococcal enterotoxins also is being examined to observe the generation of T-cell diversity and production of hematopoietic stem cells. The statistical analysis and final report will be completed after examining all 1280 survivors selected for this study.

Human radiobiological studies in a SCID-hu mouse model

A SCID-hu mouse model has been established for human radiobiological studies. In one application of this model, we have developed an experimental model of human radiation-induced epilation by engrafting human skin onto SCID mice. The results suggest that a) the diameter of the hair decreases with radiation exposure and epilation occurs as the hair breaks when its diameter decreases to approximately 20 μ m or less, and b) the dose response of the epilation rate is similar to that of severe epilation of A-bomb survivors, giving some evidence of the validity of the model. We are also in the process of establishing a SCID-hu mouse model to study the effects of radiation on the differentiation, maturation, and recovery from radiation damage of human hematopoietic stem cells by implanting human cord blood. Preliminary data indicate that human hematopoiesis can be maintained in SCID mice for as long as 2 months.

Molecular oncological studies

The objectives of our studies are a) to study whether radiation-specific molecular fingerprints or differences in gene alterations exist among cancers in A-bomb survivors and b) to provide crucial substantiation for the epidemiological differences in various cancers that occur in A-bomb survivors.

Molecular epidemiological studies

We have prepared several research protocols to perform molecular analyses of various cancers on skin, breast, liver, thyroid gland, and lung by studying closely

related genes. Because the skin cancer specimens are small, we developed a multi-primer method to amplify several DNAs simultaneously. The presence of mutations in the *ras* family and *p53* genes were detected by polymerase chain reaction–single-strand-conformation polymorphism (PCR–SSCP), and the mutants were characterized by direct sequencing. Several tumors had multiple mutations in both genes. Differing mutation spectra in the controls and the highly exposed group will be sought once the remaining samples have been analyzed.

The *ret* oncogene is strongly suspected to be involved in thyroid carcinogenesis. Using reverse transcription–polymerase chain reaction (RT–PCR), we have found that rearrangement of the *ret* oncogene can be induced by *in vitro* X-irradiation. This finding supports the evidence that some radiation-induced thyroid cancers may have developed as a consequence of *ret* oncogene rearrangement induced by the radiation exposure. We applied this approach to human thyroid cancer in A-bomb survivors and children from Chernobyl. The activated *ret* oncogene was detected in 4 of 7 cases from which RNAs were successfully extracted. In comparison with the published data, this result seems to be high. These combined clinical studies and the *in vitro* inducibility of activated *ret* oncogene by X-irradiation suggest rather strongly that some of the thyroid cancers in children from Chernobyl developed as a result of their radiation exposure.

After completion of the collection of paraffin blocks from various sources, we will commence a study of thyroid cancer tissues from a large number of A-bomb survivors.

Cryopreservation of blood cells from AHS participants

To ensure that appropriate material will be available for future studies of the late effects of human exposure to atomic bomb radiation and to allow the exploitation of potential future technological advances and scientific discoveries, blood cells from 1857 AHS participants (628 men, 1229 women) were cryopreserved at the Hiroshima Laboratory from January to December 1994. Blood cells from a total of 8636 participants have been cryopreserved to date.

Department of Radiobiology, Nagasaki

Analysis of the radiation sensitivity mechanism in the severe combined immunodeficient mouse

The purpose of this study is to elucidate the mechanism of hypersensitivity to radiation at the molecular level. The severe combined immunodeficient (SCID) mouse has a genetic mutation in chromosome 16 and shows two kinds of phenotypic abnormalities, ie, a high sensitivity to radiation and abnormal V(D)J recombination. In this study, the *SCID* gene which is responsible for these abnormalities will be cloned by using the complementing method. Through isolation and characterization of the *SCID* mutant gene, we will attempt to analyze the mechanism of radiation hypersensitivity in SCID mouse cells. Furthermore, we will attempt to elucidate the mechanisms of radiation sensitivity in humans.

We isolated three radioresistant clones by transfection of a human cDNA library into SCID mouse cells (c60-1; c34-3; c48-3) as outlined previously. The responsible genes were cloned from each cell line using pcDneo, an expression vector for the cDNA library, as a probe. In detailed analyses, it was found that the clones c60-1 and c34-3 were identical; the length of the gene was 4.5 kbp, whereas that of c48-3 was 5.3 kbp. These genes were expressed ubiquitously, and both were shown to be novel by homology search analysis. The clone c48-3 contains 2.3 kbp of an open reading frame (ORF). Surprisingly, however, the DNA sequence analysis of c60-1 and c34-3 indicated that this gene contains no conserved ORF. Unfortunately, neither of the genes was present on human chromosome 8 nor on mouse chromosome 16. However, restoration of radioresistance by reintroduction of these genes into SCID mouse cells suggested that they are likely to be related to radiosensitivity.

As mentioned previously, we established three independent, radioresistant transformants (#43; #1-1; #19-1) by genomic DNA transfection. In the next step, we attempted to isolate the responsible gene from these cell lines. However, we have been unable to recover the gene fragments of interest. Therefore, we have resorted to two other methods: first, we tagged a cellular DNA and transfected it into the SCID cell line, and second, we used the *cosmid* library for transfection. About 30 radioresistant colonies were obtained. We are now attempting to isolate the transfected DNA fragment using the tag or *cosmid* vector as a marker.

Cryopreservation of blood cells from AHS participants

Lymphocytes from 808 AHS participants (311 men, 497 women) were cryopreserved from January to December 1994 at the Nagasaki Laboratory. To date, blood-cells from 1936 participants have been cryopreserved.

Research Information Center

Background

In fall 1991, the Research Information Center (RIC) initiated a multiyear project to replace the mainframe computer with a network of personal computers (PCs) and reduced-instruction-set computing (RISC) workstations. There were two objectives in this transition. The first was to improve capabilities and procedures for a) data processing, b) integration of data into research applications, c) electronic communication, and d) accessibility to software and information resources. The second was to significantly reduce overall computing costs. Elimination of the mainframe computer was originally scheduled for March 1996. Due to budgetary difficulties facing RERF in 1993 and 1994, concerted efforts were made to accelerate the transition due to the high rental cost of the mainframe computer (approximately ¥5.2 million per month). In early 1994, the RIC revised its target date for termination of mainframe rental to 31 December 1994.

FY94 Summary of Activities

Termination of mainframe computer use

The RIC successfully met the 31 December 1994 deadline to terminate rental of the mainframe computer. This was 15 months ahead of the target date set at the initiation of this project. NEC removed the ACOS mainframe computer from RERF on 17 January 1995. This ended an era of mainframe system computing that spanned approximately 34 years at ABCC/RERF, beginning with IBM mainframe computers during the period 1961-1976, followed by NEC mainframe computers from 1976 through 1994.

The RIC met the accelerated deadline by modifying strategies for development of application systems in the new computing environment. With the cooperation of users, the RIC converted essential application system features and postponed certain modifications and enhancements to the post-mainframe phase. The RIC also put emphasis on minimizing the financial burden arising from the acquisition of new hardware and software needed to build the new PC-workstation network system. Toward that end, we were successful in negotiating with NEC a 14% decrease in the monthly mainframe rental fee for the period April-December 1994, netting a savings over that period of nearly ¥6.5 million. Funds originally reserved for mainframe rental for the final 3 months of FY94 (January-March 1995) were also freed by terminating the rental contract in December 1994, thereby providing another ¥15 million to subsidize purchases for the new computing system. The RIC also identified equipment required for the new system, the introduction of which could be postponed to FY95 in order to balance purchases over multiple fiscal years.

Enhancements to PC-workstation network

Over 40 new IBM-compatible PCs were installed in FY94 and distributed among all departments in Hiroshima and Nagasaki. Over 25% of these units were installed in the Secretariat to support business and administrative computing. Previous to the introduction of these PCs, all business computing work was carried out on the mainframe computer and proprietary office computing systems. Pentium-model IBM-compatible PCs were introduced in research areas to meet the needs of scientists whose research involves computation-intensive work. All IBM-compatible PCs are connected to the RERF network. The total number of registered users has increased about 50% over the past year to approximately 200.

Two RISC workstations were added to the network to provide more powerful servers to support database management and data analysis activities. The central processing chips of three existing workstations were replaced. This was an economical way to extend the durable life of existing machines and provide significant improvement in performance for Internet services, user file management, network printing management, and front-end interfaces between users and the RERF database.

One workstation was added to the Department of Genetics to expand the capability to conduct image analysis of DNA on two-dimensional gels.

Internet services were expanded to provide users with access to a wider array of information resources. In addition to e-mail, remote log-in via telnet, and file transfer protocol (ftp) capabilities, users can now access the World Wide Web via Netscape and Mosaic, NetNews/Usenet newsgroups, and Gopher/Archie searching and downloading tools. All services are available in both Japanese and English languages.

Improvements to communications lines and expansion of the RERF network were carried out. The network communications line linking RERF to the Internet was increased from 128 kilobits per second (kbps) to 192 kbps in March 1995 to handle the increased use of Internet services by RERF staff. Within the Nagasaki Laboratory, network cabling was extended to all floors. The Hiroshima Secretariat was connected to the network to meet requirements for the new business system. We have completed preparation work that will allow us to double the transmission speed of the dedicated line between Hiroshima and Nagasaki in early FY95.

We have increased network hard disk storage to a total of approximately 45 gigabytes (GB) for storage of the Unix operating system, application software, RERF source data, and user files. The contents of all network hard disks are backed up nightly to tape. Rarely used source data and files are archived on tape.

Data management

The RIC Database Group has used Sybase, software for relational database management, and Uniface, a fourth-generation-language software package for developing screen-driven applications for users, to develop a data management system for the Master File Sections and Tumor Registry Offices in Hiroshima and Nagasaki. Staff in these areas are using the system to record and update data for the RERF mortality and incidence studies. Data from these activities are stored in a new RERF database that integrates data for the Life Span Study cohort, F₁ cohort, tumor registries, tissue registries, and DS86. Definition of the data structure to include additional hospital information for the tumor registries has been completed. The new database design has streamlined data flow procedures and eliminated many redundancies in storage of data. For research scientists and research assistants, the new database system has greatly reduced the preparation time required to designate criteria for data retrieval and to create working files for data analysis.

All other RERF data not mentioned above were transferred from the mainframe computer to the new network and reside as independent files on disk or tape.

The RIC supplemented work efforts of the Department of Statistics to transfer the DS86 dosimetry calculation system and its related input data files to the workstation network. Conversion and testing activities have begun.

All business data management is now carried out using a combination of commercial PC software and workstation utility software that were converted from the mainframe system.

Troubleshooting support

Because of the increasing number of computer users and the many changes implemented in the new system, the RIC established an on-line trouble desk. Through e-mail, users can easily notify RIC of problems or questions. All RIC staff and computer staff in Nagasaki monitor trouble mail, enabling computer support staff to be more aware of user problems, their current status, and method of resolution. Computer staff respond as quickly as possible to users, either by e-mail or in-person visits.

Research Directions for Fiscal Year 1995

The department chiefs will here outline their plans for the coming year or two. These plans are in general accord with the recommendations of the Scientific Council.

It has been clear that RERF needs more than short-term planning by individual departments. There is no reason for optimism about future RERF budgets. If RERF is compelled to continue the policy of nonreplacement of all retirees, within 2 or 3 years the research programs of every department will be severely damaged. Clearly, the ideal solution for RERF would be full funding of our budget with a less stringent nonreplacement plan. It seems very unlikely that this will occur, especially if the value of the yen against the dollar remains high. What options remain for preserving strong research programs—or at least some of them—at RERF? Two obvious solutions that have been often suggested but never acted upon are as follows: 1) exclusion of some programs from the equal cost-sharing agreement or 2) departure from the 50:50 agreement altogether. Without discussing the pros and cons of such options, one can say that with either arrangement it might be possible to maintain all current RERF research programs intact and abandon the current 5-year downsizing plan. Thus far, the funding organizations of both governments have not made convincing efforts to discuss anything except lowering expenditures by reducing operating expenses and/or by downsizing.

It is absolutely essential that long-range strategic planning be undertaken for RERF. Working together with the two governments such a plan could include the timing for an eventual termination of support from the US government. But regardless of those details, the essential ingredient of such a plan must be prioritizing the research. A healthy exercise even in times of no budgetary crisis, it is mandatory if the funding situation does not stabilize beyond 6- to 12-month periods.

Department of Epidemiology and Department of Epidemiologic Pathology

A number of important reports now under preparation are expected to be completed within the next year. These include *LSS Report 12* on cancer mortality; updated cancer risk for the in-utero sample based on an expanded cohort; risk of second primary cancer in the LSS; effects of nonradiation factors on total mortality, cancer mortality and cardiovascular mortality; and several site-specific cancer incidence reports including salivary tumor, liver, and skin cancers.

Substantial progress also is expected in various site-specific cancer incidence studies. Data collection and diagnostic confirmation will be completed for the studies of nervous system, thyroid, and ovarian tumors, and data analysis will be started for these sites. For cancers of the lung and lymphoid systems, initial case ascertainment work will be completed. No new site-specific studies are planned.

Analyses of mail-survey data will continue. Specific objectives for the coming year will be to compile all previous mail-survey data and present basic and comprehensive descriptive summaries on various characteristics of the LSS sample. This will be followed by work on further specific topics of interest, such as female reproductive history as related to certain female cancers.

Efforts will be continued to further develop various molecular studies. In this area, contact will be needed with the local medical community for developing plans for securing tissues and sharing DNA for molecular studies.

Through the Hiroshima and Nagasaki tumor registries, updating of cancer incidence data for the RERF cohorts as well as the local community population will continue.

Efforts also will be continued to construct and expand the family pedigree database. In particular, more work is needed in the validation of matching based on the presently available information and methods.

Collaborations with outside researchers will continue. If we receive approval of the NCI/RERF project on the Mayak and Techa cohort studies, preparatory work will begin, such as documentation of the data and the development of a database. Joint analysis of the LSS and Hiroshima University cohort data will be completed in the coming year, and a report will be published.

Department of Statistics

LSS Report 12 on cancer mortality will be completed and submitted for review during the summer of 1995. The second part of *Report 12*, which will deal with noncancer mortality in the LSS, will be finished soon after the cancer mortality report. Work on a number of the site-specific cancer incidence studies in which RERF statisticians have been heavily involved will be completed and manuscripts prepared in the next few months. These include studies of nonmelanoma skin cancer, liver cancer, and tumors of the central nervous system. The parallel analysis of radiation effects data from several breast cancer studies also will be completed during 1995. Additional work on the cancer incidence and mortality data include further comparisons of excess absolute and relative risk models and investigations into the use of "biologically based" models. It is also hoped that an initial analysis of data on multiple primary cancers will be completed in the coming year.

Analysis of the expanded in-utero cancer mortality and incidence data and a comparison of risks with those seen in survivors exposed between the ages of 0 and 9 will be completed by the end of 1995. Work on new analyses of the F₁ cancer data will begin.

In addition to continuing our collaborations on the analysis of cytogenetic and somatic mutation data, we plan to carry out studies on the joint use of multiple endpoints in biological dosimetry. The initial work in this area will involve the use of data on chromosome aberrations and GPA mutations.

In the coming year, we anticipate continued involvement in a number of clinical studies. There also will be a need for data preparation and analyses related to the next comprehensive report on the health status of the AHS population (*AHS Report 8*).

A status report on efforts to establish a family pedigree database for LSS studies will be presented at this year's Scientific Council meeting. This work will continue throughout the coming year. To use these data effectively, John Cologne and other RERF statisticians are learning more about statistical methods used to analyze family data. It is hoped that progress can be made on a number of other important database activities in which statisticians are playing a major role. These include reorganization of the AHS examination and laboratory test data, and the design and development of a database for biological samples and cytogenetic data.

As noted in the progress report, as a result of budgetary cutbacks and the general reduction in foreign staff at RERF, the Department of Statistics has lost two and a half positions over the past few years. In FY95, one of the senior Japanese statisticians will retire, with little prospect for replacement. In addition, the shortage of epidemiologists means that some RERF statisticians are spending significant amounts of time and effort on epidemiological research activities that go beyond the usual role of statistical collaborators in epidemiological studies. Despite the cutbacks, there has been little if any reduction in the number of projects in which RERF statisticians must be involved. While there have not been any serious problems to date, the loss of professional staff members and the inability to recruit suitably qualified people for essential positions in the departments of Statistics and, more importantly, Epidemiology are affecting our ability to meet RERF's statistical needs. These effects are most pronounced with respect to work with the clinical and laboratory data. Although, we are taking steps to cope with the staff reductions, we hope it will soon be possible to recruit the professional staff necessary to allow the continued success of the high-quality statistical program that has been developed at RERF over the past 15 years.

Department of Clinical Studies, Hiroshima

AHS platform protocol and special clinical studies

The basic examination plan will continue, but with more emphasis placed on clinical methods to evaluate noncancer diseases and age-related disorders.

Special clinical studies will continue for the detection of hematologic, endocrinologic, and cardiovascular disorders that may be radiation-related. Investigation on benign tumors also will continue.

AHS health surveillance

Aging of the AHS population is a serious concern in terms of possible effects upon participation rate. Based upon the recommendations of the AHS Health Monitoring Workshop and the Scientific Council, pilot studies to investigate the feasibility of a surveillance program have been conducted and the feasibility of using a mail survey

followed by telephone contacting was confirmed. The new survey method is expected to be introduced into the current AHS biennial examination program in July 1995 both in Hiroshima and Nagasaki.

AHS Report 8

The work to prepare *AHS Report 8* was initiated last year. The report will cover the study period of cycles 1-18 (1958-1994). A longitudinal analysis similar to that published in *AHS Report 7* will be done on population demographics, disease morbidity, and measurements. In the population demographics part, special emphasis will be placed on possible biases resulting from long-term follow up. Confounders and risk modifiers will receive more attention in the morbidity part.

Department of Clinical Studies, Nagasaki

Hepatitis study

Although the ongoing hepatitis study is scheduled to be completed by the end of August 1995, it is expected that, due to budgetary restrictions, it will be FY96 before we will complete the various immunological assays of all stored blood samples.

Senile dementia study

As for the dementia study, by the end of November 1995, we will have studied half of the AHS participants in a 2-year cycle. In the ensuing cycle, lasting until the end of November 1997, we will study the remaining half of the participants.

Menopause study

We started the menopause study in January 1994. Presently, we are conducting the third semiannual blood examination. We will continue performing blood examinations once every 6 months until all study subjects have become menopausal.

Apoprotein and lipoprotein measurement

We started the measurement of apoprotein and lipoprotein in February 1995. We will start the diet survey in June 1995.

Department of Genetics

Laboratory of Biochemical Genetics

As described in the summary of research for FY94, cell lines that have been established from approximately 800 families are usable for future study. New families for which parental DS86 doses are available will be selected, and cell lines will be established, keeping the original goal of 1000 families in mind. This means that we shall try to add 100 families each in Hiroshima and Nagasaki over the next 2 years.

The pilot study will be continued. The minisatellite loci will be examined with several probes, and several tetranucleotide repeat sequences will be screened for mutations. The pilot study for the detection of D/I/R events will be continued by using the quantitative analysis of the intensity of chemiluminescent bands on Southern filters. There is little information about targets suitable for the effective detection of radiation-induced germinal mutations. The radiation-induced mutagenesis data in mammals were mainly obtained by the mouse specific-locus tests conducted by Russell et al and other groups. As probes, we will use human counterparts of the mouse coat-color genes or other nearby human genes that were deduced from the syntenic relationship between the mouse chromosome and human chromosome. Some of them already have been collected. In the pilot study, the technique will be improved, and the efficiency of this method will be estimated.

We also will introduce 2-DE in a pilot study. Approximately 30 families (100 individuals) will be examined. In addition, to increase the numbers of nucleotides screened for mutations in one individual, an effort will be made to develop a 2-DE pattern of 2000 new fragments. At present, the 2000 fragments (spots) are derived from *NotI/EcoRV* fragments between 1 kb and 5 kb in length. The new 2000 fragments will be obtained from the longer 5-kb to 20-kb *NotI/EcoRV* fragments. By using a method that permits target cloning of DNA spots on the 2-DE gel, variant fragments will be characterized.

To verify the usefulness of the 2-DE approach in the detecting of radiation-induced mutations in mammals, a pilot study to detect germ-cell mutations in mice (BALB/c) will be carried out. Twenty pairs of male and female mice will be used. X-ray irradiation will be carried out after mating occurs once to produce F₁ mice that will serve as a control group, derived from unirradiated germ cells. Testes of the first 10 males will be irradiated with 5 Gy and those of the second 10 males will be irradiated with 5 Gy twice at a 24-h interval and mated with females. The control and the irradiated F₁ mice will be born to the same set of parents. We expect to obtain 30 F₁ mice from each dose group. We will prepare two types of gels for each sample, one for short 1-kb to 5-kb *NotI/EcoRV* DNA fragments and the other for longer 5-kb to 20-kb DNA fragments. Thus, the study will require 200 gels (30 × 3 × 2 gels = 180 gels plus 20 gels for repeat examinations).

It is expected that basic information will be obtained from the mouse study for estimating the numerical requirement to achieve statistically significant results, assuming equal radiosensitivity in the human and the mouse.

Cytogenetics Laboratory

Future plans depend on staffing availability in the laboratory. The following activities are currently being considered.

1. Continuing FISH examination of Hiroshima survivors.
2. Initiating FISH examination of Nagasaki survivors.

3. Selecting individuals exposed in the same houses for systematic examination for the origin of variation in the chromosome-aberration frequency dose response. We expect that variation will be much less between such pairs of survivors as compared to general variation if variation is largely caused by dose error.
4. Selecting additional tooth donors for concurrent cytogenetic and ESR measurements.
5. Further studying of clonal aberration cases for BFU-E and CD34⁺ cell aberrations (about 20 cases).

Department of Radiobiology, Hiroshima

Somatic mutation studies

At the last Scientific Council meeting, we presented the potential applicability of somatic mutation studies in cancer risk assessment. We will continue to measure somatic mutation frequency at the erythrocyte glycophorin A (GPA), T-cell receptor (TCR), B-cell and granulocyte HLA-A and granulocyte Fc receptor γ III loci in A-bomb survivors and other radiation-exposed persons. By comparing these mutation frequencies, especially GPA and TCR mutations, with cancer risk in these populations, we will determine whether these biological markers correlate with cancer risks. Statistical approaches for cancer risk estimation using these somatic mutation assays will be explored in collaboration with the Department of Statistics. Statistical methods for the application of GPA and TCR mutations to biological dosimetry also will be investigated. Furthermore, molecular analyses of the mutant genes will be continued in further attempts to discern the fingerprints of radiation-induced mutations.

Immunological studies

We described abnormalities in function and genes of hematopoietic stem cells of A-bomb survivors at the Scientific Council meeting. We will propose a new research protocol to study cytokine levels in A-bomb survivors for analyzing the relationship between cytokine production and the observed hematopoietic abnormalities. This study may help to clarify the late effects of radiation on the regulatory system of human hematopoiesis. At the meeting, we also showed preliminary data demonstrating the applicability of a SCID-hu mouse model in the study of acute radiation effects in humans. Following the recommendation of the councilors, we will prepare a new research protocol to expand our SCID-hu mouse studies to other radiobiology fields including somatic mutations and radiation-induced carcinogenesis. This model makes it possible to study radiation effects on human tissues *in vivo*, the pathogenesis of which has not always been clear from studies on the survivors.

Molecular oncological studies

At the last Scientific Council meeting, we presented our efforts to search for radiation-induced molecular fingerprints that should have remained in the tumors of

atomic bomb survivors. We have established workable methods to achieve our goals. Therefore, we will continue the molecular analyses of oncogenes and tumor suppressor genes such as *p53*, *APC*, *MCC*, *DCC*, *WT*, *Rb*, *ret* and *BRCA1* in thyroid, skin, liver, and breast cancers. The current state of knowledge suggests that the *ras* family, *ret* and *p53* are the most promising loci to pursue. We believe we will be able to arrive at some conclusion regarding *p53* and skin cancers. As for other cancers, we will continue our efforts to locate and collect tissue samples.

To elucidate radiation-induced effects of genetic and epigenetic alterations in carcinogenesis, studies using a transplantation system of human tissue into SCID-hu mice and an in vitro system will be conducted. Further, disruption of the cell cycle and genetic instability are reported to be intimately involved in carcinogenesis, hinting at the possible roles of some of the aforementioned genes. Such studies will help to clarify the interaction of ionizing radiation with such genes and contribute to the understanding of the mechanisms of radiocarcinogenesis.

Department of Radiobiology, Nagasaki

Radiation sensitivity in the SCID mouse

Regarding cDNA, we will continue to further characterize these genes. Above all, we will determine which region of the gene is critical for the radioresistance function. Furthermore, we will clarify the relationship between these genes and the SCID mutant gene.

Meanwhile, we will isolate the SCID gene from the established genomic radioresistant transformants. In addition, we will establish radioresistant secondary transformants by using the primary transformants' DNA in order to isolate a responsible gene.

Cryopreservation of blood cells

We will cryopreserve the lymphocytes to be obtained from about 1,000 additional AHS participants.

Research Information Center

IBM-compatible personal computer (PC) replacement of as many old, outdated NEC PCs as possible is necessary to complete the transition of all desktop computers. This will enable all users to access the RERF network and to run Foundation-standard software. Extension of the Hiroshima network to the Library will complete the plan to make the network accessible to each section of RERF in both cities. In April 1995, we will double the transmission speed of the dedicated line between Hiroshima and Nagasaki from 64 kilobytes per second (kbps) to 128 kbps. This is necessary to improve data transmission and retrieval time for Nagasaki staff who must access the database server and other resources located in Hiroshima.

Fine-tuning of the Master File and Tumor Registry system will be carried out, since many modifications were postponed to remove the mainframe early. Additional RERF source data currently residing in independent files (eg, in-utero cohort data, tumor registry hospital information, etc) will be moved to the RERF integrated database system. Planning for incorporation of AHS data will continue. The expansion of the integrated database to include an even wider array of RERF source data than mentioned here is anticipated beyond FY95. However, the loss of RIC database management personnel will slow all development work.

Staff will continue to provide assistance to the Department of Statistics in the conversion and testing of the DS86 dosimetry calculation system on one of the Unix workstations. The RIC and the Department of Statistics are communicating with Science Applications International Corporation (SAIC), providers of the DS86 computing system, to discuss programming and data-related issues. Since SAIC also has undergone a series of computer system changes since the inception of the DS86 system, both SAIC and RERF have indicated their desire to set up production versions on Unix-based computers at both RERF and SAIC. The RERF working group hopes to have its version of the system fully operational by the end of the year. It should be noted that the work described here concerns conversion of the DS86 computer program; the DS86 estimates produced from the program have been and continue to be available on-line for use by researchers.

Accelerating the business computing transition was made possible by postponing a number of modifications and enhancements. Considerable effort will be devoted to fine-tuning this new system. It is especially desired to implement new features and capabilities made possible by the new computing environment that will better enable the business computing software systems to meet Secretariat needs and those of the RERF departments that must send/receive business information to/from the Secretariat. The RIC also will begin conversion work to move certain business computing programs from the single remaining NEC workstation to one of the existing Sun workstations. This will eventually allow us to eliminate the NEC workstation and its associated rental costs. The resulting unified hardware platform also will simplify workstation support work by allowing the same operating system to run on all workstations.

Test development of the next-generation computerized AHS examination management system will begin so that the current system can be replaced in FY96. This will involve in FY96 the replacement in the Department of Clinical Studies of all NEC PCs—most of which are nearly 10 years old, obsolete, and in deteriorating condition—that are currently used to operate this system. Thus, it will be important to replace as many non-AHS system NEC PCs in FY95 to balance the financial impact on the RERF budget.

Approximately two higher-performance workstations will be needed to support the heavier user load on the RERF database, expanded use of data analysis software, and increased use of Internet services.

Because RERF is receiving only a small subset of the NetNews/Usenet newsgroups available on the Internet, we plan to expand coverage to receive a full Usenet feed.

We hope to identify a suitable e-mail package that can be used for both Japanese and English communication and that contains the features needed by RERF users. This also would enhance the ability to communicate smoothly within RERF and streamline maintenance and technical support work.

We plan to offer training to users to complete the transition to Microsoft Word for Japanese and English word processing on IBM-compatible PCs. This will provide a solid word processing package for users; will enhance the ability to import/export information from/to other Microsoft or Windows-compatible software (eg, spreadsheet, database, presentation graphics, scientific graphics, desktop publishing); will further unify the software platform at RERF; and will reduce costs.

Using a portion of the space previously occupied by the mainframe computer, we plan to set up a small room containing 5-6 PCs where software training for workstation and PC applications can be conducted. Both the RIC and users have long desired to have training facilities that will enable users to gain maximum benefit from the computing resources available at RERF. Discussion has begun about beginning an informal seminar series to provide information to users and to gain further insight about their interests and requests.

The RIC has lost four of its technical staff within the past 12 months. The effects of this loss, while already evident within the RIC in FY94, will become readily apparent to the Foundation as we move further into FY95 and our backlog of work increases. The areas of computing resources support (for PCs, workstations, and networking) and database support have been particularly hard-hit, having lost 40% of its staff. Remaining RIC staff are already pressed to their limits, and we will not be able to keep pace with user requests for technical support, application system modifications, troubleshooting, and education/training. Database development will be negatively affected at a time when the need to make strides in this area is critical to the needs of research scientists. Although recruitment of replacements is badly needed, the current budget and US contract management uncertainties make this difficult to realize. It therefore becomes even more crucial that RERF support the continuing education and training of existing computer staff so that they can acquire as quickly as possible the technological skills required to maintain the new RERF computing system and provide support to users.

With FY95 marking a new era in computing at RERF, it should be noted that the removal of the mainframe computer does not signal that the computing transition is complete, as our FY95 plans well indicate. It is also important to understand that, with any computing system, there is a continuing need for routine upkeep and replacement

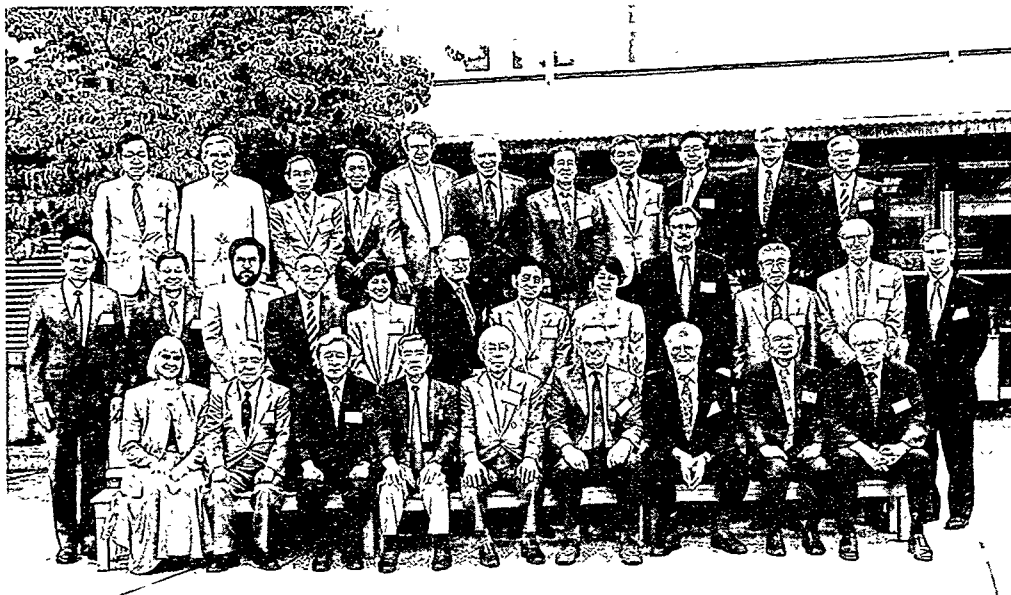
of core computing resources (eg, workstations systems, software, disk storage, communications network hardware, etc) shared by all departments. During the period 1961-1994, ABCC/RERF demonstrated its commitment to providing these resources through its yearly allocation of rental funds for the mainframe system, which at times ran as high as ¥70 million per year. In the new system, the ongoing need to replace and improve central hardware and software remains unchanged. Although the new system is much better situated to meet the technology needs of research departments and is less expensive to maintain, the effect of any operating budget shortfall at RERF has greatest impact in the areas of research and computing equipment. It is extremely important that long-term financial planning for RERF includes provisions for stable funding of these core resources if staff are to have the computing resources needed to conduct their research.

Major Meetings and Conferences

21st Scientific Council Meeting

The 21st Scientific Council meeting, held at the Hiroshima Laboratory, 13-15 June, strongly reflected tensions in research activities arising from budget reductions. This was the first time the Scientific Council met immediately before the RERF Board of Directors, instead of during the spring.

The co-chairman's summary of the council meeting warned RERF research scientists to be fully aware of uncertainties in the management and financial restraints at RERF, as well as never to lose sight of RERF's scientific mission and its significance. The council also stressed the significance of the long-term, follow-up survey of the biological and medical effects on the atomic-bomb survivors. RERF is carrying out three major research projects as follows: 1) evaluation of the lifetime health and genetic effects of radiation on the A-bomb survivors, 2) clarification of the mechanism of occurrence of radiation effects, and 3) establishment of a biological standard for evaluating radiation dose. Finally, it was stressed that progress in these areas will provide valuable data used in establishing international standards for radiation protection. Summarized minutes and detailed Scientific Council recommendations begin on page 131 of the Appendix.



Attendees of the 21st RERF Scientific Council meeting included, front row from left, S Preston-Martin, S Okada, E Ishikawa, H Matsudaira, E Matsunaga, C Heath Jr, L Herzenberg, T Hirohata, S Jablon. Middle row from left, R Sperry, J Zimbrick, T Honda, T Kono, J Ohara, S Abrahamson, R Shishido, C Satoh, E Washburn, I Shigematsu, M Mendelsohn, P Gilman. Back row from left, K Kodama, C Edington, Y Hasegawa, M Akiyama, D Preston, D Harkness, K Mabuchi, Y Shibata, A Awa, H Pettengill, Y Hirano.

11th National Institute of Radiological Sciences-RERF- Research Institute for Nuclear Medicine and Biology Exchange Seminar

Beginning in 1984, this annual seminar has been held to promote the common objective of "clarifying the physical and genetic effects of radiation on human beings." At the 11th seminar, held on 30 June 1994 at the RERF Hiroshima Laboratory, representatives of these institutions each presented results reflecting the respective institutional characteristics and discussed common problems related to assessing the effects of radiation.

This year, six researchers discussed molecular biological methods of assessing radiation effects.

- **Genetic instability in the minisatellite region in the offspring of A-bomb survivors.** Mieko Kodaira, research scientist, Department of Genetics, RERF.
- **Analysis of radiation-induced chromosomal translocation and leukemia specific chromosomal translocation using the FISH method.** Kimio Tanaka, research assistant, Department of Hematology, RINMB.
- **Conjugated control of ribosome synthesis and cell membrane synthesis.** Keiko Yoneda, research assistant, Department of Chemotherapy and Biochemistry, RINMB.
- **Mutation related to fragility syndrome X.** Masaaki Hori, chief, Department of Genetics, NIRS.
- **Cytological analysis of thymic lymphoma induced by radiation or chemical carcinogen in mice.** Toshiaki Ogiu, laboratory chief, Department of Physiology and Pathology, NIRS.
- **Relationship between the development of breast cancer induced by radiation and the growing stages of the mammary gland.** Makoto Onoda, senior researcher, Department of Pharmacology and Chemistry, NIRS.

3rd National General Meeting on Regional Cancer Registries

Held at the Hiroshima Medical Association Hall on 21 September 1994, the meeting drew more than 170 technicians engaged in regional cancer registry work from 35 regions nationwide. Participants included physicians, public health nurses, nurses, laboratory technicians, and registry workers. Related events also were held such as a meeting of registry workers, open sessions for free discussion, and a facility tour of the RERF Hiroshima Laboratory on 20 and 22 September.

The following lectures were delivered:

Keynote address

- **Role of the tumor registry in the epidemiological study of A-bomb survivors.** Kiyohiko Mabuchi, chief, RERF Department of Epidemiology and Department of Epidemiologic Pathology, and meeting chairman.

Administrative lectures

- **The 10-year strategy to defeat cancer and the role of the regional cancer registry.** Soichiro Iwao, director, Diseases Control Division, Japanese Ministry of Health and Welfare (MHW).
- **Introduction of the International Classification of Diseases, 10th revision (ICD-10), and alteration of the mode used for death statistics.** Ryuji Nomura, assistant director, Vital Statistics Division, Statistics and Information Department, MHW.

At a subsequent workshop, persons actively engaged in regional cancer registries participated in open discussions of the following topics: (1) the meaning and treatment of second primary cancers, and (2) the cancer registry in the Chugoku and Shikoku regions.

One of the objectives of this general meeting was improving the accuracy of cancer registry by training cancer registry workers. In the open discussion of cancer registry workers held at the RERF Hiroshima Laboratory, a lively exchange of questions and answers occurred on the problems accompanying the change from the ninth revision of the International Classification of Diseases to ICD-10 and their solutions. Also, the meeting participants toured the RERF Tumor Registry Office, Department of Epidemiologic Pathology, and the Master File Section, Department of Epidemiology, and observed how the RERF tumor registry ascertains and identifies cancer patients and how the computer database is maintained.

Research Protocols by RERF Program

1 April 1994-31 March 1995

Editor's note: Manuscripts (☐) as yet unpublished in scientific journals are listed under the relevant research protocols. These have been approved by the RERF directors for journal publication. Reports that have been published in scientific journals are listed with their summaries beginning on page 51.

Life Span Study


- RP 2-61** Study of mortality in children exposed in utero [Editor's note: See ABCC Technical Report 21-60 for the full text.]
- 1-75** Research plan for RERF study of life-span of A-bomb survivors, Hiroshima and Nagasaki [Editor's note: For the full text of this platform protocol, see ABCC Technical Report 4-59.]
- ☐ Væth M, Pierce DA, Preston DL: The impact of neutron radiation on cancer mortality among the A-bomb survivors
- 6-88** Comparative analysis of the LSS population and a cohort of 265,000 Japanese men and women

Adult Health Study

- RP 2-75** Research plan for RERF Adult Health Study, Hiroshima and Nagasaki [Editor's note: This is a platform protocol.]
- ☐ Yamada M, Wong FL, Kodama K, Sasaki H, Shimaoka K: Longitudinal trends in total cholesterol levels in a Japanese cohort, 1958-1986



Immunology

- RP 36-63** Blood groups in Adult Health Study and in utero ATB subjects Hiroshima and Nagasaki
- 3-87** 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
- ☐ Akiyama M, Kyoizumi S, Hirai Y, Kusunoki Y, Iwamoto KS, Nakamura N: Mutation frequency in human blood cells increases with age

- RP 7-87** X-ray radiosensitivity of lymphocytes in vitro from A-bomb survivors. Part 3: Transformation of B-cells by Epstein-Barr virus and their cryopreservation (addendum to RP 3-86)
- 7-88** Study of somatic mutations at the glycophorin A locus in erythrocytes of atomic bomb survivors
-  Akiyama M, Kyoizumi S, Hirai Y, Kusunoki Y, Iwamoto KS, Nakamura N: Mutation frequency in human blood cells increases with age
- 7-89** Screening of stem cell mutation in lymphoid lineage among A-bomb survivors and its characterization
- 9-89** Detecting erythrocyte mutations at the glycophorin A locus in Nagasaki A-bomb survivors and in Hiroshima area poison gas workers (addendum to RP 7-88)
- 11-89** A pilot study for detecting somatic mutations at the HLA-A locus in lymphocytes (reactivated)
- 2-90** Cryopreservation of blood cells from Hiroshima and Nagasaki Adult Health Study participants
- 1-93** Repertoire of T-cell antigen receptors and activity of hematopoietic progenitor cells in peripheral blood of atomic-bomb survivors (addendum to RPs 3-87, 4-87 and 7-89)
- 2-93** Development of assay for somatic mutation at the locus of the neutrophil Fcγ receptor III gene and preliminary study of atomic-bomb survivors

Special clinical studies

- RP 4-85** Incidence and risk factors of coronary heart disease (CHD) in Japanese men living in Japan and Hawaii, 1966-78 (addendum to Research Plan TR 12-71)
- 6-85** Study of M-proteinemia in the Adult Health Study sample (addendum to RP 9-79)
- 4-86** Evaluation of index of physiological measurements: A predictor of mortality or morbidity associated with aging
- 5-86** Dietary habit survey using a simple and computerized diet survey system (addendum to RP 8-83)


- RP 11-86** Prevalence of hyperparathyroidism in atomic bomb survivors during AHS cycle 15, Hiroshima and Nagasaki
- 5-87** Radiation-related damage to the developing human brain
- 1-89** Prevalence of radiation-related skin lesions in the Adult Health Study population, Hiroshima and Nagasaki
- 2-89** Hypercalcemia in A-bomb survivors, Hiroshima and Nagasaki (addendum to RP 11-86)
- 3-89** Osteoporosis in Hiroshima atomic bomb survivors
- 6-89** Incidence of radiation-related skin lesions in the Adult Health Study populations of Hiroshima and Nagasaki, 1958-89
- 3-90** The association of serum cholesterol with noncardiovascular mortality and morbidity in the Adult Health Study population
- 3-91** A comparative study of vertebral fracture prevalence among Japanese, Japanese-Americans in Hawaii, and Caucasians in Minnesota
-  Fujiwara S, Huang C, Ross PD, Yamada M, Kodama K, Davis JW, Wasnich RD: Osteoporosis risk factor profiles differ between native Japanese and Japanese-Americans
- 5-92** Study of senile dementia among the Adult Health Study subjects
- 6-92** Establishment and operation of a system for collecting and storing leukemia cells
- 9-92** Study of liver diseases in the Adult Health Study sample: Relationship between radiation dose and infection by B and C hepatitis virus
- 4-93** Epidemiologic study of antiadult T-cell leukemia-associated antigen antibodies in the Adult Health Study sample, Nagasaki (addendum to RP 1-85)
-  Oishi K, Shibata Y, Nakamura T, Tsujihata M, Akahoshi M, Matsuo T, Tomonaga M, Nagataki S, Shimaoka K: Autoantibodies and immunoglobulins in atomic bomb survivors with human T-lymphotropic virus type I
- 5-93** Longitudinal study of hormone indicators of menopause in perimenopausal female atomic-bomb survivors
- 1-95** Effects of menopause on risk factors for ischemic heart disease—a longitudinal study of the Nagasaki Adult Health Study sample

- RP 2-95** Pilot study: characterization of monoclonal gammopathy by studying the role of BSAP gene in CD19 antigen expression

Histopathology

- RP 5-89** Pathology studies in Hiroshima and Nagasaki. Revised research plan [Editor's note: Formerly RP 3-75, a platform protocol.]
- 8-89** Senile changes of the brain in Hiroshima and Nagasaki A-bomb survivors

Cell biology

- RP 18-81** Pathophysiology and radiation response of human thyroid cells in culture and in grafts in athymic nu/nu mice
- 2-86** Collection of surgically removed cancer tissues from A-bomb survivors: Special reference to thyroid and breast cancers
- 7-91** Analysis of radiation sensitivity mechanism in the severe combined immunodeficient (SCID) mouse
-  Araki R, Kaku M, Shiku H, Itoh M, Hamatani K, Abe M: RAG-1 and RAG-2 proteins expressed by the baculovirus system exist in the nuclear matrix
- 7-92** Molecular analysis of the p53 tumor-suppressor gene in breast cancers of atomic-bomb survivors (with addendum)
- 3-93** Molecular analysis of skin cancer in atomic-bomb survivors
- 7-93** Molecular analysis of thyroid cancers among atomic-bomb survivors
- 2-94** Molecular analysis of hepatocellular carcinoma among atomic-bomb survivors

Biochemical genetics

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

- ☐ Kodaira M, Satoh C, Hiyama K, Toyama K: Effects of atomic-bomb radiation on genetic instability of tandem-repetitive elements in human germ cells

Cytogenetics

- RP 2-85 Cytogenetic and pathological studies of normal and heat burn cicatricial skin fibroblasts in atomic bomb survivors
- 8-93 Cytogenetic study in the Adult Health Study population by fluorescence in situ hybridization (FISH)

F₁ studies


- RP 4-75 Research plan for RERF studies of the potential genetic effects of atomic radiation; Hiroshima and Nagasaki. Part 1. Mortality study of children of atomic bomb survivors [Editor's note: This is a platform protocol.]
- ☐ Akahoshi M, Soda M, Carter RL, Nakashima E, Shimaoka K, Seto S, Yano K: Correlation between systolic blood pressure and physical development in adolescence

Special cancer studies

- RP 29-60 Detection of leukemia and related disorders [Editor's note: See ABCC Technical Report 5-65 for full text.]
- 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
- 14-79 Interaction between radiation dose and host factors. An epidemiological case-control study of female breast cancer in atomic bomb survivors
- 15-81 Case-control study of lung cancer among atomic bomb survivors
- 8-85 Incidence study on malignant and benign genital tumors among females, Hiroshima and Nagasaki, 1950-80
- 6-86 Ultrasonographic screening of Adult Health Study participants to detect cancer and other diseases
- 9-88 Guidelines for the conduct of site-specific cancer incidence studies among A-bomb survivors, Hiroshima and Nagasaki

- RP 5-90** Primary liver cancer incidence study among atomic bomb survivors, 1958-87
- 1-91** Studies on salivary gland tumors among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950-87
- 2-91** Studies on skin cancer incidence among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950-87
- 6-91** Studies on thyroid tumor incidence among the RERF Extended Life Span Study cohort, 1950-87
- 2-92** Studies on ovarian tumor incidence among the RERF Extended Life Span Study cohort, 1950-87
- 4-92** Incidence study of tumors of the central nervous system among atomic-bomb survivors
- 6-93** Breast-cancer incidence among atomic-bomb survivors, 1950-90 (supersedes RP 1-90)
- 1-94** Studies on lung-cancer incidence among the atomic-bomb survivors, 1950-90
- 3-94** Incidence of lymphoid malignancies among the atomic-bomb survivors, 1950-90

A-bomb dosimetry studies

- RP 18-59** Shielding survey and dosimetry study [Editor's note: See ABCC Technical Report 7-67 for the full text.]
 -  Væth M, Pierce DA, Preston DL: The impact of neutron radiation on cancer mortality among the A-bomb survivors
- 10-86** Radiation dose estimates using tooth samples. Part 1. Collection of tooth samples from A-bomb exposed people in Hiroshima and Nagasaki
- 1-92** Radiation dose estimates using tooth samples. Part 2. Use of electron spin resonance on tooth enamel from Hiroshima atomic bomb survivors

Medical dosimetry studies

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

- RP 8-86** Ionizing radiation for medical reasons reported by Adult Health Study participants, Hiroshima and Nagasaki
- 8-87** Organ doses from medical X-ray exposures (addendum to RP 8-84)
- 5-91** Radiation-therapy-related cancer among Life Span Study subjects (addendum to RP 7-81)

Tumor registry and tissue registry

- RP 18-61** Tumor registry study in Hiroshima and Nagasaki [Editor's note: See ABCC Technical Report 2-61 for the full text.]

Following are tissue registry-related protocols that are also listed under the category Special Cancer Studies.

- RP 29-60** Detection of leukemia and related disorders [Editor's note: See ABCC Technical Report 5-65 for the full text.]
- 9-88** Guidelines for the conduct of site-specific cancer incidence studies among A-bomb survivors, Hiroshima and Nagasaki
- 5-90** Primary liver cancer incidence study among atomic bomb survivors, 1958-87
- 1-91** Studies of salivary gland tumors among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950-87
- 2-91** Studies on skin cancer incidence among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950-87
- 6-91** Studies on thyroid tumor incidence among the RERF Extended Life Span Study cohort, 1950-87
- 2-92** Studies on ovarian tumor incidence among the RERF Extended Life Span Study cohort, 1950-87
- 4-92** Incidence study of tumors of the central nervous system among atomic-bomb survivors
- 6-93** Breast-cancer incidence among atomic-bomb survivors, 1950-90 (supersedes RP 1-90)
- 1-94** Studies on lung-cancer incidence among the atomic-bomb survivors, 1950-90

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

List of research protocols temporarily inactivated since 1994*

- RP 7-81** Radiation therapy among Life Span Study subjects (Medical dosimetry studies)
- 16-81** Establishment of specific reagents for detection of human cancers through in vitro immunologic and biochemical assays (Immunology)
- 11-85** Hormone status in relation to cancer: A prospective epidemiologic study using stored sera (Special cancer studies)
- 9-87** The effect of pulmonary function on the subsequent risk of coronary heart disease in Japanese men living in Hiroshima and Nagasaki, Japan and Hawaii, 1966-78 (addendum to RP 4-85) (Special clinical studies)
- 4-90** Establishment of a method for HLA-DQ and DP gene typing using the polymerase chain reaction (Immunology)
- 4-91** Mail survey on epidemiologic factors in the Extended Life Span Study sample, 1991 (Life Span Study) [Editor's note: See ABCC Technical Report 11-62 for the full text.]

Manuscript based on an inactive RP*

- RP 6-78** HB antigen changes in relationship to radiation exposure, liver cancer, and liver cirrhosis in the Adult Health Study, Hiroshima and Nagasaki—a prospective study (Immunology)
- ☞ Neriishi K, Akiba S, Amano T, Ogino T, Kodama K: Prevalence of HBs antigen, HBe antigen, HBe antibody and HBs antigen subtypes in atomic-bomb survivors

*Program category is shown in parentheses at the end of each RP title.

Initiated Research Protocols

1 April 1994-31 March 1995

RP 2-94 Molecular analysis of hepatocellular carcinoma among atomic-bomb survivors. KS Iwamoto, T Seyama, T Mizuno, T Ito, N Nakamura, M Akiyama, M Tokunaga, S Tokuoka, T Fukuhara, M Yamamoto, H Itakura, T Ikeda, Y Fujita, K Mabuchi.

Following a relatively long latency period, primary liver cancer has been seen more often among the atomic-bomb (A-bomb) survivors as compared with the general Japanese population. Additionally, HBs-antigen positivity occurs often among high-dose A-bomb survivors, and it is suspected that the HB and HC viruses have a major role in the development of hepatocellular carcinoma (HCC). The mechanisms of these observations have not been examined closely; moreover, the interactions of these etiological factors in the development of HCC is not known. However, hepatocarcinogenesis is believed to involve multiple stages that include the mutations of more than one tumor-suppressor gene. Because p53 dysfunction correlates with hepatitis viral infection and because ionizing radiation produces deletion mutations, which is sufficient to disable tumor-suppressor genes, study of these genes in parallel with the hepatitis B and especially C viruses may clarify some aspects of hepatocarcinogenesis.

RP 3-94 Incidence of lymphoid malignancies among the atomic-bomb survivors, 1950-1990. K Nanba, T Matsuo, M Tokunaga, T Jubashi, Y Fujita, M Soda, H Dohy, N Kamada, M Tomonaga, LB Travis, DL Preston, K Mabuchi, CE Land, S Tokuoka.

In this study, we will investigate the incidence of lymphoid malignancies, including malignant lymphoma (ML), multiple myeloma (MM), and lymphoid leukemia (LL) between 1950 and 1990 in the RERF extended Life Span Study (LSS) population, according to the RERF guidelines for site-specific cancer incidence studies. The purpose of the proposed study is to characterize the LSS sample in terms of risk for the complete spectrum of lymphoid malignancies, by cell type, in relation to radiation dose from the atomic bombings and other factors. Emphasis will be placed on confirmation and classification of cases by standardized pathology review based on extensive case ascertainment from all sources of diagnostic information, including the tumor and tissue registries in Hiroshima and Nagasaki, death certificates, and autopsy and surgical records kept at RERF and outside institutions. Based on pathology review, ML cases will be classified as Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL) and will be subclassified according to the Rye classification and modified working

formulation scheme. Cases of NHL will also be subclassified by immunohistochemical studies into T-cell lymphomas (T-ML), B-cell lymphomas (B-ML), or others. Diagnosis of adult T-cell leukemia/lymphoma (ATL) will be based on detection of proviral DNA of HTLV-I using polymerase chain reaction (PCR) and other current technology. The study will also make full use of hematological clinical, and other diagnostic information obtained by other investigators and archived by the leukemia registry.

RP 1-95 Effects of menopause on risk factors for ischemic heart disease—a longitudinal study of the Nagasaki Adult Health Study sample. M Akahoshi, M Soda, M Tsuruta, TP Rose, Eiji Nakashima, Mari Saimei, Shinji Seto, Katsusuke Yano.

The incidence of ischemic heart disease increases after menopause and the elevation of serum cholesterol that accompanies menopause is closely associated with this increase. It seems likely that elevated serum cholesterol is related to the postmenopausal decrease in estrogen, but no longitudinal study of both serum cholesterol and serum estrogen levels during the perimenopausal period has been conducted. For this reason, we propose to measure semiannually serum cholesterol and its fractions and serum estradiol in a group of premenopausal women until 1 year after the occurrence of menopause to see if the changes in serum cholesterol and its subfractions accompanying menopause are associated with changes in estradiol.

RP 2-95 Pilot study: characterization of monoclonal gammopathy by studying the role of the BSAP gene in CD19 antigen expression. M Nobuyoshi, K Neriishi, S Kusumi, T Seyama, M Kawano, E Nakashima, K Kodama, M Akiyama, A Kuramoto.

This is a pilot study designed to characterize benign monoclonal gammopathy (BMG) in A-bomb survivors using sensitive cellular and molecular methods. We will establish assay methods to measure using flow cytometry B-cell-specific surface antigen CD19 expression on the plasma cells from these persons and to detect B-cell lineage-specific activator protein (BSAP) mRNA using reverse transcription-polymerase chain reaction to determine how CD19 correlates with BSAP. CD19 has been identified as a marker for the transformation of normal plasma cells to the malignant cells of multiple myeloma (MM), passing through an intermediate stage as BMG plasma cells (benign plasma cells are CD19⁺ and MM plasma cells are CD19⁻). Recent studies suggest that the B-cell-specific transcription factor BSAP regulates CD19 gene expression. After standardizing the assay methods, this pilot study will investigate the value of measuring the B-cell-specific surface antigen CD19 and the B-cell-specific transcription factor BSAP in the plasma cells of monoclonal gammopathy patients for the early detection and/or the prediction of transformation to a definable malignancy. Only patients who give informed consent will be studied.

Abstracts of RERF Reports Published in Journals

1 April 1994-31 March 1995

RERF Reports

Editor's note: RERF Reports begin as manuscripts that are officially approved by the RERF permanent directors for submission to journals. Upon their acceptance by a journal, such manuscripts are designated as RERF Reports. RERF Reports consist of journal-article reprints that are purchased from the publishers and bound in RERF Report covers with a Japanese summary. When the report is followed by a (J), a Japanese version of the report will be available. Variation in summary text styles reflects different journal styles.

RERF Report No. 2-93 A case-control interview study of breast cancer among Japanese A-bomb survivors: I. Main effects. CE Land, N Hayakawa, SG Machado, Y Yamada, MC Pike, S Akiba, M Tokunaga. (Published in *Cancer Causes and Control* 5:157-65, 1994.) (J)

Women with breast cancer (n = 196) and without the disease (n = 566), selected from the Life Span Study sample of A-bomb survivors and nonexposed residents of Hiroshima and Nagasaki, Japan, and matched on age at the time of the bombings, city, and estimated radiation dose, were interviewed about reproductive and medical history. A primary purpose of the study was to identify strong breast cancer risk factors that could be further investigated for possible interactions with radiation dose. As expected, age at first full-term pregnancy was strongly and positively related to risk. Inverse associations were observed with number of births and total, cumulative period of breast feeding, even after adjustment for age at first full-term pregnancy. Histories of treatment for dysmenorrhea and for uterine or ovarian surgery were positively and significantly associated with risk at ages 55 or older, a finding that requires additional study. Other factors related to risk at older ages were the Quetelet index (weight [kg]/height [cm]²) at age 50, history of thyroid disease, and hypertension. Neither age at menarche nor age at menopause was associated significantly with risk. Subjects appeared to be poorly informed about history of breast cancer or other cancer in themselves or in their close relatives; this finding suggests that innovative strategies may be required when studying familial cancer patterns in Japanese populations.

RERF Report No. 4-93 A case-control interview study of breast cancer among A-bomb survivors: II. Interactions with radiation dose. CE Land, N Hayakawa, SG Machado, Y Yamada, MC Pike, S Akiba, M Tokunaga. (Published in *Cancer Causes and Control* 5:167-76, 1994.) (J)

Three breast cancer risk factors were evaluated in terms of their interactions with radiation dose in a case-control interview study of Japanese A-bomb survivors. Cases and controls were matched on age at the time of the bombings and radiation dose, and dose-related risk was estimated from cohort rather than case-control data. Each factor—age at first full-term pregnancy, number of deliveries, and cumulative lactation period summed over births—conformed reasonably well to a multiplicative interaction model with radiation dose (the additive interaction model, in which the absolute excess risk associated with a factor is assumed to be independent of radiation dose, was rejected). An important implication of the finding is that early age at first full-term pregnancy, multiple births, and lengthy cumulative lactation are all protective against radiation-related, as well as baseline, breast cancer. Analyses by age at exposure to radiation suggest that, among women exposed to radiation in childhood or adolescence, a first full-term pregnancy at an early age *following* exposure may be protective against radiation-related risk.

RERF Report No. 6-93 Relationship of five anthropometric measurements at age 18 to radiation dose among atomic bomb survivors exposed *in utero*. E Nakashima. (Published in *Radiat Res* 138:121-6, 1994.)

Five body measurements—standing height, body weight, sitting height, chest circumference and intercrystal diameter—of 18-year-old atomic bomb survivors exposed *in utero* in Hiroshima and Nagasaki were analyzed in relation to DS86 uterine dose. Age *in utero* was divided into four periods: 0-7, 8-15, 16-25 and ≥ 26 weeks. This categorization is based upon the study of radiation-induced brain damage. The linear regression analyses for these five variables showed significant decreases with increasing dose. The regression coefficients were -2.65 cm/Gy for standing height, -2.46 kg/Gy for body weight, -0.92 cm/Gy for sitting height, -1.37 cm/Gy for chest circumference and -0.32 cm/Gy for intercrystal diameter. The multivariate test statistic for the overall dose effect on five body measurements was significant, but the interaction between dose and gestational period was not significant. Principal-component analysis was applied to the five variables. For the first-component scores, the dose effect was significant, but the interaction between dose and gestational period was not significant. For the second-component scores, the dose effect was significant specifically at 0-7 weeks. The radiation dose effect on the second principal component found at 0-7 weeks of gestation suggests that malformations occur in this period.

RERF Report No. 13-93 Increased frequency of CD4⁻8⁻ T cells bearing T-cell receptor $\alpha\beta$ chains in peripheral blood of atomic bomb survivors exposed to high doses. Y Kusunoki, S Kyoizumi, Y Hirai, S Fujita, M Akiyama. (Published in *Radiat Res* 139:67-72, 1994.)

A rare T-cell subpopulation, CD4⁻8⁻ $\alpha\beta$ T cells, may be differentiated through a pathway (or pathways) different from the pathway(s) of conventional CD4⁺ or CD8⁺ T cells. In the present study, the frequencies of CD4⁻8⁻ T cells in peripheral-blood $\alpha\beta$ T cells in 409 atomic bomb survivors (160 estimated to have been exposed to 1.5 Gy or more and 249 controls) were determined to investigate late effects of radiation on the composition of human T-cell subpopulations. The frequency of CD4⁻8⁻ $\alpha\beta$ T-cell decreased significantly with the subject's age and was higher in females than males. A significant increase in the frequency was found in the survivors exposed to more than 1.5 Gy, suggesting that the previous radiation exposure altered differentiation and development of T cells.

RERF Report No. 15-93 A positive correlation between T-cell-receptor mutant frequencies and dicentric chromosome frequencies in lymphocytes from radiotherapy patients. KS Iwamoto, Y Hirai, S Umeki, Y Kusunoki, S Kyoizumi, T Kodama, K Ohama, N Nakamura, M Akiyama. (Published in *J Radiat Res* [Tokyo] 35:92-103, 1994.)

Dose estimates for the assessment of future risks, following accidental exposure to radiation, for certain diseases such as cancer usually rely on both physical and biological quantitative analyses. A traditional biological method of choice is the measurement of chromosome aberration frequencies in peripheral-blood lymphocytes. However, thorough examination of large sample populations is time and labor intensive. Recently, it became possible to measure mutant frequencies in T lymphocytes; one method is a colony assay at the HPRT gene, and the other is a flow-cytometric assay at the T-cell-receptor (TCR) gene. To test for the possible use of these mutation assays, concurrent measurements were taken on blood samples from women who previously received a full course of radiation therapy for gynecological cancer. The results showed that the frequency of TCR mutants correlated reasonably well with that of dicentric chromosomes, whereas the frequency of HPRT mutants did not. Possible uses of the TCR mutation assay in combination with the conventional chromosome analysis or micronucleus assay after exposure of a relatively large population are discussed.

RERF Report No. 16-93 Incidence of female breast cancer among atomic bomb survivors, 1950-1985. M Tokunaga, CE Land, S Tokuoka, I Nishimori, M Soda, S Akiba. (Published in *Radiat Res* 138:209-23, 1994.) (J)

An incidence survey among atomic bomb survivors identified 807 breast cancer cases, and 20 second breast cancers. As in earlier surveys of the Life Span Study population, a strongly linear radiation dose response was found, with the highest dose-specific excess relative risk (ERR) among survivors under 20 years old at the time of the bombings. Sixty-eight of the cases were under 10 years old at exposure, strengthening earlier reports of a marked excess risk associated with exposure during infancy and childhood. A much lower, but marginally significant, dose response was seen among women exposed at 40 years and older. It was not possible, however, to discriminate statistically between age at exposure and age at observation for risk as the more important determinant of ERR per unit dose. A 13-fold ERR at 1 Sv was found for breast cancer occurring before age 35, compared to a 2-fold excess after age 35, among survivors exposed before age 20. This *a posteriori* finding, based on 27 exposed, known-dose, early-onset cases, suggests the possible existence of a susceptible genetic subgroup. Further studies, involving family histories of cancer and investigations at the molecular level, are suggested to determine whether such a subgroup exists.

RERF Report No. 17-93 Prospective cohort study of risk factors for primary liver cancer in Hiroshima and Nagasaki, Japan. MT Goodman, H Moriwaki, M Væth, S Akiba, H Hayabuchi, K Mabuchi. (Published in *Epidemiology* 6:36-41, 1995.) (J)

We investigated risk factors for primary liver cancer among a cohort of 36,133 residents in Hiroshima and Nagasaki, Japan, originally established to examine the association between exposure to atomic bomb radiation and disease. A mail survey to study the late effects of atomic bomb radiation was conducted among the cohort between 1978 and 1981. During the subsequent follow-up period (average 8.61 years), 242 cases of primary liver cancer were identified through population-based tumor registries in the two cities. The relative risk (RR) of liver cancer was 2.23 [95% confidence interval (CI) = 1.53-3.23] for tobacco smokers compared with those who had never smoked. Alcohol use was slightly positively associated with the risk of liver cancer, and men who had quit drinking had an RR of 2.33 (95% CI = 1.34-4.07) compared with those who never drank. Among alcohol drinkers, an inverse relation between years of abstinence and the rate of liver cancer was found, possibly attributable to a confounding effect of preclinical disease. The use of female hormone preparations was modestly associated with the risk of liver cancer (RR = 1.29; 95% CI = 0.59-2.84). Other risk factors included a self-reported history of radiation therapy

(RR = 1.79; 95% CI = 1.34-2.40), and a history of diabetes mellitus (RR = 1.79; 95% CI = 1.31-2.43).

RERF Report No. 19-93 Evidence of radiation-induced retardation of height and body weight from repeated measurements of adults exposed in childhood to the atomic bombs. M Otake, Y Fujikoshi, S Funamoto, WJ Schull. (Published in *Radiat Res* 140:112-22, 1994.)

Retardation of growth due to exposure to atomic-bomb radiation has been examined using individuals less than 10 years old at the time of the bombing (ATB) and a growth curve analysis based on measurements of height and weight repeatedly made in the course of the 4th-7th cycles of Adult Health Study examinations (1964-72). The largest significant difference in growth to emerge is between males and females. However, a highly significant retardation of growth associated with dose (DS86) was observed among those survivors on whom four repeated measurements of height and weight were available. Longitudinal analysis of a more extended data set (821 individuals), using expected values imputed from simple linear regression models fitted to the three available sets of measurements of height and weight on each of the 254 individuals with a missing measurement, also indicates a significant growth retardation due to radiation exposure. The possible contribution of such factors as poor nutrition and disruption of normal family life in the years immediately following the war is difficult to evaluate, but the effects of socioeconomic factors on the analysis of these data are discussed.

RERF Report No. 20-93 Cancer incidence in Hiroshima and Nagasaki, Japan, 1958-1987. MT Goodman, K Mabuchi, M Morita, M Soda, S Ochikubo, T Fukuhara, T Ikeda, M Terasaki. (Published in *Eur J Cancer* 30A:801-7, 1994.) (J)

The Hiroshima and Nagasaki tumour registries, which have been in operation since 1958, are among the few population-based cancer registries in Japan. This analysis evaluated cancer incidence in Hiroshima and Nagasaki between 1958 and 1987. The overall age-adjusted (World Population Standard) cancer incidence has increased from 217 to 301 per 100,000 among males, and from 176 to 197 per 100,000 among females during the first 30 years of cancer registration. The most recent rates are intermediate to rates in other countries. Despite a gradual decrease, gastric cancer remained the most common malignancy among males and females throughout the surveillance period, accounting for 24% of all cancers by the late 1980s. The rate of liver cancer has increased dramatically among males during the past 20 years, with a 2-fold increase in incidence in the past 10 years alone. The populations of Hiroshima and Nagasaki now have among the highest rates of liver cancer in the world. Breast cancer incidence in Hiroshima and Nagasaki, in contrast, is among the lowest in the world, although incidence rates have doubled since the 1960s. Other common malignancies include

cancers of the lung, colon and rectum among males and cancers of the colon, cervix and lung among females.

RERF Report No. 25-93 Frequent involvement of visible chromosomal deletion in X-ray-induced mutants at the HLA-A locus in human T-lymphocytes. Y Kodama, J Kushiro, Y Hirai, Y Kusunoki, N Nakamura, M Akiyama, AA Awa. (Published in *Mutat Res* 309:63-72, 1994.)

Mutant T-lymphocytes at the HLA-A locus were isolated using a recently developed flow-cytometric assay either immediately after drawing blood (in vivo mutants) or after X-irradiation in vitro. Mutants were subsequently propagated clonally for cytogenetic and molecular analyses. Among the 38 in vivo mutants, none contained an abnormal chromosome 6 on which the HLA-A locus resides (6p21.3). In contrast, mutants recovered after in vitro irradiation frequently carried abnormalities in the short arm of chromosome 6: 11/19 and 5/5 independent mutants for the 1-Gy and 2-Gy groups, respectively. Characteristically, the majority of the aberrations were deletions, commonly involving chromosome 6p21-p23. Because chromosomal deletions involving the selected gene are rare among radiation-induced mutants at the hypoxanthine phosphoribosyltransferase (chromosome X) and thymidine kinase (chromosome 17) loci, the HLA-A locus can be considered as highly prone to chromosomal deletions after radiation exposure. It is generally believed that ionizing radiation randomly breaks DNA, and the higher frequency of chromosomal deletions at the HLA-A locus is unlikely to be due to preferential induction but more likely to the better survivability of the deletion-bearing mutants. Consequently, the results suggest that the human genome is quite heterogeneous with regard to the survivability of cells bearing a chromosomal deletion including different loci.

RERF Report No. 1-94 Prevalence rate of thyroid diseases among autopsy cases of the atomic bomb survivors in Hiroshima, 1951-1985. Y Yoshimoto, H Ezaki, R Etoh, T Hiraoka, S Akiba. (Published in *Radiat Res* 141:278-86, 1995.) (J)

To examine the radiogenic risk of latent thyroid cancer, thyroid adenoma, colloid/adenomatous goiter and chronic thyroiditis, the data for 3821 subjects collected in the course of autopsies of atomic bomb survivors in Hiroshima from 1951 to 1985 by the Radiation Effects Research Foundation (RERF) were analyzed using a logistic model. About 80% of the autopsies were performed at RERF and the remainder at local hospitals. The frequencies of the above diseases were not associated with whether the underlying cause of death was cancer. However, note that our results may be influenced by potentially biasing factors associated with autopsy selection. The relative frequency of latent thyroid cancer (greatest dimension ≤ 1.5 cm but detectable on a routine microscopic slide of the thyroid gland) increased as the radiation dose increased and was about 1.4-fold greater at 1 Gy than in the 0-Gy dose group. The

relative occurrence of thyroid adenoma also increased as radiation dose increased, and was about 1.5-fold greater at 1 Gy than in the 0-Gy dose group. Sex, age at the time of the bombing or period of observation did not significantly modify the radiogenic risks for thyroid adenoma or latent thyroid cancer. No statistically significant association was found between radiation exposure and the rates of colloid/adenomatous goiter and chronic thyroiditis. The possible late effect of atomic bomb radiation on the frequency of benign thyroid diseases is discussed on the basis of these data.

RERF Report No. 2-94 *HaeIII* polymorphism in intron 1 of the human *p53* gene. T Ito, T Seyama, T Hayashi, T Mizuno, KS Iwamoto, N Tsuyama, K Dohi, N Nakamura, M Akiyama. (Published in *Hum Genet* 93:222, 1994.)

A new *HaeIII* polymorphism, which is found in the first intron of the human *p53* gene, provides a genetic marker for tumor suppressor *p53* gene alterations.

RERF Report No. 6-94 Increased rate of spontaneous mitotic recombination in T lymphocytes from a Bloom's syndrome patient using a flow-cytometric assay at HLA-A locus. Y Kusunoki, T Hayashi, Y Hirai, J Kushiro, K Tatsumi, T Kurihara, M Zghal, MR Kamoun, H Takebe, A Jeffreys, N Nakamura, M Akiyama. (Published in *Jpn J Cancer Res* 85:610-8, 1994.)

Bloom's syndrome (BS) is an autosomal recessive disorder conferring high propensity for cancer and displaying a high degree of genetic instability; the frequency of sister chromatid exchange is characteristically 10 times above background. The symmetrical four-armed chromatid interchanges are much more readily detected in peripheral blood lymphocytes of BS patients, suggesting that the frequency of somatic recombination is also increased. In the present study, the rate of spontaneous loss of *HLA-A* allele expression was estimated following fluctuation analysis in cultured T lymphocytes using a flow-cytometric assay. It was found to be 10 times or more higher than normal in lymphocytes from a BS patient. Molecular and chromosome analyses showed that all 13 independent variants from the patient were most likely derived from somatic recombinations. Further tests for loss of heterozygosity at a closely linked proximal locus, *HLA-DQA1*, showed that as many as half of the recombinants retained heterozygosity irrespective of the donor. The results suggest that the HLA region is hyperrecombinogenic in somatic cells and that the elevated recombination rate in BS cells results from the general increase at ordinary sites and not from random creation of unusual sites for recombination.

RERF Report No. 8-94 Relationship between cold pressor test and development of hypertension, based on 28-year follow-up. F Kasagi, M Akahoshi, K Shimaoka. (Published in *Hypertension* 25:71-76, 1995.)

The present study examined the relationship between blood pressure reactivity to cold stimulus and the subsequent development of hypertension based on a follow-up study from 1960 through 1988 of 824 normotensive participants (mean age 35.8 ± 10.8 years) in the Adult Health Study in Nagasaki, Japan. Hypertension developed in 343 individuals during the 28 years of follow-up, with a mean incidence rate of 24.6 per 10^3 person-years. Confounding variables, including attained age, resting systolic and diastolic blood pressures, and body mass index at baseline, were adjusted using a Poisson regression model. Systolic response was found to be an independent and significant predictor. The relative risk of hypertension for systolic hyperreactors was 1.37, with a 95% confidence interval of 1.10 to 1.71. Diastolic response was significant only when resting diastolic blood pressure was also considered. The cold pressor test appears to be useful if performed on middle-aged subjects older than 40 years at the time of examination, when hypertension is more prevalent. The current results support the hypothesis that hyperreactivity is a predictor of the development of hypertension.

RERF Report No. 9-94 Prognostic value of the cold pressor test for hypertension based on 28-year follow-up. F Kasagi. (Published in *Hiroshima J Med Sci* 43:93-103, 1994.)

Several stress tests have been used to predict the development of hypertension. No conclusion, however, has been reached on the effectiveness of these tests as a predictor of hypertension in later years.

The present study examines the prognostic values of blood pressure response to cold and resting blood pressure for future hypertension, based on a follow-up study over 28 years of 824 individuals (mean age: 35.8 ± 10.8 yr) whose resting blood pressure had been normal at baseline.

A significant determinant of blood pressure response to cold stimulus was age in these normotensive subjects. A higher response was observed as age increased. There was also a significant seasonal variation in blood pressure response to cold, suggesting the need to standardize a time to perform the cold pressor test.

Hypertension has developed in 343 individuals during the 28 years of follow-up, with a mean incidence rate of 24.6 per 10^3 person-years. Both systolic and diastolic responses were significant as a predictor of future hypertension after adjusting for attained age, resting blood pressure, and body mass index at baseline. However, a comparison between resting blood pressure and response to cold indicated that the cold pressor test is not as effective a predictor of hypertension as resting blood pressure. Radiation exposure was not significant either as a background risk or as a possible

modifier of the relationship between the blood pressure response and the development of hypertension.

The current results suggest that blood pressure response to cold supplements resting blood pressure for predicting hypertension.

RERF Report No. 11-94 Activated RET oncogene in thyroid cancers of children from areas contaminated by Chernobyl accident. T Ito, T Seyama, KS Iwamoto, T Mizuno, ND Tronko, IV Komissarenko, ED Cherstovoy, Y Satow, N Takeichi, K Dohi, M Akiyama. (Published in *The Lancet* 344:259, 1994.)

To clarify the genetic events that are involved in thyroid cancers of children residing in areas contaminated by the Chernobyl accident, inactivation of the p53, APC, MCC, and Rb tumor-suppressor genes and activation of the RET oncogene were investigated using paraffin-embedded blocks. Gene alterations of tumor-suppressor genes are detectable by polymerase chain reaction loss of heterozygosity (PCR-LOH) assays. RET oncogene activation via rearrangement can be detected by reverse transcription PCR (RT-PCR). From a total of 19 cases, 12, 8, 13, and 7 cases were informative for the p53, APC, MCC, and Rb genes, respectively. However, loss of heterozygosity (LOH) was observed in only one case. In this case, LOH of the p53 gene was observed in a poorly differentiated focus of papillary adenocarcinoma. In contrast, in 4 of 7 cases successfully analyzed using RT-PCR, RET oncogene activation via rearrangement was detected. RET oncogene activation appears to be one of the characteristic features of thyroid cancers in children residing in areas contaminated by the Chernobyl accident.

RERF Report No. 20-94 Genetic variation detected by quantitative analysis of end-labeled genomic DNA fragments. J Asakawa, R Kuick, JV Neel, M Kodaira, C Satoh, SM Hanash. (Published in *Proc Natl Acad Sci USA* 91:9052-66, 1994.)

The continuing efforts to evaluate specific human populations for altered germinal mutation rates would profit from more efficient and more specific approaches than those of the past. To this end, we have explored the potential usefulness of two-dimensional electrophoresis of DNA fragments obtained from restriction-enzyme-digested genomic DNA. This permits the analysis, on a single preparation, of ≈ 2000 DNA fragments varying in size from 1.0 to 5.0 kb in the first dimension and from 0.3 to 2.0 kb in the second dimension. To enter into a genetic analysis, these fragments must exhibit positional and quantitative stability. With respect to the latter, if spots that are the product of two homologous DNA fragments are to be distinguished with the requisite accuracy from spots that are the product of only one fragment, the coefficient of variation of spot intensity should be approximately ≤ 0.12 . At present, 482 of the spots in our preparations meet these standards. In an examination of preparations based on three Japanese mother/father/child trios, 43 of these 482 spots

were found to exhibit variation that segregated within families according to Mendelian principles. We have established the feasibility of cloning a variant fragment from such gels and establishing its nucleotide sequence. This technology should be highly efficient in monitoring for mutations resulting in loss/gain/rearrangement events in DNA fragments distributed throughout the genome.

Commentary and Review Series

Editor's note: Reports in the Commentary and Review (CR) Series begin as manuscripts that are officially approved by the RERF permanent directors for submission to journals. Upon their acceptance by a journal, such manuscripts are designated as CR reports. Reports in the CR series consist of journal-article reprints that are purchased from the publishers and bound in CR covers with a Japanese summary. CR reports are published to rapidly disseminate ideas, discussions, comments, and recommendations on research carried out by RERF scientists and directors. This series also includes working papers or invited presentations prepared for national and international organizations or conferences, discussions of research concerning atomic-bomb survivors carried out elsewhere, and in general, materials of lasting importance to RERF and atomic-bomb survivor research.

CR Report.No. 1-93 Two methods for the analysis of chromosome aberration data from the atomic-bomb survivors: quasi-likelihood moment method and beta-binominal method. E Nakashima, K Ohtaki. (Published in *J Jpn Stat Soc* 24:209-19, 1994.)

Two estimation methods, the maximum likelihood method under the beta-binomial model and the quasi-likelihood moment method based on the mean and variance relation, were applied to G-banding chromosome aberration data from Hiroshima atomic-bomb survivors. The chromosome aberration rate was empirically thought to be overdispersed by the intraindividual correlation or the radiation dose estimation error. Using the results of Pierce, Stram, Væth, and Schafer, the mean and variance relationship was formulated under the two variations to apply the quasi-likelihood method and the beta-binomial model. The quasi-likelihood moment method allows only single extra-binomial parameter but is robust, whereas the beta-binomial model allows for both dose error and intraindividual variations. Dose response parameter estimates obtained using the two methods were similar. However, the quasi-likelihood moment method is computationally less intensive than the beta-binomial maximum likelihood method. When observations are perturbed by the dose error, the quasi-likelihood method is recommended.

CR Report No. 2-93 Comparison of numerical results of repeated measurements of height based on two growth curve models with random-effects and general covariance structures. M Otake, E Nakashima, Y Fujikoshi, RL Carter, S Tanaka, Y Kubo. (Published in *J Jpn Stat Soc* 24:1-14, 1994.)

A numerical comparison of two growth curve models, one with a random-effects covariance structure, and the other a general covariance structure, was made for a complete data set of 455 individuals with measurements of stature conducted annually from ages 10 to 18 years. The components of the variance-covariance matrix of the estimators of regression coefficients for a random-effects covariance structure were larger than those of a general variance-covariance matrix, ranging from 1.1 to 3.0 for the ratios of the elements of diagonal matrices, and 2.4 for an off-diagonal matrix. The ratios of elements of two off-diagonal matrices were about 2.7 and 4.3 if evaluated by an absolute value of these ratios for all elements with opposite signs. While the absolute difference between components in the two cases are small, the test statistics are almost the same except for the test value of the sex difference. The results obtained from the two models show that both are valid for the interpretation of the data set. For the data used here, the general model seems to fit the annually measured data better than the random-effects model for females 10-18 years old at the time of examination (ATE). The fit between observed and expected values is better in the general model for males 16-18 years old ATE, but it is better in the random-effects model for males 10-15 years of age ATE. The Akaike Information Criterion (AIC) value for a complete data set of 455 individuals as a measure of goodness of fit was 20,953.76 for the random-effects covariance structure, while for the general covariance structure it was 19,013.40. The random-effects model permits the use of an incomplete data set for 1264 individuals with four or more measurements. However, the results obtained are almost equal to those of a complete data set.

CR Report No. 1-94 The current applicability of large scale biomarker programs to monitor cleanup workers. ML Mendelsohn. (Published in *Biomarkers and Occupational Health: Progress and Perspectives*, edited by ML Mendelsohn, JP Peters, MJ Normandy. Washington, DC, Joseph Henry Press, 1995. pp 9-19.)

The challenge to the US Department of Energy (DOE) in implementing a large-scale application of biological markers is summarized. The potential value of biomarkers is demonstrated using data from the atomic-bomb survivors of Hiroshima and Nagasaki. The corresponding limitations of biomarkers are described, particularly as they would apply in a DOE setting. It is concluded that biomarkers have great potential but are not yet ready for the role that the DOE envisages. Specific recommendations are made to correct this situation by advancing the state of the art of biomarkers.

Publications in the Scientific Literature

Editor's note: These journal articles differ from RERF Reports (see preceding section) in the following ways. Most are based on collaborative studies with outside researchers and/or the work was unrelated to a specific RERF research protocol. Some articles may be invited summaries of reanalyses of previously reported RERF findings.

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Honda T, Urakawa Y, Morikawa A: Cytogenetic effects of atomic-bomb radioactive fallout—chromosome study on inhabitants in the Nishiyama district, Nagasaki. pp 37-9

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Mabuchi K, Ito C, Takahashi T: Investigation and review of registry procedures in the follow-up study of atomic-bomb survivors living in North America, using NDI. NDI retrieval for American examinees. p 50

Mine M, Honda S, Okumura Y, Matsuura M, Hoshi M, Hayakawa N, Shibata Y, Kono T: Estimation of doses received by Nagasaki atomic-bomb survivors. pp 124-6

Nakamura N: Evaluation of radiation dose using tooth enamel by means of the electron spin resonance (ESR) method. pp 30-1

Soda M, Akahoshi M, Ikeda T: Significance of RERF Adult Health Study as a cancer screening program. Colorectal cancer. pp 73-5

Oral Presentations

1 April 1994-31 March 1995

Editor's note: The asterisk indicates the person who presented the talk.

**67th Meeting of the Japanese Tissue Culture Association, 21-22 April 1994,
Okayama**

- Possible spontaneous immortalization of cultured fibroblastic cells obtained from a high dose A-bomb survivor
Honda T,* Sadamori N, Komatsu K, Watanabe M

**43rd Meeting of the Japanese Association of Medical Technologists, 12-13 May
1994, Matsuyama**

- Determination of HCV antibody titer in middle-aged and aged people
Izumi R,* Kitagawa T, Watanabe K, Inoue M, Matsuura S, Kishi T, Mori S, Sora M, Ishii K, Kusumi S

**1994 Annual Scientific Meeting of the American Geriatrics Society, 19-22 May
1994, Los Angeles, California**

- Study of dementia in the Hiroshima cohort
Kodama K*

**30th Anniversary Meeting of the Nuclear Safety Research Association, 1-2 June
1994, Tokyo**

- Some mechanistic insights from RERF cancer epidemiology
Mendelsohn ML*

**33rd Chugoku-Shikoku Area Meeting of the Japan Lung Cancer Association,
3-4 June 1994, Kagawa**

- Establishment of an in vivo experimental system for human lung cancer using SCID mice
Teraoka S,* Kyoizumi S, Okumichi T, Fukuhara T, Yamakido M, Akiyama M

**International Symposium on Biomedical and Psychosocial Consequences of
Radiation from Manmade Radionuclides in the Biosphere, 5-10 June 1994,
Kongsvold Fjeldstue, Norway**

- Radiation risks to human health: The perspective from Hiroshima and Nagasaki
Mendelsohn ML*

35th Late A-bomb Effects Research Meeting, 5 June 1994, Nagasaki

- Effects of atomic-bomb radiation on genetic instability of tandem-repetitive elements in human germ cells
Kodaira M,* Satoh C
- Psychological effects of wide-area radiation exposure due to the Chernobyl accident (Report from the international symposium held under the auspices of the Ukraine Scientific Center for Radiation Medicine)
Kusumi S,* Yamaguchi S, Inoue Y, Nakamura S, Shigematsu I
- Study of long-term psychological disorder among A-bomb survivors
Yamada M*
- Relationship of five anthropometric measurements at age 18 to radiation dose among atomic-bomb survivors exposed *in utero*
Nakashima E*
- Summary of study on frequency of somatic mutants of erythrocyte glycoprotein A genes among atomic bomb survivors
Akiyama M,* Kyoizumi S, Cologne JB, Tanabe K, Nakamura N, Hirai Y, Umeki S, Yamakido T
- Gene changes in childhood thyroid cancer in contaminated area of Chernobyl
Seyama T,* Ito T, Iwamoto KS, Mizuno T, Satow Y, Takeichi N, Dohi K, Akiyama M
- Differentiation of a mutant stem cell into T-cells in an A-bomb survivor
Hirai Y,* Kusunoki Y, Takahashi K, Abe N, Kyoizumi S, Akiyama M
- Analysis of radiation-induced epilation in human using SCID-hu mice
Kyoizumi S,* Teraoka S, Yamakido T, Seyama T, Akiyama M
- Contribution of hepatitis B virus to occurrence of liver cancer among A-bomb survivors
Mizuno T,* Seyama T, Ito T, Iwamoto KS, Ishii N, Fujii S, Tokunaga M, Tokuoka S, Mabuchi K, Akiyama M
- Immortalization of cultured skin cells obtained from a high dose A-bomb survivor and dynamic karyotypical alterations
Honda T,* Sadamori N, Komatsu K, Watanabe M

US-Japan Joint Symposium on Cardiovascular Research, 20-22 June 1994, Osaka

- Epidemiological studies on cardiovascular diseases in a Japanese population—Hiroshima/Nagasaki study
Kodama K*

**11th American Statistical Association Conference on Radiation and Health,
26 June-1 July 1994, Boston, Massachusetts**

- Cancer mortality among atomic bomb survivors
Preston DL,* Pierce DA, Shimizu Y, Mabuchi K

**11th National Institute of Radiological Sciences-RERF-Research Institute for
Nuclear Medicine and Biology Research Exchange Seminar, 30 June 1994,
Hiroshima**

- Genetic instability of minisatellites in the children of the A-bomb survivors
Kodaira M,* Satoh C, Hiyama K, Toyama K

**12th General Meeting of the Japanese Society of Bone Metabolism, 21-23 July
1994, Niigata**

- Calcium intake and bone mineral density
Fujiwara S,* Hayabuchi H, Yamada M, Masunari N, Kodama K

62nd Annual Meeting of the Japan Statistical Society, 23-26 July 1994, Tokyo

- Binary (cataract) data and threshold model
Otake M*
- An analysis of chromosome-aberration data using the quasilikelihood/
pseudolikelihood method
Nakashima E,* Ohtaki K

1994 Joint Statistical Meeting, 14-18 August 1994, Toronto, Canada

- An analysis of stable chromosome aberrations among A-bomb survivors
Pawel DJ,* Awa AA

25th Meeting of the Japan Nursing Society, 25-26 August 1994, Kanazawa

- Degree of independence in daily life of aged A-bomb survivors and its
relationship to daily life habits
Kuwamoto M,* Kunihara M

**16th Annual Meeting of the American Society for Bone and Mineral Research,
9-13 September 1994, Kansas City, Missouri**

- Serum 25-hydroxyvitamin D levels are lower in Japan compared to US Japanese
Fujiwara S,* Huang C, Ross PD, Kodama K, Davis JW, Wasnich RD

**Joint 12th World Congress and 16th Congress of the European Society of
Cardiology, 10-14 September 1994, Berlin, Germany**

- World trends in cardiovascular disease—experience in Asia
Kodama K*

International Searle Foundation Workshop on Biological Indicators of Exposure to Ionizing Radiation, 26-30 September 1994, Ulm, Germany

- Current status of RERF cancer studies
Preston DL*

8th Japan-Korea Statistical Conference, 2-4 October 1994, Okayama

- Threshold models and applications to cataract binary data
Otake M*

10th International Symposium on Atherosclerosis, 9-14 October 1994, Montreal, Canada

- Aging and arteriosclerosis—study of effects of aging on blood thrombin production and thrombin receptor expression in endothelial cells
Kusumi S,* Nobuyoshi M

53rd Annual Meeting of the Japanese Society of Public Health, 13-15 October 1994, Tottori

- Bone mineral density and proportion of fat by sex and age among the general population
Kurisu T,* Fujiwara S, Kodama K
- The importance of guidance on health at health examinations
Takeda T*
- Report on the status of the use of medicines among the RERF Adult Health Study population (report 2)
Masunari N,* Fujiwara S, Nakamura T, Kodama K
- Evaluation of effects of physical activity on prevention of aging in a longitudinal study
Kodama K,* Shimizu Y, Kasagi F, Fujita Y
- Relationship between grip strength and subsequent death
Fujita S,* Kasagi F, Kodama K

39th Meeting of the Japan Society of Human Genetics, 18-20 October 1994, Chiba

- Genetic variation detected by quantitative analysis of end-labeled genomic DNA fragments
Asakawa J,* Kuick R, Neel JV, Hanash SM, Kaneoka S, Kodaira M, Satoh C
- Cloning and sequencing of genetic variants detected by two-dimensional electrophoresis of end-labeled genomic DNA fragments
Kodaira M,* Asakawa J, Kuick R, Neel JV, Hanash SM, Kaneoka S, Imanaka M, Satoh C

- Dose-response relationship of stable chromosome aberration frequencies in lymphocytes of A-bomb survivors
Awa AA*
- Tetranucleotide repeat instability in the children of atomic bomb survivors
Satoh C,* Yasunaga K, Miura A
- Denaturing gradient gel electrophoresis of PCR-amplified DNA fragments for detection of variation in DNA. Part 4. Variations observed in the p53 gene
Takahashi N,* Omine H, Miura A, Kaneko J, Satoh C

53rd Annual Meeting of the Japanese Cancer Association, 19-21 October 1994, Nagoya

- Summary of the erythrocyte glycophorin A gene mutation study among atomic bomb survivors
Akiyama M,* Kyoizumi S, Nakamura N, Hirai Y, Umeki S, Yamakido T
- Activated RET oncogene in thyroid cancers of children residing in contaminated areas of Chernobyl accident
Seyama T,* Ito T, Iwamoto KS, Mizuno T, Satow Y, Takeichi N, Dohi K, Akiyama M
- Induction of WAF1/sd1 gene expression by ionizing radiation
Tsuyama N,* Seyama T, Ito T, Mizuno T, Iwamoto KS, Ide T, Noda A, Akiyama M
- Measurement of somatic mutation frequency at the T-cell antigen receptor genes in mice with genetic abnormalities
Yamakido T,* Umeki S, Kyoizumi S, Aizawa S, Watanabe H, Akiyama M
- Growth suppressive efficacy of human LAK cells against human lung cancer cells implanted into SCID mice
Teraoka S,* Kyoizumi S, Seyama T, Yamakido M, Akiyama M
- Molecular analysis of a renal tumor from a thorotrast patient
Iwamoto KS,* Seyama T, Mizuno T, Ito T, Inai K, Akiyama M
- Molecular analysis of HBV in liver cancers among atomic bomb survivors
Mizuno T,* Seyama T, Ito T, Iwamoto KS, Fujita Y, Tokunaga M, Tokuoka S, Mabuchi K, Akiyama M
- Human colon tumor progression observed in severe combined immunodeficient mice
Ito T,* Seyama T, Kyoizumi S, Teraoka S, Iwamoto KS, Mizuno T, Tsuyama N, Asahara T, Dohi K, Akiyama M
- Clonality of HPRT-deficient mutant cells in the peripheral blood of A-bomb survivors
Hirai Y,* Kusunoki Y, Kyoizumi S, Akiyama M
- Analysis of radiation-induced epilation in humans using SCID-hu mice
Kyoizumi S,* Teraoka S, Yamakido T, Seyama T, Akiyama M

**8th International Conference of the International Society of Differentiation,
22-26 October 1994, Hiroshima**

- X-irradiation induces the expression of the WAF1/sdi1 gene in a p53 dependent manner

Seyama T,* Tsuyama N, Iwamoto KS, Mizuno T, Ide T, Noda A, Akiyama M

International Conference on Radiation and Society: Comprehending Radiation Risk, 24-28 October 1994, Paris, France

- Dose response of radiation-induced cancer at low-dose level among atomic-bomb survivor

Fujita S,* Shimizu Y, Mabuchi K, Shigematsu I

- Cancer risk among atomic-bomb survivors

Shimizu Y,* Mabuchi K, Shigematsu I

**Annual Meeting of the International Association of Cancer Registries,
25-28 October 1994, Bangalore, India**

- Cancer incidence trends in Hiroshima, Japan, 1958-1987

Fujita Y,* Mabuchi K

37th Annual Meeting of the Japan Radiation Research Society, 27-29 October 1994, Fukuoka

- Association between brain damage and physical measurements or IQ values in prenatally exposed A-bomb survivors

Otake M,* Yoshimaru H, Schull WJ, Funamoto S

- Dose estimation by ESR using tooth enamel from Hiroshima A-bomb survivors. Part 2. Correlation between chromosome aberration frequency and ESR signal intensity

Nakamura N,* Iwasaki M, Miyazawa C, Niwa K, Sawada S, Akiyama M, Awa AA

- Prevalence of HBs antigen, HBe antigen, HBe antibody, and HBs antigen subtypes in atomic-bomb survivors

Neriishi K,* Akiba S, Amano T, Ogino T, Kodama K

- Comparison of conventional and fluorescence-in-situ-hybridization methods for the translocation frequency of lymphocytes from atomic-bomb survivors

Nakano M,* Kodama Y, Ohtaki K, Awa AA, Nakamura N

- Clustering of interstitial deletions on chromosome 5q in lymphocytes from A-bomb survivors

Ohtaki K,* Nakamura N, Awa AA

- Estimation of minimum length of translocated chromosome tips detectable by FISH

Kodama Y,* Nakano M, Ohtaki K, Awa AA, Nakamura N

- Dose-response relationship of stable chromosome aberration frequencies among A-bomb survivors with a special reference to shielding conditions
Awa AA,* Nakamura N, Pawel DJ, Honda T
- Genetic instability of minisatellites in the children of the A-bomb survivors
Kodaira M,* Satoh C, Hiyama K, Toyama K
- Cancer susceptibility in A-bomb survivors predicted by increased levels of X-ray-induced micronuclei
Ban S,* Neriishi K, Cologne JB
- Isolation of full length cDNA which has the ability to complement the SCID (severe combined immunodeficient) mouse mutation
Hamatani K,* Araki R, Itoh M, Abe M
- Analysis of V(D)J recombination in lymphoid tissue of the SCID mouse
Abe M,* Hamatani K, Itoh M, Araki R
- Isolation of the gene complementing high radiosensitivity in SCID mouse
Itoh M,* Hamatani K, Araki R, Abe M
- Development of a novel assay system to detect human somatic mutations using neutrophils. I. At the Fcγ receptor III locus
Hirai Y,* Kitahira M, Takahashi K, Ishioka N, Kusunoki Y, Kyoizumi S, Akiyama M
- Analysis of radiation-induced glycophorin A gene mutation: Summarizing a study of atomic-bomb survivors and molecular analysis of mutants
Nagamura H,* Kyoizumi S, Cologne JB, Tanabe K, Kubo Y
- The SCID-hu mouse model for human radiation biology: Establishment of an epilation model
Kyoizumi S,* Teraoka S, Yamakido T, Seyama T, Akiyama M
- Detection of hepatitis B virus in liver cancer among atomic-bomb survivors
Seyama T,* Mizuno T, Iwamoto KS, Ishii N, Fujii S, Akiyama M, Fujita Y, Mabuchi K
- Activated RET oncogene in thyroid cancers of children residing in areas contaminated by the Chernobyl accident
Akiyama M,* Seyama T, Ito T, Mizuno T, Iwamoto KS, Takeichi N, Satow Y
- Search for the BCR-ABL gene in the peripheral blood of A-bomb survivors and radiotherapy patients
Mizuno T,* Seyama T, Iwamoto KS, Ishii N, Akiyama M, Kodama T, Ohama K

3rd Japanese General Osteoporosis Meeting, 27-28 October 1994, Osaka

- Comparison of osteoporosis risk factors in Japanese and Japanese-Americans—serum 25-hydroxyvitamin D levels
Fujiwara S,* Kodama K, Huang C, Ross PD, Davis JW, Wasnich RD

10th Vitamin D Symposium: What Are the Most Important Factors in Determining Bone Mass, 4-5 November 1994, Yokohama

- Reproductive factors and osteoporosis: the Hiroshima/Nagasaki study
Fujiwara S*

45th Annual Meeting of the Society of Chromosome Research, 4-6 November 1994, Kochi

- Scoring and classification of structural aberrations detected by chromosome painting
Awa AA*

35th General Meeting of the Japan Lung Cancer Society, 7-8 November 1994, Nagasaki

- Growth suppressive efficacy of human LAK cells against human lung cancer cells implanted into SCID mice
Teraoka S,* Kyoizumi S, Yamakido M, Akiyama M

23rd Annual Meeting of the Japan Environmental Mutagen Society, 24-26 November 1994, Shizuoka

- Development of a new assay system to detect mutations in vivo using mice
Akiyama M,* Umeki S, Yamakido T, Hirai Y, Kyoizumi S
- Detection of mutants in various blood cells using a single commonmarker
Hirai Y,* Kubo Y, Kyoizumi S, Akiyama M

24th Annual Meeting of the Japanese Society for Immunology, 29 November-1 December 1994, Kyoto

- Long-term single cell culture of cord blood stem cells using a murine bone marrow stroma cell line
Kyoizumi S,* Hirai Y, Yamakido T, Teraoka S, Akiyama M

Symposium for Two-dimensional Electrophoresis of Protein and Nucleic Acid, 2 December 1994, Tokyo

- Genome scanning two-dimensional electrophoresis of DNA; molecular genetic analysis of variable genes identified by a modified method
Asakawa J*

26th Symposium of the National Institute of Radiological Sciences, 8-9 December 1994, Tokyo

- Issues in risk modeling
Mabuchi K*

- A simple reductionist model for cancer risk in atomic bomb survivors
Mendelsohn ML*

2nd International Symposium on Biomedical Diagnostic and Prognostic Indicators—Impact of Biotechnology on Predictive Oncology and Therapy, 11–13 December 1994, Boston, Massachusetts

- External and internal comparisons of mortality among the offspring of atomic bomb survivors
Yoshimoto Y,* Mabuchi K
- Activated RET oncogene in thyroid cancer among children residing in areas contaminated by the Chernobyl accident and among atomic-bomb survivors
Akiyama M,* Seyama T, Ito T, Mizuno T, Iwamoto KS, Takeichi N, Satow Y

17th Annual Meeting of the Molecular Biology Society of Japan, 13–16 December 1994, Kobe

- High yield of restriction fragment length polymorphisms in two-dimensional separations of human genomic DNA
Asakawa J,* Kuick R, Neel JV, Kodaira M, Kaneoka S, Satoh C, Hanash SM
- Cloning of full length cDNA capable of complementing the SCID mouse mutation
Hamatani K,* Araki R, Itoh M, Abe M

1st International Symposium on Chronic Radiation Exposure: Risk of Late Effects, 9–13 January 1995, Chelyabinsk, Russia

- Cancer mortality in atomic bomb survivors, 1950–1990
Preston DL,* Pierce DA, Shimizu Y, Mabuchi K, Væth M
- Somatic cell mutations at the glycophorin A and the TCR genes in atomic bomb survivors and chronic radiation exposures
Akiyama M,* Kyoizumi S, Cologne JB, Tanabe K
- Preliminary results for ESR on tooth enamel and chromosome aberration in lymphocytes from atomic bomb survivors
Nakamura N,* Iwasaki M, Miyazawa C, Niwa K, Akiyama M, Sawada S, Awa AA
- Radiation, lifestyle factors, heart disease and cancer
Mabuchi K,* Goodman MT, Cologne JB

5th General Meeting of the Japan Epidemiological Association, 26–27 January 1995, Osaka

- Risk factors for thyroid cancer: a case-control study in Hiroshima–Nagasaki
Yoshimoto Y,* Konda M, Hayashi M, Mabuchi K, Land CE

- Cancer risk among atomic bomb survivors
Shimizu Y,* Moriwaki H, Mabuchi K, Preston DL
- Trend and associated factors of sudden death based on the 40-year prospective study
Kasagi F,* Kodama K, Yamada M, Ueda H, Fujita Y

13th Conference of Molecular Pathology, 27-28 January 1995, Tokyo

- Molecular analysis of ras and p53 genes in skin cancer among A-bomb survivors
Mizuno T,* Seyama T, Akiyama M

International Workshop on Low-dose Radiation Risk Assessment, 7-9 February 1995, Kiev, Ukraine

- RET oncogene rearrangement in childhood thyroid cancer in contaminated area of Chernobyl
Akiyama M,* Seyama T, Ito T, Iwamoto KS, Mizuno T, Satow Y, Takeichi N, Dohi K

3rd Joint Conference of the American Association for Cancer Research/Japanese Cancer Association, 13-18 February 1995, Honolulu, Hawaii

- Somatic cell mutations at the glycophorin A locus in erythrocytes of atomic bomb survivors, Hiroshima and Nagasaki: implications for radiation carcinogenesis
Kyoizumi S,* Cologne JB, Tanabe K, Akiyama M
- Genomic instability at the T-cell antigen receptor in a p53 dependent manner
Akiyama M,* Iwamoto KS, Seyama T, Mizuno T, Tsuyama N, Ban S, Kyoizumi S

12th International Conference on Calcium Regulating Hormones, 14-19 February 1995, Melbourne, Australia

- Weight change since early adulthood predicts bone mineral density
Fujiwara S,* Kodama K, Kasagi F, Fukunaga M

RADTEST Workshop, 27-31 March 1995, Brussels/Liege, Belgium

- Chromosome aberration data on atomic bomb survivors in Hiroshima and Nagasaki
Awa AA*

Scientific Lectures and Seminars

April 1994-March 1995

Colin Muirhead, leader, Epidemiology Group, United Kingdom National Radiological Protection Board: "Recent childhood leukemia studies in the UK," 11 April

Shoichi Sasabuchi, associate professor, Department of Mathematics, Faculty of Science, Hiroshima University. 137th Hiroshima Joint Statistics Seminar: "Statistical inference under inequality restrictions," 15 April

Eugene O Major, chief, Laboratory of Molecular Medicine and Neuroscience; AIDS coordinator, Intramural Program, National Institute of Neurological Disorders and Stroke, US National Institutes of Health (US NIH): "The association of JC virus infection in lymphocytes with demyelination in the brain and chromosome damage in the 'rogue cells,'" 3 June

Anup Dewanji, associate professor, Indian Statistical Institute, Calcutta: "Two stage model for carcinogenesis: Some results, implications and applications," 9 June

Eiji Nakashima, research scientist, Department of Statistics, RERF. 138th Hiroshima Joint Statistics Seminar: "An analysis of chromosome-aberration data from atomic-bomb survivors using the quasi-likelihood/pseudo-likelihood method," 17 June

Tore Straume, senior investigator, Lawrence Livermore National Laboratory, Livermore, California: "An update of neutron activation measurements in Hiroshima and Nagasaki," 3 August

Bernard S Pasternack, professor, New York University Medical Center, Department of Environmental Medicine, New York. 139th Hiroshima Joint Statistics Seminar: "An application of spline regression to a problem in biostatistics: Estradiol and the risk of premenopausal breast cancer," 30 September

Ryuei Nishii, assistant professor, Faculty of Integrated Arts and Sciences, Hiroshima University. 140th Hiroshima Joint Statistics Seminar: "Statistical analysis of Landsat data," 7 October

Yoshiaki Kodama, research scientist, Department of Genetics, RERF. Interdepartmental seminar: "Estimation of minimum length of translocated chromosome tips detectable by chromosome painting," 14 October

Nori Nakamura, assistant chief, Department of Genetics, RERF. Interdepartmental seminar: "Preliminary results of dose estimation by ESR using teeth from A-bomb survivors," 14 October

Curtis C Harris, chief, Laboratory of Human Carcinogenesis, National Cancer Institute, US NIH: "Mutational and functional analyses of the p53 and p16^{INK4} tumor suppressor genes," 26 October

Kelly H Clifton, professor, Human Oncology and Radiology, Wisconsin Clinical Cancer Center, University of Wisconsin, Madison: "Radiation-induced thyroid cancer: the nature of cancer initiation," 4 November

Valerie Beral, director, Imperial Cancer Research Fund, Cancer Epidemiology Unit, University of Oxford: "Research in the ICRF Cancer Epidemiology Unit, Oxford, with special emphasis on breast cancer," 9 November

Sarah C Darby, researcher, Imperial Cancer Research Fund, Cancer Epidemiology Unit, University of Oxford: "Mortality and AIDS in UK hemophiliacs," 9 November

Bruce Alberts, president, US National Academy of Sciences: "Avoiding a train wreck: What happens when RNA polymerase and DNA polymerase collide?" 11 November

John B Cologne, associate senior scientist, Department of Statistics, RERF. Interdepartmental seminar: "Random dosimetry error and radiation sensitivity," 18 November

John B Cologne, associate senior scientist, Department of Statistics, RERF. 141th Hiroshima Joint Statistics Seminar: "Use of biological dosimeters for risk estimation," 25 November

Saeko Fujiwara, chief, Division of Clinical Laboratories, Department of Clinical Studies, RERF. Interdepartmental seminar: "Radiation and benign tumor—prevalence of myoma uteri screened by ultrasonography," 2 December

Hironori Ueda, research scientist, Department of Clinical Studies, RERF. Interdepartmental seminar: "Radiation and atherosclerosis—an analysis of pulse wave velocity," 2 December

E John Ainsworth, scientific director, US Armed Forces Radiobiology Research Institute (AFRRI), Bethesda, Maryland: "Early and late effects of radiation on mouse marrow CFU-S: Life span shortening in mice irradiated with gammas, neutrons, or heavy charged particles," 5 December

Robert L Bumgarner, director, AFRRI: "An overview of the program at AFRRI," 5 December

Keisuke S Iwamoto, research scientist, Department of Radiobiology, RERF. Interdepartmental seminar: "Genetic instability induced by p53 mutations and radiation," 9 December

Seishi Kyoizumi, chief, Immunology Laboratory, Department of Radiobiology, RERF. Interdepartmental seminar: "The SCID-hu mouse model for human radiobiological studies," 9 December

Terumi Mizuno, research scientist, Department of Radiobiology, RERF. Interdepartmental seminar: "Preliminary results of molecular analysis of skin cancer among A-bomb survivors," 9 December

Jim Piper, acting director, Automated Cytogenetics Department, Human Genetics Unit, Medical Research Council, Edinburgh, Scotland, UK: "Automated aberration scoring for radiation dosimetry using whole-chromosome fluorescence in situ hybridization," 12 December

Kiyohiko Mabuchi, chief, Department of Epidemiology, RERF. Interdepartmental seminar: "Dosimetry System 1986 and ABS93D," 16 December [*Editor's note: ABS93D is an atomic-bomb-survivor dosimetry calculated by Hiroshima University researchers.*]

Jozef Sabol, professor, Department of Dosimetry and Application of Ionizing Radiation, Faculty of Nuclear Sciences and Physical Engineering, Czech Technical University, Prague, Czech Republic: "Radiological consequences of the Chernobyl accident in the Czech Republic," 23 January

Yoko Watamori, research assistant, Department of Mathematics, Faculty of Science, Hiroshima University. 142nd Hiroshima Joint Statistics Seminar: "Statistical inference of Langevin distribution," 27 January

Gary F Strniste, group leader, Life Sciences Division, Los Alamos National Laboratory, Los Alamos, New Mexico: "Radiobiological research in the Life Sciences Division at Los Alamos," 22 March

Periodicals Produced by RERF

During FY94, the RERF Publication and Documentation Center produced the following periodicals to provide information for the local scientific community and for members of the national and international radiation-research community, and for RERF employees—past and present.

Journal of the Hiroshima Medical Association

Since 1960, the monthly *Journal of the Hiroshima Medical Association (JHMA)* has included a section devoted to ABCC-RERF research findings. During FY94, original English-language articles written for *RERF Update* (see below) have been translated into Japanese for this purpose. In addition, bibliographic information and the Scientific Council report have been published. Page charges (approximately ¥680,000 in FY94) are contributed by RERF to disseminate this material to the 5,500 members of the local medical association. In addition, about 100 reprints are purchased and distributed by RERF to a mailing list of 51 persons, local media, and medical institutions.

See Table 1 for a list of articles published in Japanese in the *JHMA* RERF Section during FY94.

RERF Update

Since 1989, RERF has published a quarterly English-language newsletter, *RERF Update*, to inform international radiation researchers about RERF's recent journal publications, about institutional news, and about ongoing scientific projects. During FY94, four issues of *RERF Update* were published and distributed to 957 persons or institutions free of charge.

See Table 1 for a list of major articles published in English in *RERF Update* during FY94.

RERF Newsletter

Since 1975, the monthly *RERF Newsletter* has been published in Japanese to disseminate institutional, scientific, and employee news. During FY94, 12 issues were published and distributed to 755 persons or institutions free of charge. A removable employee news insert was distributed in the newsletter only to RERF's 505 present and past employees.

RERF Annual Report

Recipients of the *Fiscal Year 1993 Annual Report* were asked to indicate by return postcard if they wished to continue receiving the *RERF Annual Report*. About 60% of recipients replied, thus reducing the mailing list to 410 persons or institutions. RERF will distribute 199 copies of the Japanese-language *FY94 Annual Report* and 223 copies of the English-language version free of charge to individuals and institutions, including 130 libraries.

RERF Reports

After the termination of the in-house RERF Technical Report Series in 1992, RERF began to purchase journal-article reprints, which are bound into RERF Report covers with Japanese summaries. Although distribution of RERF Reports varies depending on the subject matter, at least 100 are disseminated to Japanese and American governmental ministries and agencies, local hospitals and atomic-bomb survivor groups, libraries, and to RERF directors and consultants.

Table 1. Articles published in the RERF Section of the *Journal of the Hiroshima Medical Association (JHMA)* and in *RERF Update* during FY94. The symbol ♦ designates a FY94 publication. When articles exist in both languages, bibliographic citations are given even if they date from previous fiscal years.

Article title and author(s)	JHMA bibliographic citation	RERF Update bibliographic citation
Cancer incidence in the atomic-bomb survivors K Mabuchi	n/a	6(1):3-4, 1994♦
The origin of clonal chromosome aberrations Y Kusunoki, Y Kodama, Y Hirai, N Nakamura, M Akiyama	n/a	6(1):5-7, 1994♦
How much does accuracy of information about shielding for individual survivors influence dosimetry error? M Nakano, Y Kodama, K Ohtaki, AA Awa	n/a	6(1):8, 1994♦
Facts & figures. Multiple cancers in the atomic-bomb survivors TP Rose	Part 2. 47:1466-7, 1994♦	6(1):11, 1994♦
Science, radiation protection, and the NCRP WK Sinclair	n/a	6(2):3-5, 1994♦
Assessing radiation dose recorded in tooth enamel N Nakamura, M Iwasaki, C Miyazawa, M Akiyama, AA Awa	n/a	6(2):6-7, 1994♦
Facts & figures. Estimating doses to service- men stationed near Hiroshima S Fujita	Part 3. 47:1468, 1994♦	6(2):11, 1994♦

Continued on next page

Table 1. *continued*

Article title and author(s)	JHMA bibliographic citation	RERF Update bibliographic citation
Progress in the RERF biochemical genetics study C Satoh, M Kodaira	n/a	6(3):3-4, 1994♦
A message from the reticulocytes S Kyoizumi, M Akiyama	n/a	6(3):5, 1994♦
Investigating the link between liver cancer and hepatitis T Mizuno, T Seyama, M Akiyama	n/a	6(3):6-7, 1994♦
Facts & figures. Dosimetry System 1986 dose: distance and shielding S Izumi, D Pierce, D Preston	n/a	6(3):8, 1994♦
Two-dimensional electrophoresis of end-labeled genomic DNA fragments J Asakawa	n/a	7(1):3-5, 1995♦
Site-specific cancer incidence: an interim report S Tokuoka, M Tokunaga, K Mabuchi	n/a	7(1):6-7, 1995♦
Facts & figures. In-utero-exposed atomic-bomb survivors: cancer risk update R Delongchamp, Y Yoshimoto, K Mabuchi	n/a	7(1):8, 1995♦
Growth and development of atomic-bomb survivors exposed during childhood M Otake	47:657-9, 1994♦	5(3):3-4, 1993
Cardiovascular disease in atomic-bomb survivors K Kodama	47:800-1, 1994♦	5(4):3-4, 1993
Cholesterol levels in the Adult Health Study, 1958-1986 M Yamada	47:940-2, 1994♦	5(4):5-6, 1993
RERF Reports approved for publication in the scientific literature, 1993 through July 1994 RERF	47:1118-22, 1994♦	n/a

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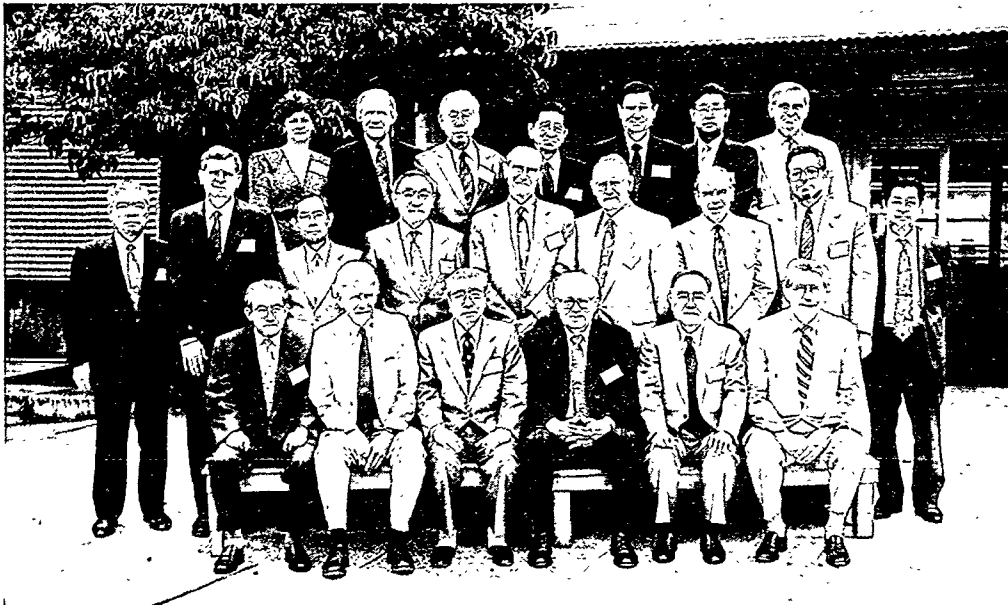
Table 1. *continued*

Article title and author(s)	<i>JHMA</i> bibliographic citation	<i>RERF Update</i> bibliographic citation
RERF bibliography of publications, 1993 RERF	47:1239-51, 1994 ♦	n/a
Introduction of the RERF officers and research staff members (1 September 1994) RERF	47:1387-92, 1994 ♦	n/a
Fact & figures. Coefficient of variation in radiation-induced micronuclei JB Cologne	Part 1. 47:1466, 1994♦	5(4):10, 1993
Comments and recommendations of the 21st Scientific Councilors meeting RERF	47:1589-94, 1994 ♦	

Report from the Secretariat

28th Board of Directors Meeting

The 28th meeting of the Board of Directors was held 22-24 June 1994 at the Hiroshima Laboratory. Present personnel status and the resolution to request the United Nations to identify and support RERF as the United Nations International Radiation Health Effects Advisory Institute were reported. Also, the progress of Japan-US talks on budgetary issues was explained. (The report on the Board meeting begins in the Appendix on page 119 and details of the talks between RERF's funding agencies are in a separate report, starting on page 97.)



Attendees of the 28th RERF Board of Directors meeting included, front row from left, T Kumatori, J Rall, I Shigematsu, S Jablon, K Arichi, W Sinclair. Middle row from left, Y Hirano, R Sperry, Y Hasegawa, T Kono, M Mendelsohn, S Abrahamson, D Harkness, R Hyams, T Nakaoka. Back row from left, C Berkley, D Williams, E Matsunaga, A Shishido, J Zimbrick, A Awa, C Edington.

Personnel

RERF employees totaled 377 as of 31 March 1995, a decrease of 36 compared to a year ago. Because of the policy of gradually reducing the number of budgeted positions, new employment of general employees is being kept to a minimum. (See Table 2 on page 86 and Table 3 on page 87.)

Donald R Harkness, permanent director, was elected as successor to Chief of Research Seymour Abrahamson. Yasukiyo Hirano, operations administrator, was elected as successor to Chief of Secretariat Tomoyuki Kono. Both Abrahamson and Kono resigned on 30 June 1994.

Table 2a. Full-time personnel as of 31 March 1995

Full-time personnel	Hiroshima	Nagasaki	Total
Directors	5 (2)		5 (2)
Professionals*	42 (8)	8	50 (8)
General	230 (1)	92	322 (1)
Total	277 (11)	100	377 (11)

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

Table 2b. Other RERF personnel

Department/division	Consul- tants*	Expert advisors*	Part-time professionals			Total
			H	N	Total	
Clinical Studies	31	5	12	13	25	61
Genetics	9	1	2	0	2	12
Radiobiology	6	1	1	1	2	9
Epidemiology	8	2	1	0	1	11
Statistics	4	4	1	0	1	9
Epidemiologic Pathology	10	12	2	1	3	25
Research Information Center	3	1	0	0	0	4
Secretariat	2	0	1	0	1	3
Total	73	26	20	15	35	134

*See Appendix, pp 144-149, for the list of consultants and expert advisors.

Note: H = Hiroshima. N = Nagasaki.

Table 3. Personnel composition

As of 31 March 1995

Department or section		Directors	Research scientists	A Administrative	B Manual & gen. tech.	C Medical & technical (I)	D Medical & technical (II)	Total	Visiting scientists	Temporary employees*
Hiroshima	Directors	4						4		
	Chief of Secretariat	1						1		
	Associate chief of research		1					1		
	Clinical Studies		7	20	1	11	13	52		
	Genetics		8	3	2	16		29	1	
	Radiobiology		11	4	2	15		32		
	Epidemiology		3	24				27	1	
	Statistics		1	16				19	1	
	Epidemiologic Pathology		8	5		2		13		
	Research Information Ctr		2	16				18		
	Publication & Docum. Ctr		1	28				29		
	Radioisotope Facility					1		1		
	Secretariat			40	11			51		
Total	5	42	156	16	45	13	277	3		
Nagasaki	Clinical Studies		2	18		11	7	38		
	Radiobiology		4	1	1	7		13		
	Epidemiologic Biometrics		1	14				15		
	Epidemiologic Pathology		1	9		3		13		3
	Radioisotope Facility					1		1		
	Secretariat			18	2			20		
Total		8	60	3	22	7	100		3	
Grand total	5	50	216	19	67	20	377	3	3	

*Supported by entrusted funds

Note: Among the 216 administrative and clerical staff, 158 are in research support units and 58 are in the Secretariat.

Professional staff appointments

Seymour Abrahamson resigned from the posts of permanent director and chief of research as of 30 June 1994.

Robert L Allen, research scientist, Information Systems Laboratory, Research Information Center, Hiroshima, terminated employment as of 31 December 1994.

Donald R Harkness, permanent director, was appointed, effective 1 July 1994, chief of research.

Takeo Honda, chief, Department of Radiobiology, Nagasaki, terminated employment as of 31 March 1995.

Shinichi Ishioka, from the 2nd Department of Internal Medicine, Hiroshima University School of Medicine, was appointed, effective 8 June 1994, industrial health physician, Hiroshima Laboratory. On 17 October, he completed his term of appointment.

Tomoyuki Kono resigned from the posts of permanent director and chief of the Secretariat as of 30 June 1994.

Robert Masterson, research scientist, Editorial and Publication Section, Publication and Documentation Center, Hiroshima, retired as of 1 April 1994.

Hiroaki Nonaka, acting chief, Division of Clinical Laboratories, Department of Clinical Study, Nagasaki, terminated employment as of 30 June 1994.

Kiyosumi Oishi, research scientist, Division of Medicine, Department of Clinical Studies, Nagasaki (industrial health physician), terminated employment as of 31 August 1994.

David Pawel, research scientist, Department of Statistics, Hiroshima, terminated employment as of 2 August 1994.

Scott Pohlman, assistant chief, Information Systems Laboratory, Research Information Center, Hiroshima, terminated employment as of 12 December 1994.

Thanne P Rose, research scientist, Department of Epidemiology, Hiroshima, terminated employment as of 30 June 1994.

Hidetoshi Tahara, from the Hiroshima University doctoral course in molecular pharmacology, was appointed, effective 1 April 1994, a visiting research scientist with the Department of Radiobiology, Hiroshima. On 31 October, he completed his term of appointment.

Seigo Teraoka, research scientist, Laboratory of Epidemiology, Department of Radiobiology, Hiroshima, terminated employment as of 31 March 1995.

Shoji Tokuoka, RERF senior consulting scientist, was appointed, effective 1 July 1994, RERF consultant.

Masako Tsuruta, chief, Division of Clinical Laboratories, Department of Clinical Studies, Nagasaki, was appointed, effective 1 September 1994, industrial health physician.

Mandatory retirement

The following employees, 12 in Hiroshima and 4 in Nagasaki, reached the mandatory retirement age in FY94.

Hiroshima Laboratory

April: Robert Masterson

June: Yasukiyo Hirano, Takahiko Saeki, Yoshihiro Kurakawa, Michiko Takagi, and Shizuo Inoue

December: Tae Kitagawa, Itsuji Okibayashi, Masashi Hiramoto, Yasuko Uemoto, Kunie Atsuta, and Kiyoshi Nakaso

Nagasaki Laboratory

June: Moritaka Taniguchi and Tsutomu Nakamura

December: Giichi Ohta and Miyoko Aoki

Long Service Award ceremonies

Long Service Award ceremonies were held on 12 April in Hiroshima and on 8 April in Nagasaki to express appreciation to employees (16 in Hiroshima and 5 in Nagasaki) for their many years of devoted service.

Hiroshima Laboratory

- **Thirty-year award recipients:** Masashi Sakurai, Tsunemaro Ohmoto, Junko Houta, Itsuji Okibayashi, Naoya Kagimoto, and Toyoko Nakamura
- **Twenty-year award recipient:** Chiyoko Satoh
- **Ten-year award recipients:** Tadaaki Watanabe, Yutaka Nakamori, Hiroyuki Yamane, Masahiro Yamaguchi, Tetsuji Kurihara, Kenji Ohnishi, Masumi Hirota, Hiroaki Katayama, and Dale L Preston

Nagasaki Laboratory

- **Thirty-year award recipients:** Koki Sonoda, Yasuyuki Takeda, and Akihiro Yamauchi
- **Ten-year award recipients:** Tomoaki Yamashita and Hirosuke Tasaki

Organizational structure of RERF

As a result of the present stringent fiscal policy of the US government and the appreciation in the value of the yen versus the US dollar, the organizational structure of the RERF laboratories and Secretariat was changed during FY94 to reduce costs.

Hiroshima Laboratory

In July 1994, the External Affairs Section was combined with the General Affairs Section. The activities of the Operations Section were partly integrated into the General Affairs Section and the remainder into the Supply and Property Section. In addition, the Food Service Unit at Hijiyama Hall was closed. In this way, six sections were reduced to four.

Nagasaki Laboratory

In January 1995, the Laboratory of Cytogenetics, Department of Radiobiology, was closed.

Figures 1, 2, and 3, which follow on pages 91, 92, and 93, respectively, show the present structure of RERF.

Fiscal and property report

The RERF budget, settlement of accounts (Table 5 on page 94 and Table 6 on page 95) and property (Table 7 on page 96) for FY94 are presented here. The subsidy income, which is the main source of regular income, is equally provided by the governments of Japan and the United States based on the principle of equal support (Table 5 on page 94).

The total RERF budget for operations was ¥5,468,070,000, an increase of ¥182,762,000 (+3.5%) over the previous year. The major increase and decrease were a ¥246,430,000 (+5.6%) increase in personnel expenses and a ¥63,668,000 (-7.5%) decrease in operational expenses (Table 4 below).

In the settlement of accounts for FY94, there was a surplus of ¥76,686,070 in personnel funds, of which ¥75,522,535 was returned to the Japanese government and ¥1,163,535 to the US government (Table 5 on page 94).

Table 4. Increase and decrease in operating costs (in yen)

Category	Fiscal year		
	1992	1993	1994
Personnel expenses	4,318,030,000 (106.4%)	4,439,544,000 (102.8%)	4,685,974,000 (105.6%)
Operational expenses	855,612,000 (103.7%)	845,764,000 (98.8%)	782,096,000 (92.5%)
Total	5,173,642,000 (105.9%)	5,285,308,000 (102.2%)	5,468,070,000 (103.5%)

Figure 1. Organization of RERF

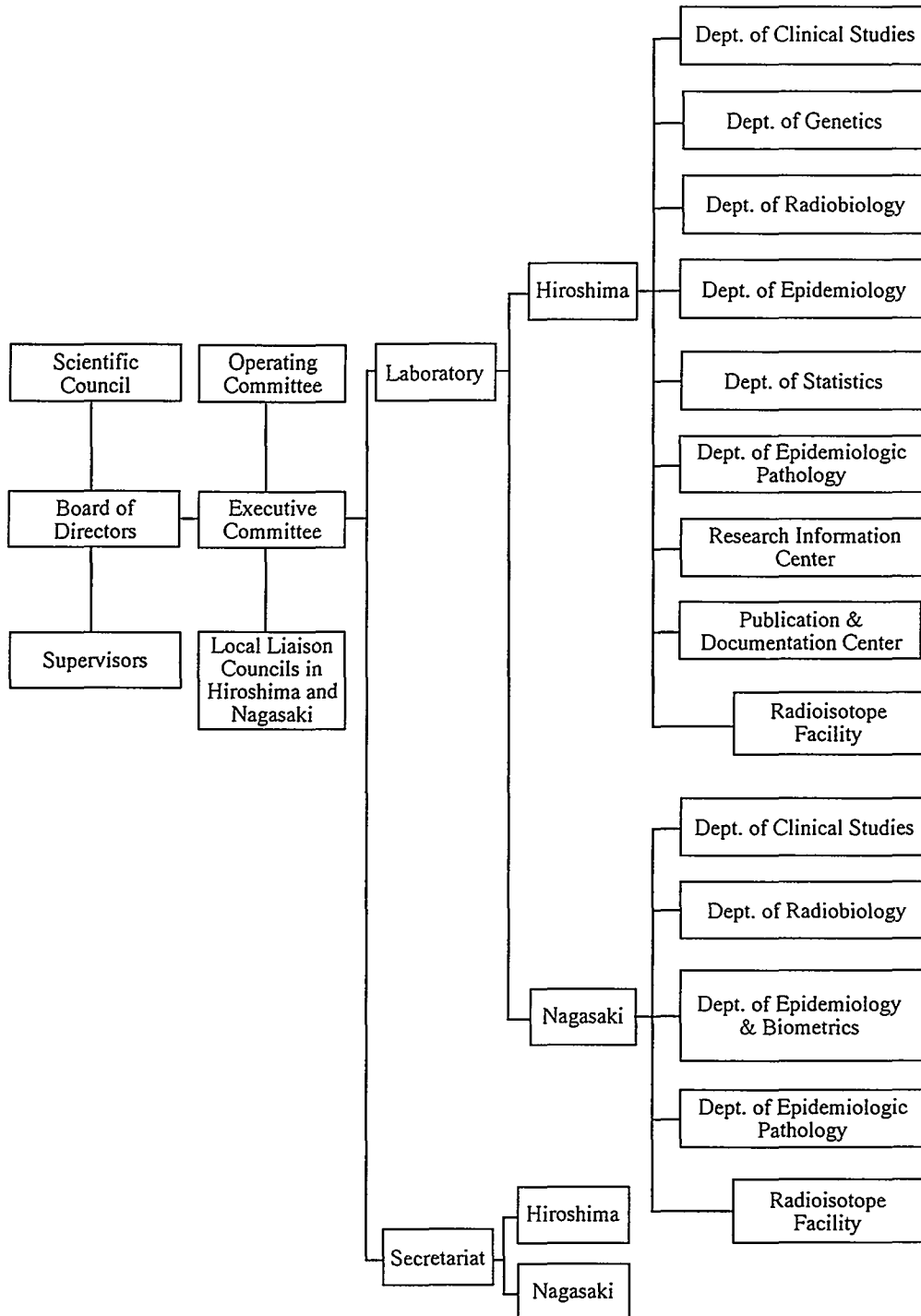


Figure 2. Organization of the laboratories

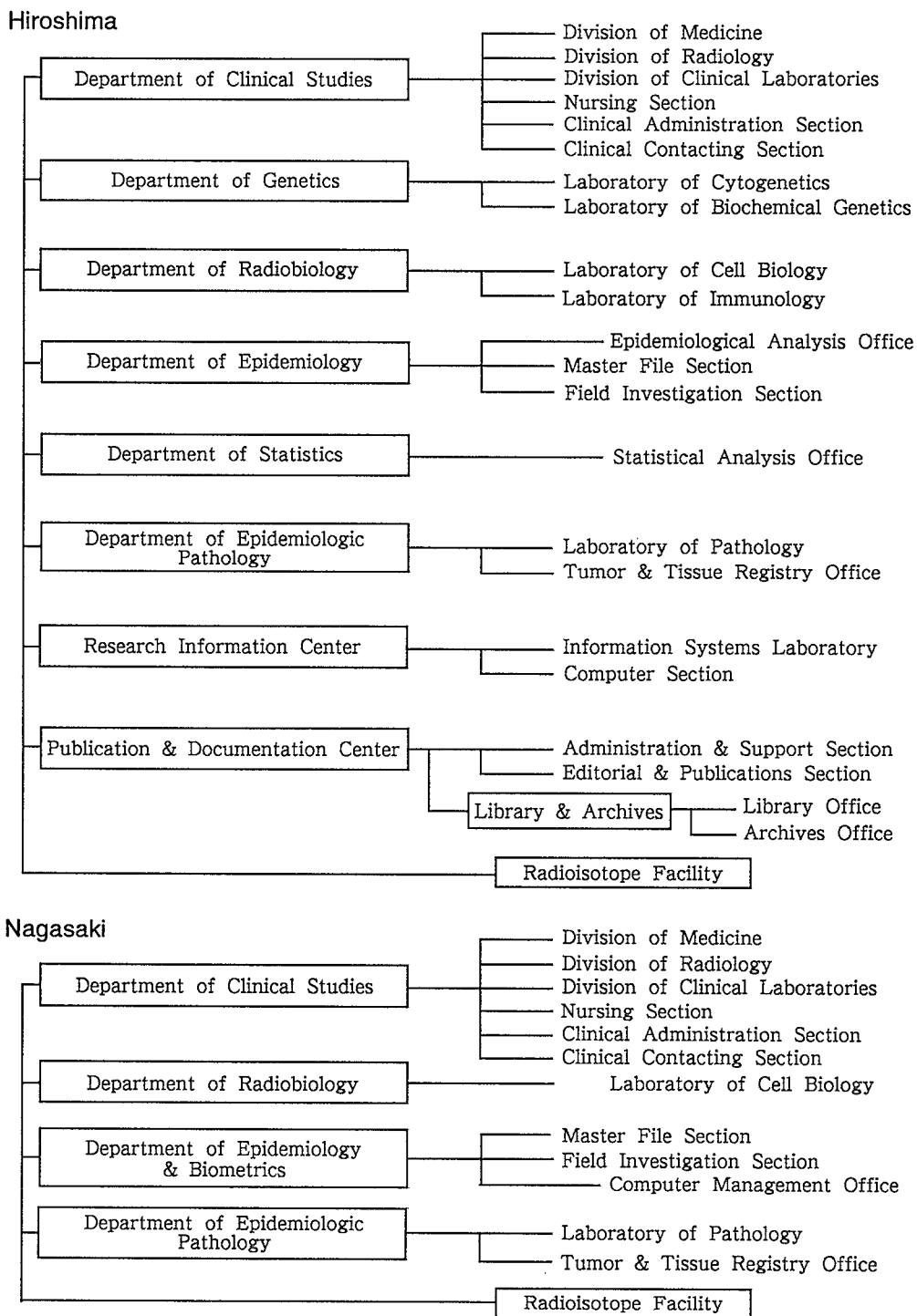
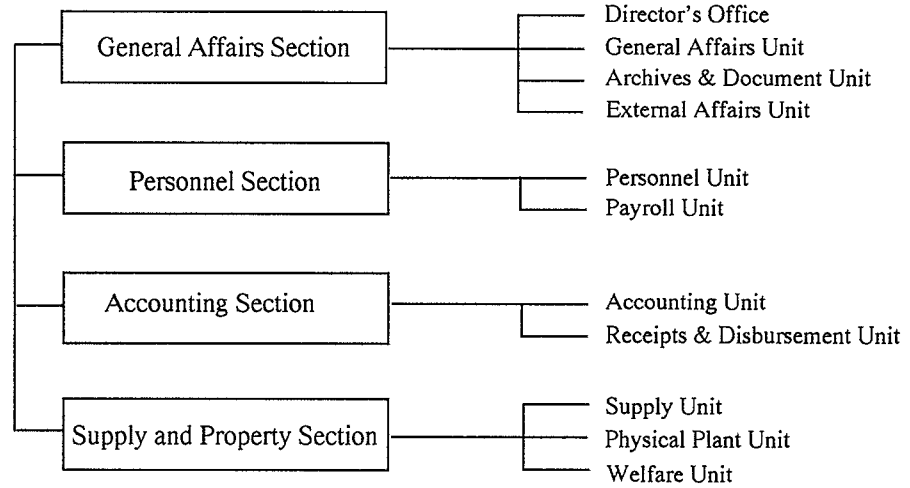


Figure 3. Organization of the Secretariat

Hiroshima



Nagasaki

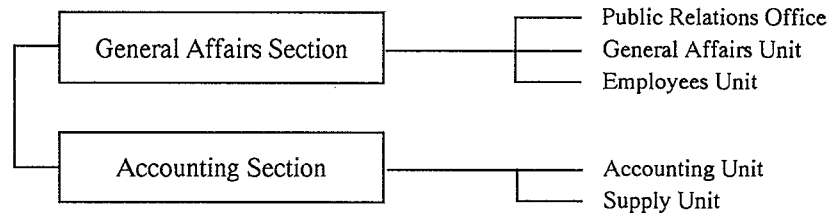


Table 5. Statement of income and expenditures, regular account, 1 April 1994-31 March 1995

Category	Budget A	Settlement B	Balance A - B
Income (yen)			
Subsidy income	¥(5,439,448,000)	¥(4,381,317,000)	¥(1,058,131,000)
GOJ treasury	2,719,724,000	2,227,838,000	491,886,000
GUS treasury	2,719,724,000	2,153,479,000	566,245,000
Independent income	(28,622,000)	(54,295,303)	(Δ 25,673,303)
Medical exams (ABSMTL)	28,622,000	24,454,542	4,167,458
Miscellaneous	0	29,840,761	Δ 29,840,761
Brought forward from special account	(0)	(17,064)	(Δ 17,064)
Dining room account	0	17,064	(Δ 17,064)
Total income (A)	5,468,070,000	4,435,629,367	1,032,440,633
Expenditures			
Personnel expenses	(4,685,974,000)	(3,559,650,930)	(1,126,323,070)
Operational expenses	(782,096,000)	(799,292,367)	(Δ 17,196,367)
Fees & gratuities	38,233,000	30,978,268	7,254,732
Travel, directors & staff	21,663,000	21,243,254	419,746
Travel, committee	5,972,000	4,375,995	1,596,005
Travel, relocation	17,651,000	14,231,274	3,419,726
Travel, overseas	5,030,000	6,452,057	Δ 1,422,057
Office & lab. expenses	608,923,000	637,462,046	Δ 28,539,046
Rent, land & buildings	53,724,000	52,843,388	880,612
Maintenance & repair	30,000,000	30,931,665	Δ 931,665
Taxes	900,000	774,420	125,580
Total expenditures (B)	5,468,070,000	4,358,943,297	1,109,126,703
Balance (A) - (B) (FY94 personnel expenditures surplus)		76,686,070	

Note: ABSMTL stands for Atomic Bomb Survivors' Medical Treatment Law. RERF receives a fee for every medical examination of an atomic-bomb survivor, as specified in the national law.

Δ Indicates income or expenditures in excess of budget

Table 6. Settlement of accounts, summary sheet

1 April 1994-31 March 1995

Category	Total	Regular account	Cancer case-LSS SP acct	Radiation risk assessment SP acct	Shigematsu colla. study SP acct	Termination trust fund SP acct	NAS housing SP acct	HH dining room SP acct	Nagasaki Pref. Cancer Registry SP acct	A-bomb memorial SP acct	Non-subsidy expenses SP acct
Income											
Subsidy	4,381,317,000	4,381,317,000									
Operational income (interest, etc.)	82,250,531	54,295,303	12,125		3,648	22,057,050	861,157	1,421,493			3,599,755
Transferred from special account	17,064	17,064									
Entrustment fund	104,317,534		34,843,400	2,987,000	22,000,000		2,570,134		7,500,000	34,417,000	
Carried over from previous year	961,881,772		2,211,763			958,601,533	1,068,476				
Total income	5,529,783,901	4,435,629,367	37,067,288	2,987,000	22,003,648	980,658,583	4,499,767	1,421,493	7,500,000	34,417,000	3,599,755
Expenditures											
Personel expenses	3,727,349,448	3,559,650,930	3,200,028	0		149,577,221			5,743,085	9,178,184	0
Operational expenses	873,002,242	799,292,367	13,337,020	2,987,000	22,003,648		3,238,998	1,547,723	1,756,915	25,238,816	3,599,755
Transferred to regular account	17,064							17,064			
Total expenses	4,600,368,754	4,358,943,297	16,537,048	2,987,000	22,003,648	149,577,221	3,238,998	1,564,787	7,500,000	34,417,000	,599,755
Balance, income minus expenses	929,415,147	76,686,070	20,530,240	0	0	831,081,362	1,260,769	△143,294	0	0	0

Note: SP acct = special account; LSS = Life Span Study; NAS = National Academy of Sciences; HH = Hijiyama Hall; Colla. = collaborative; all amounts are in yen.
 △ = Indicates expenditures in excess of income.

Table 7. Regular account balance sheet as of 31 March 1995

	Category	Amount
<i>Assets</i>		
Current assets:	Cash, deposits	¥129,558,291
	Accounts receivable	2,692,042
	Accounts prepaid	4,038,016
	Interfund receivable	9,996,692
	Deposit	949,940
	Total current assets	147,234,981
Fixed assets:	Buildings	239,831,843
	Equipment	447,912,000
	Total fixed assets	687,743,843
Total assets:		834,978,824
<i>Liabilities</i>		
Current liabilities:	Accounts payable	25,839,893
	Interfunds receivable	23,949,752
	Salary deductions on hand	20,759,266
	Balance of subsidy (personnel fund to be returned)	76,686,070
	Total current liabilities	147,234,981
Total liabilities:		147,234,981
Property funds:	Basic property (buildings)	239,831,843
	Operating property (equipment)	447,912,000
	Total current liabilities	687,743,843
Total liabilities and property funds:		834,978,824

Discussions between the US Department of Energy and the Japanese Ministry of Health and Welfare

Representatives of the US Department of Energy (DOE), the Japanese Ministry of Health and Welfare (MHW), and other officials have met several times since early 1994 to discuss the RERF budget reduction issue. This issue arose when DOE requested MHW to consider cost reduction in August 1993 because of the austerity policy of the Clinton administration, which was inaugurated in 1993, and due to the appreciation of the yen versus the dollar. As a result, RERF was requested to submit a specific budget reduction plan to be negotiated by the two funding agencies.

The negotiations and meetings among the parties held in FY94 are summarized below.

• 23-24 May 1994, Tokyo

At meetings held on 17 February 1994 and 9 March 1994, respectively, DOE Deputy Assistant Secretary for Health Harry Pettengill repeatedly insisted that it was impossible for DOE to provide more than \$18 million per year during US Fiscal Years 1994 and 1995. However, as a result of negotiations at this meeting, he promised to make efforts to allocate an additional \$2 million in US FY95, which would begin 1 October 1994.

RERF was asked to reduce operating expenses as much as possible without affecting the major research activities. In line with this demand, it was decided that the vacancies created by mandatory retirements in FY94 would not be filled as a rule, the filling of the vacancies created by voluntary retirements would be restricted to a minimum, salary increases would be limited, operating expenses would be reduced (by 10% compared to the previous fiscal year) by simplifying the organization (by integrating and abolishing departments and sections), and the 5-year rationalization plan would be reviewed.

Participants

Ministry of Health and Welfare: Shuichi Tani, director-general, Health Service Bureau; Shin Kawabe, director, Planning Division; Akira Hashizume, assistant director, Planning Division; Fumio Sakamoto, assistant director, Planning Division; Shuichi Ohshige, supervisor, Medical Care Unit; Shintaro Nakamura, supervisor, Legal Affairs Unit.

US Department of Energy: Harry Pettengill, deputy assistant secretary for health; Timothy S Fox, RERF project manager, Office of Health.

National Academy of Sciences: David Williams, senior financial advisor; John D Zimbrick, director, Board on Radiation Effects Research.

US Embassy: Milton Eaton, representative, US Department of Energy; Robert S Hyams, first secretary, Environmental, Scientific and Technological Affairs, US Department of State.

RERF: Itsuzo Shigematsu, chairman; Mortimer L Mendelsohn, vice chairman; Tomoyuki Kono, permanent director and chief of the Secretariat.

- **16 June 1994, Hiroshima Laboratory**

Despite previous intentions to compile a 5-year plan covering Fiscal Years 1994-98, the MHW presented a draft 2-year plan at this meeting because it was felt that too many uncertainties were involved in a 5-year period.

According to this 2-year plan, vacancies created by retiring research scientists would be filled, whereas those created by mandatory retirements of general employees would not be filled as a rule. Filling of vacancies created by voluntary retirements would be kept to a minimum. Thus, it was estimated that in the coming 2 years the number of employees would be reduced by approximately 62 (the expected number of mandatory retirements and voluntary retirements being approximately 83 in total).

US and Japanese representatives agreed that the total budget for FY94 would be approximately ¥4.35 billion, conditional on restricted salary increases to limit personnel expenses. It also was reported that restructuring of RERF departments was being considered to minimize the adverse effects on the major research programs of a decrease in the number of employees.

Participants

DOE: Harry Pettengill, deputy assistant secretary for health; Edward P Washburn, staff scientist for international programs.

NAS: Paul Gilman, executive director, Commission on Life Sciences, National Research Council; John D Zimbrick, director, Board on Radiation Effects Research; Charles W Edington, director, Radiation Effects Research Program.

MHW: Akira Hashizume, assistant director, Planning Division, Health Service Bureau

Observers

RERF: All permanent directors attended as observers.

- **7-8 October 1994, Honolulu, Hawaii**

At this meeting, representatives of the US and Japanese governments, recognizing that RERF's mission would continue to be important in the future, agreed to continue to provide financial support for RERF activities.

At the June 1994 meeting, the US representatives explained that they would request an additional budget of \$2 million above its original budget of \$18 million for the

Japanese FY94 (1 April 1994–31 March 1995) and that they would make efforts to bear half of RERF's annual budget of ¥4.35 billion.

However, at this meeting, the US representatives said that only \$18 million would be available for Japanese FY94 because the additional \$2 million mentioned by Dr Pettengill in May 1994 was not approved by the US Congress. DOE representatives proposed that to cover the shortfall they would advance funds from the DOE FY95 budget while continuing to seek approval of additional funds. Although RERF's FY94 budget was thus secured, resolving the funding shortfall was to be postponed until the following year. For Japanese FY95, the DOE officials proposed during these negotiations that the equal sharing of expenses for the Adult Health Study be reconsidered, suggesting that the expenses be borne entirely by Japan. The next US–Japan meeting, when the US proposal to reconsider the equal cost sharing system would be discussed, was scheduled to be held in Tokyo in November 1994, but was never held.

Participants

DOE: Paul Seligman, deputy assistant secretary for health; Harry Pettengill, acting director, Office of International Health Studies; Timothy S Fox, RERF project manager, Office of Health; Edward Podolak, special assistant, Office of International Health Studies.

MHW: Shin Kawabe, director, Planning Division, Health Service Bureau; Akira Hashizume, assistant director, Planning Division; Tomomi Hihara, chief, Legal Affairs Unit.

Observers

NAS: Paul Gilman, executive director, Commission on Life Sciences, National Research Council; John D Zimbrick, director, Board on Radiation Effects Research.

US Embassy: Milton Eaton, representative, US Department of Energy; Robert S Hyams, first secretary, Environmental, Scientific and Technological Affairs, US Department of State.

Japanese Ministry of Foreign Affairs: Shuichiro Kawaguchi, assistant director, First North American Affairs Division.

RERF: Itsuzo Shigematsu, chairman; Mortimer L Mendelsohn, vice chairman; Yasukiyo Hirano, chief of Secretariat; Shizuo Inoue, advisor.

• 23 and 30–31 January 1995, Hiroshima Laboratory; 1 February, Tokyo

Originally, DOE Assistant Secretary for Environment, Safety and Health Tara O'Toole was scheduled to participate in a meeting scheduled for 23–24 January 1995.

Because MHW officials were occupied with relief activities immediately after the Great Hanshin Earthquake, the meeting was postponed.

NAS-RERF discussions, 23 January 1995, Hiroshima Laboratory

After a 23 November 1994 meeting between NAS President Bruce Alberts and O'Toole, NAS staff members were told informally of DOE's intention to replace NAS in overseeing the American component of RERF. Although the NAS 5-year grant was due to expire on 31 March 1995, NAS was discouraged from submitting a renewal proposal. A letter, dated 5 December 1994, from Alberts to O'Toole proposed that a "blue ribbon committee" be appointed to review RERF's research efforts, and, despite his disappointment in the DOE decision to replace NAS, Alberts offered to facilitate the managerial transition.

On 23 January, John D Zimbrick and David Williams of NAS visited RERF to inform the NAS staff members that employment conditions would change with the proposed administrative transfer. A day or two later, NAS staff received letters officially notifying them of dismissal as of 31 March 1995.

DOE-RERF discussions, 30-31 January 1995, Hiroshima Laboratory

Relative to the proposed administrative changes, Harry Pettengill, Edward Podolak and Timothy Fox of DOE made a hasty visit to RERF at the end of January, and on the 30th and 31st explained to the RERF directors, NAS staff members, research scientists, and Labor Union representatives why the management and operation of RERF would be transferred from NAS to another academic institution. Dr Pettengill stated that DOE was considering another organization because the routine, 5-year contract between DOE and NAS would expire at the end of March 1995, adding that the DOE wished to develop and reinforce RERF as a core institute in the field of radiation effects research and wanted to give young American researchers opportunities to engage in research activities through RERF. RERF expressed strong apprehension over the sudden termination of the 48-year-long relationship with NAS, which is widely considered to be a scientifically sound and politically neutral body. Dr Pettengill emphasized that the relationship between DOE and RERF would not change with the selection of a new institute.

The memorandum on items agreed upon at this impromptu DOE-RERF meeting on 30 and 31 January, signed by RERF Chairman Itsuzo Shigematsu and Dr Pettengill, states: "It is guaranteed that the relationship between RERF and DOE will hereafter be strictly in line with the Act of Endowment." This statement should be construed as guaranteeing that RERF's present research policy and decision-making process, ie, from recommendation by the Scientific Council to approval by the Board of Directors as stipulated in the Act of Endowment, will continue to be followed in the future.

MHW-DOE-NAS-RERF meeting, 1 February 1995, Tokyo

After the DOE's explanation at the Hiroshima Laboratory, the officials from DOE and NAS attended another impromptu meeting, this time with MHW officials at the US Embassy on 1 February. RERF Chairman Shigematsu and Vice Chairman Mendelsohn also participated.

At the meeting in Tokyo, the following agenda items and others were discussed. 1) DOE's intention to change the funding channel from NAS to the US Department of State and the US Embassy in Japan beginning 1 April 1995. 2) DOE's shortage of funds for the July-September 1995 period. 3) Reconsideration of the US-Japan equal cost sharing system. 4) Scheduling a meeting between the MHW director-general and the DOE assistant secretary. Regarding the problem of DOE's shortage of funds, it was decided that MHW would consider temporarily paying the funds for DOE. As for reconsidering the US-Japan equal cost sharing system, it was agreed that since this matter must be negotiated between the Japanese Ministry of Foreign Affairs and the US Department of State, it should first be discussed at the working group level. DOE Assistant Secretary O'Toole's visit to Japan would come later.

Although the institute to succeed NAS was not specifically named by DOE at these meetings, the letters notifying the NAS staff of their dismissal, delivered by Dr Zimbrick to the 11 NAS employees, cited Columbia University as the candidate. This university was also cited in the 3 February issue of *Science* (Vol 267, p 611, 1995) and the 6 February issue of the *Inside Energy* newsletter. Subsequently, however, DOE informed MHW of its intention to postpone the 31 March 1995 expiration date of the contract with NAS by 6 months, ie, till 30 September 1995. It appeared then that DOE intended to select a successor to NAS among several universities.

Participants

DOE: Harry Pettengill, director, Office of International Health Studies; Edward Podolak, special assistant, Office of International Health Studies; Timothy S Fox, RERF project manager, Office of Health.

US Embassy: Robert S Hyams, first secretary, Environmental, Scientific and Technological Affairs, US Department of State.

NAS: John D Zimbrick, director, Board on Radiation Effects Research; David Williams, senior financial advisor.

MHW: (Only at the Tokyo meeting.) Akira Hashizume, assistant director, Planning Division, Health Service Bureau; Fumio Sakamoto, assistant director, Planning Division; Shuichi Ohshige, chief, Medical Care Activities Unit, Planning Division.

RERF: Itsuzo Shigematsu, chairman; Mortimer L Mendelsohn, vice chairman. The following only participated at the Hiroshima meetings: Donald R Harkness, chief of research; Yutaka Hasegawa, permanent director; and Yasukiyo Hirano, chief of the Secretariat.

DOE-RERF discussion, 28 March 1995, Hiroshima Laboratory

At this meeting of DOE representatives and RERF staff, Steve Galson, DOE's chief medical officer for environment, safety and health, presented counterarguments to the statements of the RERF department chiefs, as published in the 24 February issue of *Science* (Vol 267, p 1077, 1995) and tried to resolve the mutual misunderstandings stemming from preceding discussions. RERF department chiefs tried to clarify some of the issues concerning the DOE's reasons for choosing a new contractor, the methods to be used in evaluating RERF's research achievements and deciding its policies, the DOE's proposed training of young US scientists at RERF, and reduction of the budget.

The DOE officials apologized for past miscommunications with RERF personnel and expressed their wish to restart discussions with a clean slate by changing the DOE's negotiators. Then DOE officials clearly acknowledged the neutral stance taken by the Ministry of Health and Welfare regarding continuation of NAS as the US contractor. Although they recognized NAS's achievements during its 48-year management of ABCC-RERF, the officials stated that DOE had been dissatisfied with the academy's financial management of the program. The DOE representatives clarified that the research policy would continue to be decided by the RERF Scientific Council, and they emphasized that a university or a research institution would be better than NAS for the purpose of training young scientists.

Since the DOE did not intend to change its decision to publicly recruit a different management contractor, the meeting closed without concessions by either side.

Participants

DOE: Steve Galson, chief medical officer for environment, safety and health; Paul Seligman, deputy assistant secretary for health; Timothy S Fox, RERF project manager, Office of Health

US Embassy: Milton Eaton, representative, US Department of Energy; Robert S Hyams, first secretary, Environmental, Scientific and Technological Affairs, US Department of State.

RERF: Itsuzo Shigematsu, chairman; Mortimer L Mendelsohn, vice chairman; Donald R Harkness, chief of research; Yutaka Hasegawa, permanent director; department chiefs; research scientists; and representatives of the RERF Labor Union.

International collaborative activities

Editor's note: This listing does not include participation in international scientific meetings. For a list of papers delivered at national and international meetings, see p 68. Also, see the Appendix, p 166, for agreements on RERF international collaborations.

Participation in international collaborative activities by RERF staff members

Chernobyl-related collaborative activities

- **Sasakawa Memorial Health Foundation**

1. Yoshisada Shibata, chief, Department of Epidemiology and Biometrics (Nagasaki), participated in the 1994 Chernobyl workshop in Moscow and also consulted with researchers at facilities in Mogilev, Gomel, and Kiev. (Russia, Belarus, Ukraine, May 1994)

2. RERF Chairman Itsuzo Shigematsu; Yoshisada Shibata, chief, Department of Epidemiology and Biometrics, Nagasaki Laboratory; and Shizuyo Kusumi, assistant chief, Department of Clinical Studies, participated in the Chernobyl Sasakawa Medical Symposium. Shibata also provided on-site technical guidance for the Chernobyl Medical Cooperation Project. (Russia, Belarus, September 1994)

3. Yoshisada Shibata, chief, Department of Epidemiology and Biometrics (Nagasaki), provided on-site technical guidance to the Chernobyl Medical Cooperation Project. (Belarus, February 1995)

- **Hiroshima International Council for Health Care of the Radiation-exposed (HICARE)**

Kiyohiko Mabuchi, chief, Department of Epidemiology, consulted on a project about the health of the Chernobyl accident recovery workers. (Russia, June 1994)

- **Japanese Atomic Energy Research Commission**

Kiyohiko Mabuchi, chief, Department of Epidemiology, and Nori Nakamura, assistant chief, Department of Genetics, participated in a symposium on radiation effects held in Moscow. (Russia, October 1994)

- **Japanese Ministry of Foreign Affairs**

Shoichiro Fujita, chief, Statistical Analysis Laboratory, Department of Statistics, and Fumiyoshi Kasagi, research scientist, Department of Statistics, participated in the Chernobyl Nuclear Accident Project. (Belarus, Russia, Ukraine, December 1994)

- **Radiation Effects Association**

Mitoshi Akiyama, chief, Department of Radiobiology, attended a workshop on low-dose radiation risk assessment and also visited three medical institutions. (Ukraine, February 1995)

- **World Health Organization (WHO)**

Yutaka Hasegawa, permanent director, attended a meeting of the WHO Chernobyl Project in Obninsk. (Russia, March 1995)

Chelyabinsk-related cooperation

- **HICARE**

Kiyohiko Mabuchi, chief, Department of Epidemiology, participated in the joint projects to investigate the radiation exposure accidents in the southern Ural Mountains. (Russia, July 1994)

- Kiyohiko Mabuchi, chief, Department of Epidemiology; Mitoshi Akiyama, chief, Department of Radiobiology; Dale Preston, chief, Department of Statistics, and Nori Nakamura, assistant chief, Department of Genetics, attended an international symposium on the Ural nuclear accidents. (Russia, January 1995)

Other international collaborative activities

- **HICARE**

1. Itsuzo Shigematsu, RERF chairman; Kiyohiko Mabuchi, chief, Department of Epidemiology; Yukiko Shimizu, assistant chief, Department of Epidemiology, and Shoichiro Fujita, chief, Statistical Analysis Laboratory, Department of Statistics, attended an international meeting sponsored by the International Atomic Energy Agency (IAEA), where they reported on HICARE-related activities. (France, October 1994)

2. Yutaka Hasegawa, permanent director, attended a WHO-sponsored meeting of the Radiation Emergency Medical Preparedness and Assistance Network, where he reported on HICARE-related activities. (France, December 1994)

- **IAEA and WHO**

Mitoshi Akiyama, chief, Department of Radiobiology and Terumi Mizuno, research scientist, Department of Radiobiology, attended an international meeting jointly sponsored by IAEA and WHO.

- Akio Awa, associate chief of research, participated in the RADTEST workshop sponsored by the Scientific Committee on Problems of the Environment. (Belgium, March 1995)

**Acceptance of visitors from overseas for briefing and training
(total: 285 persons)**

• **Visitors related to Chernobyl accepted through HICARE (58 persons)**

1. WHO. For studying brain damage among in-utero exposed children, six psychiatrists from the Republic of Belarus, the Russian Federation, and Ukraine from 18 to 20 April, and one specialist from Obninsk, the Russian Federation, from 18 July to 26 August.

2. Sendai Municipal Hospital. Two doctors of pediatrics and obstetrics and gynecology from Minsk, the Republic of Belarus, on 16 May 1994 and 7 March 1995, respectively.

3. Sasakawa Memorial Health Cooperation Foundation. Eighteen radiation dosimetry specialists from the Russian Federation, the Republic of Belarus, and Ukraine: 10 persons on 28 July and 8 doctors and medical technologists on 15 December.

4. HICARE. Three specialists in ophthalmology, radiation epidemiology and hematology, respectively, from the Russian Federation and the Republic of Belarus from 5 to 31 October, and one specialist from Kiev, Ukraine, from 14 to 16 December. The three visited Nagasaki Laboratory on 25 October.

5. Japan Red Cross. Three trainees of the FY94 Japan Red Cross Chernobyl Nuclear Power Plant Accident Victims Relief Project from the Russian Federation, the Republic of Belarus, and Ukraine on 6 and 7 October.

6. Radiation Effects Association. Four epidemiologists from Kiev, Ukraine, on 21 November.

7. Junod Group. One doctor from Chernigov, Ukraine, on 15 December.

8. Japanese Ministry of Foreign Affairs. Eight data-processing specialists from Ukraine, the Russian Federation, and the republics of Belarus, Latvia, and Lithuania from 24 February to 3 March 1995; four leukemia specialists from Ukraine, and the republics of Latvia and Estonia on 3 March; and five dosimetry specialists from the Russian Federation, the Republic of Belarus, and Ukraine on 23 March. These 17 specialists also visited Nagasaki Laboratory on 6 March.

9. Nagasaki Association for Hibakushas' Medical Care (NASHIM). Five specialists from the Russian Federation, the Republic of Belarus, and Ukraine on 17 August visited Nagasaki Laboratory.

• **Visitors related to Chelyabinsk accepted through HICARE (1 person)**

RERF/Urals Research Center for Radiation Medicine (URCRM) collaboration agreement. One specialist from Chelyabinsk, the Russian Federation, continued training from 1 to 28 April. Training had started on 25 March of the previous fiscal year.

• **Visitors related to Semipalatinsk accepted through HICARE (4 persons)**

1. HICARE. One doctor from Alma-Ata, Kazakhstan, from 16 to 18 May, and one doctor from Semipalatinsk, Kazakhstan, from 6 to 8 July.

2. All Japan Democratic Medical Organization Federation. One oncologist from Semipalatinsk, Kazakhstan, on 5 August.

3. International Physicians for the Prevention of Nuclear War. One specialist in radiation medicine, allergy, and clinical immunology from Semipalatinsk, Kazakhstan, from 25 November to 7 December.

• **Other visitors related to HICARE (15 persons)**

1. Los Angeles Medical Association. One specialist from the Los Angeles Medical Association on 7 March, and another from 16 to 17 March 1995.

2. Japan International Cooperation Agency (JICA). Twelve trainees from the 1994 course on health administration for central Asian and Caucasus countries from Azerbaijan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan on 17 November.

3. Brazil. One doctor from the Leide das Neves Ferreira Foundation, São Paulo, Brazil, on 25 November.

• **Visitors related to JICA (52 persons)**

1. Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association. Ten trainees enrolled in a training course for leaders of anti-tuberculosis measures from Bangladesh, Brazil, Cambodia, People's Republic of China, Egypt, Republic of Honduras, Indonesia, Nepal, Senegal, and Thailand on 30 May.

2. National Pediatrics Hospital. Five trainees from Republic of Ghana, Republic of Guyana, Nepal, Thailand, and United Arab Emirates enrolled in the 1994 pediatrics and pediatric surgery course on 2 June.

3. Japan Analysis Center. Five trainees from the Republic of Korea, Mongolia, Pakistan, Thailand, and Indonesia enrolled in an environmental radioactivity analysis course on 7 October.

4. National Cancer Center. Eleven trainees from Bangladesh, Brazil, Bulgaria, People's Republic of China, Jordan, Peru, Thailand, Turkey, Uruguay, Zambia, and Argentina enrolled in the 1994 clinical oncology II course on 27 October.

5. JICA Osaka International Training Center. Seven trainees from Bangladesh, Thailand, Egypt, Zambia, Argentina, Brazil, and Peru enrolled in the 1994 cardiovascular disease control course on 10 November.

6. Osaka University Medical School. Eight trainees from Latin America, Africa, and Southeast Asia enrolled in an advanced medical radiological technology course on 10 March 1995.

7. JICA Okinawa International Training Center. Six trainees from Bolivia, People's Republic of China, Peru, Philippines, and Thailand enrolled in a public hygiene and environmental contamination analysis course on 10 November.

• **Other visitors (161 persons)**

A total of 161 other visitors came to RERF for briefings. Only a few are listed below.

1. Laboratory of Industrial Hygiene, Ministry of Public Health, People's Republic of China. Two specialists on 21 June.

2. Society of Nuclear Medicine, Taiwan. One specialist from Taipei on 27 and 28 June.

3. Hiroshima International Culture Foundation. Four reporters from Cambodia, Singapore, and Taiwan who were part of a project to invite newspaper reporters from Asia on 29 July.

4. IPPNW. Nineteen IPPNW medical students from the Republic of Korea on 13 January 1995.

Visitors to RERF

Beginning in April 1994 through March 1995, a total of 1,000 trainees, medical-related persons, and visitors from abroad who were accepted through international exchange organizations, as well as government officials, medical-related persons, students, and members of citizen's groups from inside Japan visited RERF. For groups of trainees from abroad, see the section on the acceptance of visitors from overseas beginning on p 105. Also see the Appendix, p 166, for agreements related to international collaborations.

Following is a selective list of visitors to RERF, excluding attendees of RERF's Board of Directors and Scientific Council meeting, and scheduled lecturers.

National Academy of Sciences President Visits Hiroshima Laboratory

On 11 November, US National Academy of Sciences (NAS) President Bruce M Alberts visited the RERF Hiroshima Laboratory during a 2-day stay in the city.

Alberts met individually with research department chiefs in the morning to gain perspective on the day-to-day work ongoing at the laboratories in Hiroshima and Nagasaki. Later in the day to a



From left, RERF Permanent Director Donald Harkness, NAS President Bruce M Alberts, and RERF Chairman Itsuzo Shigematsu.

packed auditorium, he described years of research and the efforts of numerous collaborators who helped unravel the complexities and flexibilities of DNA transcription and replication.

On the previous day, Alberts had visited Hiroshima Peace Memorial Museum, and he reciprocated Hiroshima Mayor Takashi Hiraoka's visit to NAS headquarters in Washington, DC, earlier in the year. Alberts presented to the mayor a certificate of gratitude and a medallion from NAS for the decades of cooperation extended to the ABCC-RERF research program by the citizens of Hiroshima.

On 26 January 1995, on behalf of Alberts, who had been unable to visit Nagasaki in November, John Zimbrick, director of the NAS Board on Radiation Effects Research, presented to Nagasaki Mayor Hitoshi Motojima the same tokens of appreciation.

Both mayors expressed favorable views of RERF's body of work.

April 1994

Hiroshima Laboratory

Alan E Waltar, vice president, American Nuclear Society, La Grange Park, Illinois
Takashi Mukaibo, president, and **Masataka Izawa**, chief of secretaries, Japan Atomic Industrial Forum, Inc, Tokyo

Toyozo Terashima, member, Atomic Energy Safety Commission; **Kaoru Naito**, chief, Nuclear Safety Inspection Office, Nuclear Safety Bureau, Science and Technology Agency, Tokyo

Eizo Tajima, chairman, Nuclear Safety Research Association, Tokyo

Yuji Kaneki, chief, Planning and Information Department, Japan Atomic Industrial Forum, Inc, Tokyo

Nagasaki Laboratory

Steven Okazaki, film director, Farallon Films, San Francisco, CA

May 1994

Hiroshima Laboratory

Sadao Araya, councilor, Power Reactor and Nuclear Fuel Development Corporation, and director, Ningyo Toge Works, Okayama

Yoshio Kobayashi, vice director, Osaka Red Cross Blood Center

Robert G Rapson, consul, American Consulate General, Osaka-Kobe, Osaka

Donald Smith, reporter, *National Geographic*, Washington, DC

June 1994

Hiroshima Laboratory

Anna Karaoglou, scientific officer, Directorate-general XII—Science, Research and Development, Radiation Protection Research Action, Commission of the European Communities, Brussels, Belgium

Anup Dewanji, associate professor, Indian Statistical Institute, Calcutta, India

Tsuneyuki Murakami, chief of secretariat, and **Kazumi Makino**, director, Hiroshima Liaison Council of A-bomb Victims Exposed to Black Rain Under Care at Home, Hiroshima; **Yoshinobu Masuda**, secretary general, Association for a Tokyo Non-Nuclear Government

Kedao Wei, director, and **Ren Tianshan**, division director, Laboratory of Industrial Hygiene, Ministry of Public Health, Beijing, People's Republic of China

Weilian Chen, vice chairman, Society of Nuclear Medicine, Taipei, Taiwan

Eric B Larson, medical director, University of Washington, Medical Center, Seattle, WA; **James Bowen**, neurologist, Pacific Medical Center, Seattle, WA

Nagasaki Laboratory

Katsumi Sakurai, chief, A-bomb Survivors Relief Unit, Special Disease Control Section, Medical Welfare Department, Tokyo Metropolitan Health Bureau

Robert S Hyams, first secretary, Environmental, Scientific and Technological Affairs, US Department of State, US Embassy, Tokyo

Hitoshi Motojima, Nagasaki City mayor

Shiro Yukawa, Nagasaki City deputy mayor

July 1994

Hiroshima Laboratory

Akira Yoshimura, director, Hiroshima Prefectural Chapter, Japan Red Cross Society

Ryuji Ogiwara, director general, Chugoku-Shikoku Regional Medical Affairs Office, Ministry of Health and Welfare, Hiroshima

Koichi Onishi, vice director, Ningyo Toge Works, Power Reactor and Nuclear Fuel Development Corporation, Okayama

Noikaseumsy Sithivong, technical staff, Bacteriology Unit, National Institute of Hygiene and Epidemiology, Vientiane, People's Democratic Republic of Laos;

Tomoko Owan, graduate student, Department of Bacteriology, Faculty of Medicine, and **Yasuo Iifuchi**, professor, School of Health Sciences, Faculty of Medicine, University of the Ryukyus, Okinawa

Group from "Asian Reporters Invitation Project" invited by Hiroshima International Cultural Foundation Inc.

August 1994

Hiroshima Laboratory

Tokushi Shibata, professor, and **Mineo Imamura**, assistant professor, Nuclear Research Institute, Tokyo University; **Takashi Nakanishi**, assistant professor, Kanazawa University School of Science, Ishikawa; **Kazuo Iwatani**, assistant professor, Hiroshima University Faculty of Engineering

Kenji Taguchi, member of the House of Representatives, Nagasaki

Eikichi Inukai, advisor, Nagoya Institute of Technology, Cooperation Research Center, Aichi; **Yoshihiro Murooka**, professor, National Defense Academy, Kanagawa

Noriaki Shigeno, executive manager, Wakunaga Pharmaceutical Co, Ltd, Tokyo, and **Toru Fuwa**, senior managing director and chief, Hiroshima Branch

Takesaburo Mori, lecturer, Yokohama City University School of Medicine and Teikyo University School of Medicine, Kanagawa

Group of 6 representatives from the General Council of Volgograd Labor Unions, Russian Federation

September 1994

Hiroshima Laboratory

Isaburo Fujimoto, former chief, Epidemiology and Investigation, Center for Adult Diseases, Nara

Michael Campbell, assistant dean for relations, College of Agricultural and Environmental Sciences, University of California, Davis, CA

Group of 48 attendees of the 3rd general meeting of the National Council of Local Cancer Registries

Nagasaki Laboratory

Mitsuo Oshimura, professor, Molecular & Cell Genetics, School of Life Sciences, Faculty of Medicine, Tottori University

Y Yoshida, professor, Chromosome Research Unit, Faculty of Science, Hokkaido University

October 1994

Hiroshima Laboratory

Tsukasa Namekata, director of research, Nikkei Disease Prevention Center, Seattle, WA

Jorma Aaltonen, professor, Department of Radiation Science, University of Helsinki, Finland

November 1994

Hiroshima Laboratory

Kazuhiko Sekine, staff member in charge of nuclear fuel facility planning, Power Reactor and Nuclear Fuel Development Corporation, Tokyo

Mitsuo Tomozawa, president, Committee of A-Bomb Survivors in the USA, San Francisco, CA, and **Kanji Kuramoto**, honorary president, Alameda, CA

Fumihiko Munakata, director, Building Maintenance Education Center, Tokyo; former RERF permanent director

Ian Maddocks, professor, Flanders University, Adelaide, Australia

Bruce M Alberts, president, and **Mildred S Dresselhaus**, treasurer, US National Academy of Sciences (NAS). **E William Colglazier**, executive officer, NAS-National Research Council, and executive director, Office of International Affairs, NAS, Washington, DC

John MacKinney, environmental scientist, Radiation Studies Division, and **H Ben Hull**, geologist, Office of Radiation Programs, US Environmental Protection Agency, Washington, DC

Keichu Teranishi, president, American Society of Hiroshima-Nagasaki A-bomb Survivors, Los Angeles, CA

Nagasaki Laboratory

Teruo Omae, president, National Cardiovascular Center, Osaka

JW Thiessen, former RERF vice chairman, Somers, MT

Ma Xiuping, assistant professor, Department of Internal Medicine, Xian Medical University, People's Republic of China

December 1994

Hiroshima Laboratory

Olga A Tsvetkova, consultant, US Department of Energy, Kiev, Ukraine

Warren H Soiffer, consul, and **Yasuo Satake**, public affairs program specialist, American Consulate General, Osaka-Kobe, Osaka

Shigeru Kumazawa, principal scientist, and **Hideaki Yamamoto**, research scientist, Department of Health Physics, Tokai Research Institute, Japan Atomic Energy Research Institute, Ibaragi

Nagasaki Laboratory

Eric Lord, Bauhaus (environment protection group), Dessau, Federal Republic of Germany

January 1995

Hiroshima Laboratory

Bob Minzesheimer, politics editor, *USA Today*, Arlington, VA

Seven-member broadcast crew from British Broadcasting Corporation for a TV series on genetics, London, United Kingdom

John D Zimbrick, director, Board on Radiation Effects Research, US National Academy of Sciences, Washington, DC

David Williams, RERF supervisor, senior financial advisor, National Academy of Sciences, Washington, DC

Harry Pettengill, director, Office of International Health Studies, US Department of Energy, Washington, DC

Edward Podolak, special assistant, Office of International Health Studies, US Department of Energy, Washington, DC

Timothy S Fox, RERF project manager, Office of Health, US Department of Energy, Washington, DC

Robert S Hyams, first secretary, Environmental, Scientific and Technological Affairs, US Department of State, US Embassy, Tokyo

Nagasaki Laboratory

Takemi Yanamoto, professor, Regional Statistics Research, Institute of Statistical Mathematics, Tokyo

John D Zimbrick, director, Board on Radiation Effects Research, US National Academy of Sciences, Washington, DC

David Williams, RERF supervisor, senior financial advisor, National Academy of Sciences, Washington, DC

February 1995

Hiroshima Laboratory

Yoshiyuki Matsumoto, director general, General Department of Health and Environment, Iwate Prefecural Office

Kiyoshi Kamekawa, permanent director, Nationwide Environmental Hygiene Business Guidance Center, Tokyo

Group of 4 persons from Japan Telecommunications Workers Union (JTWU) Hiroshima and Nagasaki Council of Second Generation of A-Bomb Survivors, Hiroshima and Nagasaki

March 1995

Hiroshima Laboratory

Eddy Baertsoen, TV director, Science Department, Belgischer Radio en Televisie-Nederland uitzendingen (Belgian Broadcasting Company-Dutch-language Programs), Brussel, Belgium

Keiki Ogino, professor, Department of Public Health, School of Medicine, Kanazawa University, Ishikawa

Hidenobu Aoki, director general, Hiroshima Environment and Health Association

Nagasaki Laboratory

Yuriko Funakoshi, US consular attaché in charge of science and technology, Fukuoka

Commendations

Chairman Shigematsu receives Timofeev Medal

On 23 August 1994, Chairman Itsuzo Shigematsu was awarded the Timofeev Medal by the Scientific Council of the Medical Radiological Research Center, the Russian Academy of Medical Sciences, for his distinguished service in the fields of radiology and radiological epidemiology. Shigematsu is the first Japanese scientist to receive this medal.

The Timofeev Medal was instituted in commemoration of the 90th anniversary of the birth of N V Timofeev-Resovsky (1900-1981), a Russian radiobiologist, for the purpose of rewarding scientists who have made outstanding contributions in the fields of radiation effects research, evolution theory, and environmental protection. Timofeev-Resovsky is known for his neo-Darwinism and target theory.

Shigematsu chaired the International Atomic Energy Agency's post-Chernobyl environmental and public health assessment project from 1990-1991 and continues to forge cooperative research projects between RERF and researchers in the former Soviet Union who have been conducting long-term follow-up studies in radiation-contaminated areas.

Vice Chairman Mendelsohn receives imperial award

On 3 November 1994, RERF Vice Chairman Mortimer L Mendelsohn received the Third Order of the Sacred Treasure, the highest imperial award bestowed upon those who are not citizens of Japan.

Mendelsohn graduated from the Harvard University School of Medicine in 1948. After serving as a radiology professor at the University of Pennsylvania, he spent 20 years at Lawrence Livermore National Laboratory, where he engaged in studies to develop a method of quantitating radiation injuries and concurrently served as associate director for biomedical and environmental research. Mendelsohn had served

as cochairman of the RERF Scientific Council for 11 years before becoming one of RERF's six permanent directors in June 1992 and RERF vice chairman in July 1993.

In memoriam: George B Darling

George B Darling, director of the Atomic Bomb Casualty Commission from 1957 to 1972, died at his home in Hamden, Connecticut, on 30 March 1995 at the age of 89.

Darling's appointment by the US National Academy of Sciences (NAS) in 1957 came at a turning point in the work of ABCC, and his administrative leadership was responsible for the implementation of the recommendations of the Francis Committee that converted individual research projects into a structured population study. His efforts to make ABCC's work truly binational were untiring and included the following:

- Establishment based on formal agreement of the Japanese Advisory Committee and the *kyogikai* (consultative bodies) for the three major ABCC studies composed of Japanese and American experts.
- Initiation of publication of all ABCC research reports in bilingual format, and establishment of an ABCC Section in the *Journal of the Hiroshima Medical Association* to promote communication with the local medical community.
- The signing of formal agreements by ABCC and the Japanese National Institute of Health establishing joint "platform protocols" that clearly defined binational research programs.

Darling worked continuously to create a stable relationship with Japanese scientists and conveyed a better understanding of ABCC's scientific merit to the decision makers and citizens in Hiroshima and Nagasaki and throughout Japan.

Darling graduated from the Massachusetts Institute of Technology and received his doctorate degree in public health from the University of Michigan. He was president of the Kellogg Foundation and director of Medical Affairs at Yale University before becoming the ABCC director. He received the Japanese Medical Association's Supreme Award of the Golden Orchid in 1967, and 1970 a citation and medal from the US Atomic Energy Commission, predecessor of the US Department of Energy.



Darling in 1965.

Ministry of Health and Welfare—entrusted database development

RERF has been developing an A-bomb-related materials database system under a contract with the Japanese Ministry of Health and Welfare (MHW) since Fiscal Year 1991. The work actually is being carried out under the direction and coordination of the Committee on A-bomb Materials and Information Network, which is chaired by Professor Emeritus Yasuo Yoshizawa, Tokyo University. At the Hiroshima Laboratory, office space is being provided for a 3-person staff.

In FY94, the committee conducted the following work:

1. Preparing a list of locations of documents relating to measures for the care of A-bomb survivors

The listing of relevant documents possessed by major organizations and institutions in Hiroshima and Nagasaki is well in progress. Work continues and lists of relevant documents located in areas other than Hiroshima and Nagasaki also are being compiled.

2. Creating an optical-disk filing system for data from MHW surveys on the actual conditions of A-bomb survivors

The MHW surveyed the actual conditions of A-bomb survivors three times: in Fiscal Years 1965, 1975, and 1985. Coded data already are recorded in a database but the survey forms, which include handwritten opinions, are being scanned and stored on optical disk. These opinions may be of great value and can be digitally stored in this way.

3. Preparing explanatory notes on major A-bomb-related terms and developing a computerized display system

The committee is preparing succinct explanations for laypersons, including school children, who might not be familiar with A-bomb-related matters (eg, the *Enola Gay*).

The explanatory notes will be supplemented by pictures, films, sounds, etc, as deemed appropriate, to make them more appealing to the audience. For example, a video with sound, showing the *Enola Gay* flying, will be displayed on the PC monitor together with a short explanation.

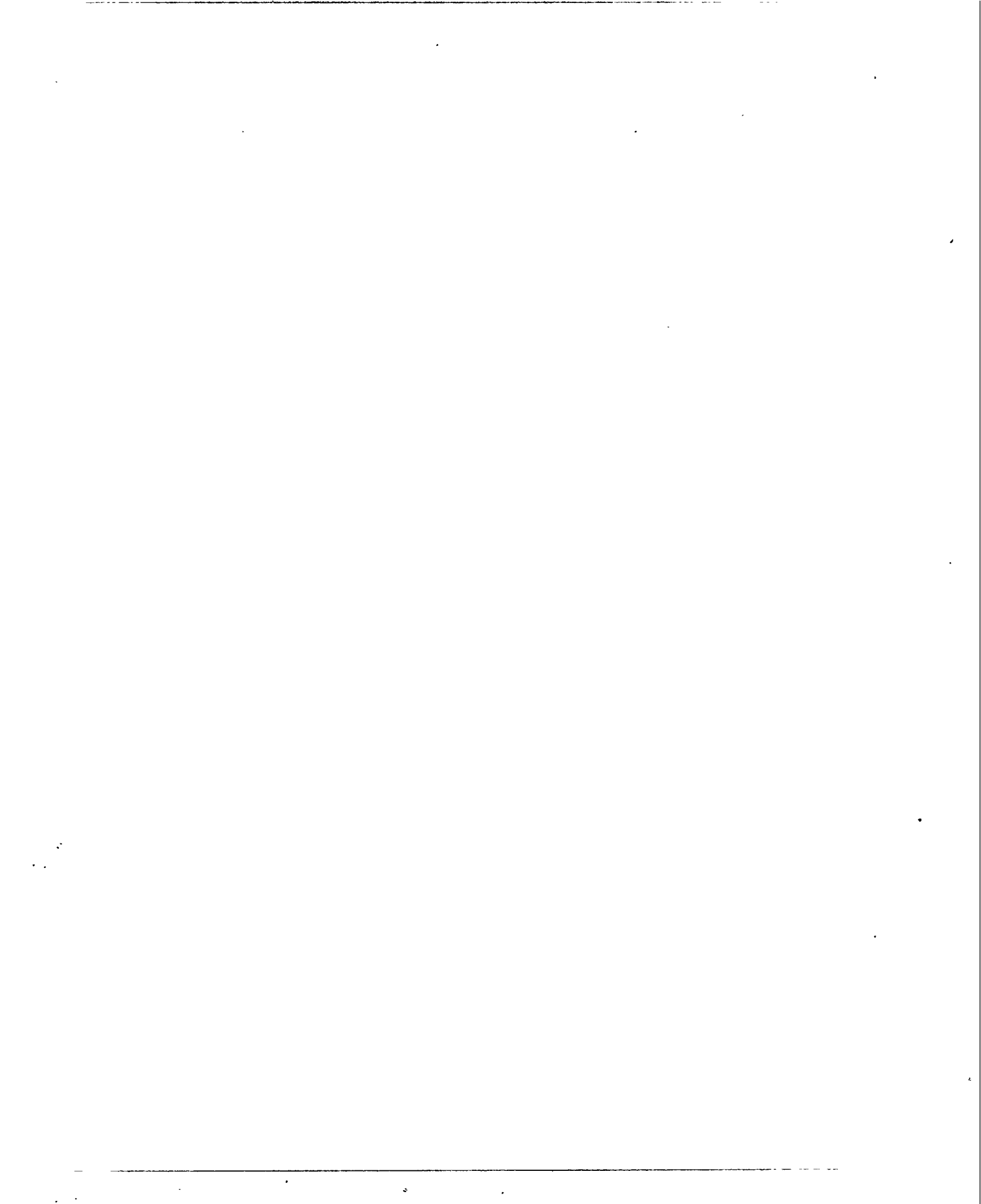
In FY94, the committee developed a pilot multimedia display system for several items.

4. Investigations of overseas organizations that might possess A-bomb-related materials

A survey team dispatched by the committee visited the Veterans Benefits Administration and the Defense Nuclear Agency in Washington, DC, and obtained information and materials concerning the compensation that veterans stationed in the Hiroshima and Nagasaki areas immediately after the atomic bombings and POWs who were then in these areas are eligible to receive because they have contracted diseases considered to be related to A-bomb radiation exposure.

The team also visited the Holocaust Memorial Museum in Washington, DC, to see its displays and the multimedia database system being used.

Appendix



28th Board of Directors Meeting

22-24 June 1994

*Auditorium, Radiation Effects Research Foundation
Hiroshima*

Agenda

I. Minutes of the 27th meeting of the Board of Directors

II. Items for information

1. Present personnel status
2. Fiscal Year 1993 (FY93) salary revision
3. Labor Union's Fiscal Year 1994 (FY94) demands for improvement of working conditions, etc.
4. Others
 - (1) Dosimetry reassessment
 - (2) International collaboration
 - (3) Development of an A-bomb-related materials database system
 - (4) Request to United Nations for support (resolution of the 27th board meeting)
 - (5) US-Japan negotiations

III. Items for deliberation and action

1. Recommendations of the 21st meeting of the Scientific Council
2. FY93 research activities report and audit report
3. FY94 research plans
4. FY93 settlement of accounts and audit report
5. FY94 working budget
6. Fiscal Year 1995 (FY95) budget request
7. Revision of rules and regulations
8. Election/appointment of directors and others
9. Schedule of next board meeting

Participants

Full-time officers

Itsuzo Shigematsu, chairman

Mortimer L Mendelsohn, vice chairman

Seymour Abrahamson, permanent director and chief of research

Donald R Harkness, permanent director
Yutaka Hasegawa, permanent director
Tomoyuki Kono, permanent director and chief of Secretariat

Visiting directors

Toshiyuki Kumatori, chairman, Radiation Effects Association
Kazuaki Arichi, director, Japan Institute of International Affairs
Warren K Sinclair, former president, US National Council on Radiation Protection and Measurements
Joseph E Rall, deputy director for intramural research, US National Institutes of Health
Seymour Jablon, expert, Radiation Epidemiology Branch, Division of Cancer Etiology, US National Cancer Institute

Supervisors

Akira Shishido, former director, Japanese National Institute of Health
David Williams, senior financial advisor, US National Academy of Sciences (NAS)

Co-chairman of the RERF Scientific Council

Ei Matsunaga, professor emeritus, Japanese National Institute of Genetics

Observers

Fumio Sakamoto, assistant director, Planning Division, Japanese Health Service Bureau, Japanese Ministry of Health and Welfare (MHW)
Ken Miyashita, Planning Division, Health Service Bureau, MHW
Shigeru Ise, regional coordinator, North American Affairs Bureau, Japanese Ministry of Foreign Affairs
John D Zimbrick, director, Board on Radiation Effects Research, Commission on Life Sciences, National Research Council, NAS
Charles W Edington, director, Radiation Effects Research Program, Commission on Life Sciences, National Research Council, NAS
Catherine Slover Berkley, administrative associate, Commission on Life Sciences, National Research Council, NAS
Robert S Hyams, first secretary, Environment, Science and Technological Affairs Office, US Embassy, Tokyo

Operating Committee Members of RERF

Akio Awa, associate chief of research
Richard D Sperry, business administrator
Yasukiyo Hirano, operations administrator
Tadashi Nakaoka, chief of administration, Secretariat, Nagasaki Laboratory

Minutes of the meeting

The 28th meeting of the Board of Directors of the Radiation Effects Research Foundation was held 22-24 June 1994 in the auditorium of RERF's Hiroshima Laboratory. The meeting originally had been scheduled for Woods Hole, Massachusetts, but was changed due to various circumstances.

All members of the board except for Dr Saburi were present. This satisfied the quorum required under the Act of Endowment and formally constituted the board meeting. Dr Shishido and Mr Williams, the RERF supervisors, and Dr Matsunaga, co-chairman of the RERF Scientific Council also were present. The observers in attendance included representatives from the Japanese Ministry of Health and Welfare, the Japanese Ministry of Foreign Affairs, the US Embassy, and the US National Academy of Sciences.

Dr Shigematsu, chairman of RERF, presided over the meeting, as provided in the Act of Endowment. He, with the consent of the board members, appointed Dr Harkness and Dr Hasegawa as signatories to the minutes of this meeting.

I. Minutes of the 27th meeting of the Board of Directors (presented by Itsuzo Shigematsu)

The minutes were approved without any objection after the need for correction of a few words was pointed out.

II. Items for information

1. Present personnel status (presented by Tomoyuki Kono)

The personnel strength as of 1 April 1994 was 6 directors, 57 research scientists, and 349 general employees, totaling 412. There are 234 general employees in administrative positions, but of these 168 are engaged in research-support activities such as record keeping, tumor registries, and computing. The remaining 66 are in the Secretariat. In addition, 91 are in medical technical positions, and 24 in manual and general technical positions.

The personnel strength of 588 at the time of RERF's establishment has decreased to the present 412. The number of research scientists has increased by 17, whereas that of general employees has decreased by 195, necessitating further efficiency of operation and rationalization of the organization.

Several years from now, many employees hired in the days of the Atomic Bomb Casualty Commission will reach the mandatory retirement age. The number of mandatory retirements due in FY94 and FY95 are 18 and 31, respectively, and a total of 105 are due for retirement within the next 5 years. Among them, 65 are in the positions of assistant section chiefs or above.

2. FY93 salary revision (presented by Tomoyuki Kono)

The pay scales were revised by using as a guide the revision of the pay scales applicable to national government employees. The base pay for professional

employees (average age being 43.0 years) and that for general employees (43.1 years) was increased by 1.80% and 1.86% on average, respectively, whereas the increase for national government employees (average age 39.6 years) was 1.92%. Dependents allowance and housing allowance were increased, but seasonal allowance was decreased by an amount equal to 0.15 month of base pay annually.

The rate of the revision was the second lowest since the establishment of RERF. The salaries of the directors and senior consulting scientists were improved, taking into consideration the balance between their salaries and the salaries of the staff.

3. Labor union's FY94 demands for improvement of working conditions, etc. (presented by Tomoyuki Kono)

The RERF Labor Union is 244 members strong, which accounts for 59% of the entire staff. Excluding 168 persons who are not eligible for union membership such as directors, research scientists, and managerial staff, the enrollment rate is 93%.

The union is affiliated with the All Japan Prefectural and Municipal Workers' Union (membership: 1,100,000 workers). The RERF Countermeasures Committee established in the Hiroshima Prefectural Headquarters of the nationwide union is supporting the activities of the RERF Labor Union.

Most of the demands are for improving the working conditions. The union demanded this year also that the system of equal funding be changed and that RERF be developed as an international organization. Specifically, it demanded early relocation of Hiroshima facilities and development of the Foundation into an organization in which research, therapy, and health management are integrated, strengthening of clinical activities, and establishment of an international relief center for radiation-exposed persons, which would be operated with the initiative of the Japanese.

4. Others

(1) Dosimetry reassessment (presented by Warren K Sinclair)

The US Dosimetry Committee decided at its meeting held in May 1994 that it had to address the problem of thermal neutron activation to resolve the discrepancy between calculated Dosimetry System 1986 (DS86) and measured neutron doses in Hiroshima. The committee made five recommendations, of which two are particularly important to RERF. One concerns the attempt to measure fast neutrons directly. Copper cables at defined distances from the hypocenter in Hiroshima will be measured in terms of the amount of nickel-63 that might have been generated by a fast neutron reaction. The second recommendation concerns presentation of analyses of risk estimates. It is recommended that data be analyzed separately

for Hiroshima and Nagasaki as well as together, the assumption being that the total dose equivalent in Hiroshima was underestimated and, therefore, the risks were overestimated.

From RERF, Shoichiro Fujita, chief of the Statistical Analysis Laboratory, and Donald Pierce, senior scientist, reported on the activities of the Japanese Dosimetry Committee and RERF with respect to the recommendations of the US Dosimetry Committee.

According to Dr Fujita, the Japanese Dosimetry Committee feels that it is difficult to locate copper samples after so many years. However, with luck, it might be possible to retrieve the lightning rod of the former building of the Hiroshima Branch of the Bank of Japan. Also the committee is unable to see much scientific basis for analyzing the data for Hiroshima and Nagasaki separately. As for the accuracy of DS86, while measurement of doses is important, the committee feels that the scientific adequacy of DS86 should be examined once again.

Dr Pierce commented on the recommendation that the Hiroshima and Nagasaki data be analyzed separately in *Life Span Study Report 12* (LSS), which is now being compiled. He mentioned four inter-related issues as follows: 1) How would it fit in the most critical needs arising in the report? 2) What are the likely consequences of a revision and would results from the Nagasaki data alone have useful bearing on this? 3) Is it inappropriate at this time to undermine confidence in the general results from the LSS? 4) Might it be appropriate to give in this report some tentative indications of the likely consequences of a revision?

On grounds relating primarily to 1) and 2) above, Dr Pierce felt that it would be wrong to focus on separate analyses by city, mainly because of the need to describe risk in terms of the important effects of sex, age at exposure, and time since exposure, which cannot be done in separate analyses by city. However, he said that he planned to discuss city differences and give factors by which the main results could be adjusted to either city.

(2) *International collaboration (presented by Itsuzo Shigematsu)*

Last year 372 official visitors came to RERF to see the facilities and to receive briefing or training. RERF has been cooperating similarly with other foreign institutions to the extent that it does not interfere with RERF's primary activities. Due to further budget cutbacks likely in the future, the question is how to respond to the increasing requests for briefings and training.

(3) *Development of an A-bomb related materials database system (presented by Yutaka Hasegawa)*

Since Fiscal Year 1991, RERF has been developing an A-bomb-related materials database system under a contract with the MHW. The purpose of

the database is to make available information on the whereabouts of A-bomb-related materials in Japan and abroad. Committee representatives visited the National Diet Library, the Diplomatic Materials Museum of the Ministry of Foreign Affairs, and some other places in Japan, and available materials were reviewed. Visits also were made to the Public Record Office in the United Kingdom, the Roosevelt Library in the US, and several other institutions abroad to examine the archived materials. The conceptual design work for the database system will begin during FY94.

(4) Request to the United Nations for support (presented by Itsuzo Shigematsu)

Considering the increasing number of physicians and scientists who come to RERF for advice, a resolution was passed last year at the Board meeting that the United Nations be requested to establish and support at RERF the United Nations International Radiation Health Effects Advisory Center. To this request, RERF has received favorable responses from N P Napalkov, assistant director-general of the World Health Organization, Burton G Bennett, secretary, United Nations Scientific Committee on the Effects of Atomic Radiation, and some others.

(5) US-Japan Negotiations (presented by Itsuzo Shigematsu)

Dr Shigematsu expressed his appreciation to the US directors and other interested persons for their help in resolving the recent budget problems and reported on the development of affairs as follows:

The RERF Board of Directors discussed at its meeting held in June 1993 plans for relocation and construction of the Hiroshima Laboratory. Subsequently in August, the US Department of Energy (DOE) informed the Japanese Ministry of Health and Welfare (MHW) that the DOE was unable to share the costs of relocation because of the Clinton Administration's stringent budget reduction plan. Furthermore, the DOE requested a drastic reduction of the yearly operating costs and development of a 5-year plan by 31 October 1993.

RERF, upon consultation with MHW, developed a 5-year plan and forwarded it to DOE, which was not satisfied and said, in February 1994, that it could not provide more than \$18 million each for FY94 and FY95. Since RERF could not be expected to manage with \$18 million from the US, in May 1994 negotiations were conducted between MHW and DOE, at which time, the DOE's Deputy Assistant Secretary for Health Harry J Pettengill promised to make maximum efforts to provide an additional \$2 million.

Since the 5-year RERF plan included too many uncertainties, MHW asked RERF to prepare a 2-year plan, which was discussed at the binational meeting held on 16 June 1994. DOE accepted the outline of the 2-year plan.

According to this plan, a net reduction of 34 employees is expected in FY94 and 28 in FY95, a total of 62 in 2 years.

It is conceivable that the US will ask Japan to bear the full cost of A-bomb survivors medical examinations and anti-cancer projects, such as the Adult Health Study and tumor registry, which could be considered the responsibility of Japan. However, these are basic programs of great importance to RERF and also, from the quality-control viewpoint, transfer of these programs to other institutions would require careful study.

III. Items for deliberation and action

1. Recommendations of the 21st meeting of the Scientific Council (presented by Ei Matsunaga)

The meeting of the Scientific Council, usually held in March, was held in June this year. Given the short time available, the final version of the recommendations could not be completed in time for the board meeting. Dr Matsunaga commented on the recommendations as follows with the understanding that they were not final and some changes in the details might be made later:

RERF focuses on three critical research areas: 1) the assessment of health events over the lifetime of exposed persons, 2) the assessment of genetic effects in particular, and 3) the elucidation of mechanisms by which radiation effects occur with subsequent development of biologic measures of radiation dose. Those three phases of work, taken as a whole, are of unique value for the world in providing a basis for international standards of radiation safety.

Dr Matsunaga also commented that persons exposed at young ages, when radiation sensitivity may be highest, are approaching the cancer-prone ages. These individuals should be followed up until they reach, at least, the age of 70, which is until about the year 2015, or beyond if long-term F_1 follow-up becomes advisable.

Specifically, in the areas of epidemiology and statistics, the following should be continued and promoted: analysis of risk patterns (particularly of the young ATB cohort) by using incidence combined with mortality information made available by the high-quality cancer registry systems, lifetime risk analysis of in-utero A-bomb survivors, analysis of site-specific cancer risks, and analysis using family pedigree data.

In the field of radiobiology, the studies on somatic mutation using T-cell receptors and glycoprotein A are first-class studies, useful in developing methods of biological dosimetry. These studies can probably be done nowhere else in the world.

In genetics, steady progress is being made in establishing the family-based DNA repository. Exploratory studies with further refinement and testing using

stored family specimens should be continued. Fluorescence in situ hybridization is an excellent procedure for identifying chromosome aberrations and may become a worldwide benchmark for dosimetry.

In the Adult Health Study (AHS), the declining participation rate due to the advanced age of the A-bomb survivors is a matter of concern. Prompt implementation of combined approaches, such as follow-up by means of telephone or mail questionnaire, home visits in selected cases, and reviews of insurance claims for health-care services is recommended.

As for international collaborative studies, RERF, as an international, scientific resource, has an important role to play in the areas of dosimetry and risk estimates. The collaborative projects with Chelyabinsk for studying the long-term effects of low-dose irradiation are important scientifically, providing the data that might complement the data from Hiroshima and Nagasaki.

Dr Rall had some questions regarding the wisdom of giving strong support to the genetic studies. Dr Matsunaga replied that the genetic studies conducted at RERF could not be done elsewhere and that they were important because they provide data for developing international criteria for risk estimates. Mr Jablon supported the studies and expressed the view that, with progress in technology, new and more-sensitive measurement techniques might become available.

With the above, the recommendations of the Scientific Council were approved.

2. FY93 research activities report and audit report (presented by Seymour Abrahamson)

Dr Abrahamson briefly reported, referring participants to the supporting materials prepared for the board meeting.

In FY93, nine new research protocols were approved, such as the cytogenetic study on the AHS cohort using the FISH assay, an incidence study of breast cancer among A-bomb survivors, and a molecular biological study of skin cancer among A-bomb survivors. Research protocols that are inactive would be terminated. Some of the major achievements were as follows: molecular biological analysis of somatic mutation and DNA analysis of genes using spot tests that score thousands of segments of gels simultaneously in the 2-D gel system and the correlation of dose estimates based on the mutation frequencies in the somatic cells of the survivors with dose estimates based on electron spin resonance of the dentin and enamel from the teeth of A-bomb survivors.

Dr Hasegawa pointed out that some descriptions of the honors and awards of the research scientists in the prepared materials did not correctly reflect the actual situation. It was agreed to exercise greater care in the future to assure accuracy.

After Supervisor Shishido deemed the contents of the scientific activities report for FY93 to be true and correct, the activities report presented by Dr Abrahamson was approved.

3. FY94 research plans (presented by Seymour Abrahamson)

Considering the present financial conditions, prioritizing of the research plans for FY94 was discussed, and the order of priority was approved as follows: 1) epidemiological studies including tumor and tissue registry, 2) clinical studies and other promising basic studies, and 3) programs and activities to be dispensed with or curtailed, such as discontinuing research programs at the Department of Radiobiology in Nagasaki (at the end of March 1996) and reducing the frequency of publication of the Japanese-language *RERF Newsletter* and the English-language *RERF Update*.

As some of the major activities expected to be completed during FY94, preparation of *LSS Report 12* and transition from ACOS mainframe computer to workstations and personal computers were cited.

4. FY93 settlement of accounts and audit report (presented by Tomoyuki Kono)

Reports on the regular account and the special accounts for FY93 were presented.

The total income given in the regular account was ¥4,568,015,329, which included the binational subsidy income of ¥4,508,859,000, operational income of ¥58,576,982, and ¥579,347 transferred from the special account of the Hijiyama Hall Dining Room. The total expenditure was ¥4,487,141,582, which included ¥3,635,153,253 for personnel expenses and ¥851,988,329 for operating expenses. The difference of ¥80,873,747 between the total income and expenditure is to be returned to the treasury of Japan (¥77,287,373) and the US (¥3,586,374).

At the beginning, a deficit of ¥60,000,000 in the budget for personnel costs had been estimated, but the gap was closed by restricting employment of replacements to the minimum level, holding down the rate of the general salary increase, adjusting downward the rate of seasonal allowances, and as a result of payment of less termination allowance than expected.

A special account for non-allowable expenses was newly established. This special account will cover expenditures for summer and year-end gifts and alcoholic beverages, which are not allowed by the accounting criteria of the US government. Interest earned on bank deposits is used to fund this account.

Mr Williams pointed out that the unfunded termination liability was about ¥3,200,000,000 on an accrual basis and reported that the A-133 audit (audit by the US Office of Management and Budget) and the DOE closeout audit had been completed satisfactorily.

With the above, the settlement of accounts report for FY93 was approved.

5. FY94 working budget (presented by Tomoyuki Kono)

The FY94 working budget was developed within a total budget of the order of ¥4.3 billion, which had been approved as the budget for this fiscal year as a result of the US-Japan negotiations. It is based on reducing the number of permanent directors by one each from the US and Japanese sides, reducing the staff by 34 slots by the end of FY94, abolishing the positions of business administrator and operations administrator of the Secretariat, reducing the number of sections in the Secretariat from six to four, and reducing the rate of the general salary increase (about 1.5%; increases for assistant department chiefs or above will be frozen).

Of the total budget of ¥4,349,686,000, ¥3,567,349,000 is for personnel costs. The amount for salaries has been decreased by ¥202,434,000 compared to that of the previous year, whereas that for termination allowance has been increased by ¥134,629,000.

Of the operating budget of ¥782,337,000, ¥38,233,000 is for fees and honoraria, ¥15,837,000 for relocation travel, and ¥610,978,000 for laboratory expenses. The operating budget for this year is in practice about ¥27,600,000 larger than the figure given in the settlement of accounts of last year, which included a carry-over of ¥97,246,000 from the operating budget of the previous year.

The board appreciated the difficulties in developing the budget under heavy constraints and approved the proposed FY94 working budget.

6. FY95 budget request (presented by Tomoyuki Kono)

The total amount of the budget requested is ¥4,457,698,000, of which ¥3,663,626,000 is for personnel costs, assuming a 3.8% salary increase (a pay scale revision of 2% and periodical salary increases of 1.8%) for the staff of 378 (4 directors, 1 chief of secretariat, 49 research associates, and 324 general employees) on the payroll as of the beginning of the fiscal year and considering the cost of joining the Welfare Pension Fund (¥39,600,000). The operating budget is ¥794,072,000, 1.5% greater than the previous year.

The board approved the FY95 budget request, taking into account the possibility that the request might be changed due to governmental negotiations still underway and the fluctuating yen-dollar exchange rate.

It was proposed to hold some kind of a commemorative event in 1995, which would be the 20th anniversary of the establishment of RERF. The board approved the proposal to organize a working committee responsible for developing plans.

7. Revision of rules and regulations (presented by Tomoyuki Kono)

The following revisions of rules and regulations were proposed and approved:

(1) Regulations Concerning Organization of the Laboratory (Research Departments)

- 1) An Epidemiological Analysis Office and a Statistical Analysis Office will be established in the Departments of Epidemiology and Statistics, respectively.
- 2) The Coding Section of the Department of Epidemiology will be absorbed into the Master File Section of the same department.
- 3) The Coding Unit of the Field Investigation Section, Department of Epidemiology and Biometrics, Nagasaki, will be transferred to the Master File Section of the same department.
- 4) The Operations Unit of the Research Information Center will be divided into two units.
- 5) The Japanese titles *shocho* and *fuku-shocho* (one of the two Japanese titles used for associate chief of research) of Nagasaki Laboratory will be abolished.

(Effective dates: 1 October 1993 [items 1-4], 1 January 1994 [item 5])

(2) Rules of Employment

- 1) Leave necessary for donation or examination of bone marrow aspirate for bone marrow transplantation will be granted as special leave.
- 2) Three months were set as the extendable period of probational employment.

(Effective date: 1 January 1994)

(3) Regulations Governing Salaries of Directors and Chief of Secretariat

The base pay of the directors and the chief of the Secretariat will be increased by 1.93% on average, based on the revised National Government Pay Scale for Designated Positions.

(Effective date: 25 November 1993)

(4) Employee Wage Regulations

- 1) Base pay of employees will be increased using as a guide the revisions effected for national government employees (1.86% for general employees and 1.80% for research scientists).
- 2) Dependents allowance, housing allowance, and industrial physician's allowance will be increased.
- 3) Termination allowance will not be paid to employees who are terminated before expiration of probational period.
- 4) Following revision of the Labor Standards Law, the rate of overtime allowance for working on holidays will be increased to 135%.

(Effective dates: 25 November 1993 [items 1, 2], 1 January 1994 [item 3], 1 April 1994 [item 4])

(5) Act of Endowment

Changes will be made so that the number of directors can be increased or decreased depending on the situation.

- 1) "Permanent directors: four" will be changed to "permanent directors: four or fewer" and "directors: six" into "directors: six or fewer" in Paragraph 1 of Article 12, in which the number of officers is prescribed.
- 2) Paragraph 2 of Article 6, Paragraph 2 of Article 14, Paragraph 2 of Article 21, Article 33, and Paragraph 1 of Article 34, which prescribe the numbers of officers required for decision-making, will be revised.
- 3) The effective date will be the date when approval of the appropriate Minister(s) is obtained.

(Effective date: 30 June 1994)

8. Election/appointment of directors and others (presented by Itsuzo Shigematsu)

(1) Resignation of directors

Dr Shigematsu reported that Seymour Abrahamson, permanent director (chief of research) and Tomoyuki Kono, permanent director and chief of the Secretariat, had tendered their resignations as of 30 June. The Board decided to approve their resignations as of the date of approval of the revision of the Act of Endowment.

(2) Appointment of chief of research, chief of the Secretariat, and an operating committee member

Permanent Director Donald Harkness was appointed chief of research to succeed Dr Abrahamson, and Hiroshima Laboratory Operations Administrator Yasukiyo Hirano was appointed chief of the Secretariat to succeed Mr Kono. Their appointments would be effective as of 1 July. The term of chief of the Secretariat will be 1 year as Mr Hirano requested.

Appointment of a member of the Operating Committee was entrusted to the Executive Committee.

9. Schedule of next board meeting

It was agreed to schedule the next board meeting for 3 days from 26-28 June 1995 at the Hiroshima Laboratory.

Upon completion of discussion of all items on the agenda, Dr Shigematsu declared the meeting closed.

21st Scientific Council Meeting

13-15 June 1994
Hiroshima, Japan

Agenda

Day 1

Executive session	Ei Matsunaga Clark W Heath Jr
Greetings by the RERF chairman	Itsuzo Shigematsu
Report by the chief of research	Seymour Abrahamson

Departments of Statistics and Epidemiology

Department of Statistics overview	Dale L Preston
Department of Epidemiology overview	Kiyohiko Mabuchi
<i>LSS Report 12</i> progress report	Donald A Pierce
Cohort definition (in utero, F ₁ , etc) and dosimetry status	Shoichiro Fujita
Site-specific cancer program	Shoji Tokuoka
In utero cohort: comparison of risks for the 0-10 ATB group	Robert R Delongchamp Yasuhiko Yoshimoto
Studies on second primary cancers	Thanne P Rose
Status of family pedigree project	John B Cologne

Research Information Center

Network environment and database management progress report	Scott Pohlman Robert L Allen
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International Collaborative Studies

Parallel analyses of breast cancer incidence	Dale L Preston
Introduction to Chelyabinsk population exposures and epidemiology issues	Dale L Preston Akio A Awa
Introduction of Chelyabinsk collaborative studies: cytogenetics studies	Akio A Awa

Chelyabinsk somatic mutation study and other studies	Mitoshi Akiyama
Discussion of Chelyabinsk program	
Chernobyl studies.....	Shizuyo Kusumi

Day 2**Department of Radiobiology**

Departmental overview.....	Mitoshi Akiyama
Somatic mutation in the GPA gene.....	Seishi Kyoizumi
Role of hepatitis B virus in liver cancer, molecular studies	Terumi Mizuno

Departments of Genetics and Statistics

Departmental overview and progress in the DNA pilot study on the children of the A-bomb survivors	Chiyoko Satoh
Genetic instability of VNTRs in the children of the A-bomb survivors.....	Mieko Kodaira
Computerized analysis of 2-DE DNA gels	Jun-ichi Asakawa
Cytogenetics overview	Nori Nakamura
Cytogenetics: the FISH project.....	Yoshiaki Kodama
Chromosome aberrations/statistical analysis	David J Pawel
Biodosimetry and cancer relationships.....	Mortimer L Mendelsohn

Department of Clinical Studies

Departmental overview/responses.....	Kazunori Kodama
Health surveillance: pilot studies.....	Kazunori Kodama
Medical dosimetry: epidemiologic issues	Michiko Yamada
	Shoichiro Fujita
Medical dosimetry: experimental issues.....	Kazuo Kato
	Yasuyuki Fujita
Menopause data	Midori Soda
	Masazumi Akahoshi
Menopause—new study.....	Thanne P Rose

Informal Session

Science councilors met with the individual research groups.

Day 3

Executive session (closed)
Preparation of recommendations

Council recommendations	Clark W Heath Jr Ei Matsunaga
Closing remarks by RERF vice chairman	Mortimer L Mendelsohn
RERF Chairman Shigematsu and co-chairmen met with members of the press.	

Participants

Scientific Councilors

- Tomio Hirohata**, professor of public health, Kyushu University Faculty of Medicine
- Eisei Ishikawa**, professor emeritus, Jikeikai University School of Medicine, Tokyo
- Hikomichi Matsudaira**, chairman, Research Development Corporation of Japan, Kawaguchi
- Ei Matsunaga**, professor emeritus, National Institute of Genetics, Mishima
- Shigefumi Okada**, professor emeritus, University of Tokyo
- Clark W Heath Jr**, vice president for epidemiology and statistics, American Cancer Society
- Leonard A Herzenberg**, professor of genetics, Stanford University School of Medicine

Observers

- Akira Hashizume**, Planning Division, Health Service Bureau, Ministry of Health and Welfare (MHW)
- Harry J Pettengill**, deputy assistant secretary for health, US Department of Energy (DOE)
- Seymour Jablon**, expert, Radiation Epidemiology Branch, Division of Cancer Etiology, US National Cancer Institute
- Paul Gilman**, executive director, Commission on Life Sciences, National Research Council, US National Academy of Sciences (NAS)
- John D Zimbrick**, director, Board on Radiation Effects Research, Commission on Life Sciences, National Research Council, NAS
- Charles W Edington**, director, Radiation Effects Research Program, Commission on Life Sciences, National Research Council, NAS
- Susan Preston Martin**, professor, Department of Preventive Medicine, University of Southern California
- Edward P Washburn**, staff scientist for international programs, Office of Health, DOE

Supervisor

- Akira Shishido**, former director, Japanese National Institute of Health

Directors

Itsuzo Shigematsu, chairman

Mortimer L Mendelsohn, vice chairman

Seymour Abrahamson, permanent director and chief of research

Yutaka Hasegawa, permanent director

Donald R Harkness, permanent director

Tomoyuki Kono, permanent director and chief of the Secretariat

Comments and recommendations

The Scientific Council appreciates the thoughtful and thorough arrangements which all the RERF staff made. The meeting went well, the presentations were carefully prepared and delivered, and the discussion sessions, including the excellent informal group meetings, were stimulating and productive. We especially appreciate the availability, prior to the meeting, of copies of the slides and overheads and the photographs of investigators to help us link particular persons with particular research projects. These will be valuable practices to continue in the future.

We are very much aware of the administrative uncertainties and fiscal constraints that have surrounded this year's meeting and that caused its earlier postponement, and the absence now of three American councilors. As solutions to these administrative and fiscal difficulties are sought, it is important that we not lose sight of the scientific mission of RERF and its vital importance. That mission remains as it was originally stated in 1946: "a long-range, continuing study of the biological and medical effects of the atomic bomb in man." In conducting that study, RERF focuses on three critical research areas: 1) the assessment of health events over the lifetime of exposed persons, 2) the assessment of genetic effects in survivors and their offspring, and 3) the elucidation of mechanisms by which radiation effects occur with subsequent development of biologic measures of radiation dose. *These three phases of work, taken as a whole, can be done only at RERF and are of unique value for the entire world in providing a basis for international standards of radiation safety.*

Much work remains in each area. In particular, the lifetime follow-up of A-bomb survivors is more important now than ever before. Persons exposed at young ages, when radiation sensitivity may be highest, are now entering the later adult years in which cancers and other conditions become increasingly frequent. The youngest members of the cohort deserve such follow-up at least through age 70 (about the year 2015 or beyond if long-term F₁ follow-up becomes advisable). The process of follow-up has three essential components in RERF operations: mortality linkage, incidence data from the Hiroshima and Nagasaki cancer registries, and Adult Health Study (AHS) evaluations.

For genetic studies and radiobiologic dosimetry work, the A-bomb survivor populations are an irreplaceable resource for specimens of blood, tissues, DNA, and other materials by which current and future research advances can address

fundamental questions of radiation action. None of these research efforts must be allowed to falter. Those charged with support of this long-term research work must recognize the unique value of the entire RERF resource and its critical importance for mankind.

Epidemiology and Statistics

The major emphasis in epidemiology and statistics continues to rest with the maintenance of survivor follow-up through mortality and cancer incidence registry sources. This work concerns all three cohorts of interest: the LSS cohort, the in utero cohort, and the F₁ cohort. Particular attention is being paid to incidence analyses with the recent publication of papers in a special issue of *Radiation Research* [Volume 137, 1994] and with the ongoing analyses of incidence at particular tissue sites. *The long-term support of the Hiroshima and Nagasaki tumor registries is essential for the continuity of this work; the council urges that support for these population-based registries be kept closely allied with the operation of RERF itself.*

Life span risk studies

Work with the Life Span Study (LSS) cohort continues to provide significant information about radiation effects on health. This information has been widely used in UNSCEAR, BEIR, ICRP, and other reports regarding the health effects of radiation in humans. Nearly half a century has passed since the A-bomb exposures and about half of the LSS cohort members are now deceased. Yet continuation of LSS surveillance remains critical for RERF programs since over 85 percent of those who were young at the time of exposure, and who may therefore have been more sensitive to irradiation, are still living. Their lifetime risk for cancer and other chronic conditions has yet to be determined. *With the existence now of high-quality cancer registry systems, the council hopes that future analyses of risk patterns, particularly among those who were young at the time of the bombings (ATB), will increasingly use incidence in combination with mortality information.*

In utero and F₁ cohorts

We are pleased to see efforts underway to unify cohort information regarding persons exposed in utero, as well as persons in the F₁ generation. It is essential that both groups be as clearly defined as possible for the sake of future analyses. Full identification of the in utero cohort is particularly important, although its limited size may hamper ability to determine risk. *The council encourages continued emphasis on lifetime risk analyses in the in utero group in view of its potential for heightened sensitivity to A-bomb radiation.*

Site-specific cancer risks

Progress was reported regarding special risk analyses for specific cancer sites, using information from tumor registry and pathology sources. Studies are now complete for

liver, salivary gland, skin, and central nervous system (CNS) sites and are in progress or being planned for thyroid, ovary, lymphoid tissue, and lung. *Such work is an essential component of evaluating overall cancer risk in relation to A-bomb irradiation, and it deserves continued attention.* Particular mention was made of significantly increased relative risk of salivary gland tumors, potentially high frequencies of meningioma and schwannoma, and increased incidence of basal cell cancer, but not squamous cell cancer, with increasing A-bomb dose. These observations deserve continued scrutiny. While no relationship was apparently seen with skin keloid formation, this warrants special attention since either fibrosarcoma or malignant fibrous histiocytoma sometimes develops 10 or more years after radiation therapy. One might expect to encounter such tumors more frequently in A-bomb survivors than in the general population.

Second primary cancers

Analyses have been conducted regarding the occurrence of second primary cancers in A-bomb survivors and their possible relationship to A-bomb dose. The calculations are complicated and are influenced by first primary survival patterns as well as treatment experience. The results to date are difficult to interpret biologically, with excess risk values differing by sex. Further calculations taking close account of treatment factors may clarify the observations.

Family pedigree data

Considerable progress has been made in extending the LSS database to include family relationships between cohort members. Although the work will require at least another year to complete, it holds considerable promise as an approach for examining A-bomb effects in the context of genetic epidemiology. Many sources of data must be used, as well as a specially designed computer database, so it will be important to proceed with caution in constructing and recording the pedigree relationships. *The council strongly supports this project and would urge that it continue to receive priority attention.* Specific ideas for possible analyses using the pedigree database are suggested in Appendix to this Scientific Council report provided by Dr Matsunaga (see p 141).

Staffing considerations

Sustained staff expertise in both epidemiology and statistics is essential for productive work at RERF since such staff are responsible not just for assembling and analyzing life span risk information but for providing ongoing support in joint studies with the RERF laboratory groups. Both the Epidemiology Department and the Statistics Department have a long tradition of attracting excellent expert staff from within Japan and from the United States and abroad. *It is important that this process not be interrupted and that sufficient numbers of high-quality professional staff be maintained.*

Research Information Center

The council is pleased to know that great progress has been made in restructuring RERF computing facilities and that within the year it will be possible to discontinue use of the mainframe computer, thus achieving a considerable cost saving. This general shift to more versatile network technologies will greatly improve communications and data access in all departments. It should have substantial impact on interdisciplinary productivity in the near future. Accompanying this migration to more modern technology will be a redesign of database structures that will eventually eliminate redundant data sets and greatly enhance analytic access to research information contained in diverse registry systems. *The council urges that the work underway for modernizing computing facilities and data management be completed without delay.*

International Collaborative Studies

RERF continues to fill an important role as an international scientific resource with respect to radiation dosimetry and risk assessment. Recent consultations were described in relation to the Chernobyl disaster in the Ukraine and the long-standing radiation pollution situation associated with populations near Chelyabinsk in the Techa River valley in central Russia. From the viewpoint of professional academic growth at RERF, such collaborative work is important, and it often is essential from the standpoint of international politics. Of particular interest at present is a joint agreement reached between RERF and the Urals Research Center for Radiation Medicine to provide consultation services in risk estimation, biodosimetry, medical follow-up, and cohort definition in the Techa River area. *While continuation of such international collaborations is important, it must not be allowed to interfere with progress in ongoing research regarding the Japanese A-bomb survivors themselves.* If needed, funds to support collaborative consultation studies should be sought from sources outside of the RERF budget itself.

Radiobiology

Excellent progress was reported regarding work undertaken in the Department of Radiobiology. In support of that work, the council was assured that the frozen blood cells and lymphocyte cell lines are fully viable and culturable. This is an invaluable resource for genetic material from A-bomb survivors and members of the F₁ generation that is uniquely available and maintained at RERF. Molecular analysis and cell analysis (flow cytometric and sorting) studies on GPA and TCR are providing world-class genetic (mutational) and dosimetry results. *It is important that these studies be continued and extended with high priority.*

T-cell receptor

The T-cell receptor (TCR) studies being conducted are truly "state of the art." Loss of surface expression of TCR alpha or beta chains by somatic mutation is detected first by loss of staining for CD3 among CD4 cells. This is followed by obtaining clones of CD3⁻CD4⁺ cells and using gene amplification (RT-PCR) to show that either TCR alpha or TCR beta RNA is missing in each clone. Specific TCR rearrangements will be studied in the coming year. These studies should be encouraged.

Glycophorin A

Glycophorin A somatic mutations have been described in previous council reports. Using MN reticulocytes or nucleated red blood cells, MO, NO, MM, or NN cells detected by flow cytometry are taken as evidence of somatic mutants. The frequency of such mutants is a biological dosimeter since it increases with dose of ionizing radiation exposure. A similar dose responsiveness was reported for loss or change (mutational?) of human leukocyte antigens and T-cell receptors in CD45RA⁺ cells (memory cell markers), also measured by flow cytometry. This is important and scientifically exciting work which can be done well at RERF and probably nowhere else in the world.

Hepatitis B virus in liver cancer

Studies of hepatic cancer cases have shown no relationship between hepatitis B virus infection and A-bomb radiation dose. The report presented did not indicate whether underlying liver cirrhosis or chronic hepatitis might play a role in a possible virus-radiation pathogenesis. The studies might well be extended to explore this possibility.

Genetics

Biochemical studies

Chiyoko Satoh's group continues to make steady progress in establishing the family-based repository, and it is expected that specimen collection will be complete within a year (1000 family sets). Progress also has been made in pilot studies using 1) denaturing gradient gel electrophoresis of target sequences amplified by PCR for the detection of nucleotide substitutions, 2) Southern blotting of the conventional gel electrophoresis product for the detection of large insertions/deletions/rearrangements in unique sequences and of changes in number of repeats in VNTRs, and 3) high-resolution electrophoresis for microsatellites amplified by PCR. We were particularly interested in the development of techniques for two-dimensional gel electrophoresis (2-DE) of DNA, termed restriction landmark genomic scanning, which could detect 2000-3000 restriction landmarks, including deletions and insertions as well as base pair substitutions in the restriction sites, distributed throughout the genome. With this latter technique, electrophoresis of DNA samples from three mother/father/child trios has been carried out with good reproducibility of results. Another study has examined

the genetic instability of VNTRs. Six mini-satellite probes were used to compare the bands of children with those of their parents. New mutations were identified at three loci (unrelated to parental A-bomb exposure). *We strongly urge that the biochemical genetics group continue its exploratory studies with further refinement and testing using stored family specimens.*

Cytogenetics studies

The cytogenetics group, with Nori Nakamura taking over for Akio Awa, continues its work with biodosimetric systems measuring frequencies of stable chromosomal aberrations (translocations). The systems include conventional analysis and G-banding, and more recently, fluorescence in-situ hybridization (FISH). The latter technique may well become a worldwide benchmark for dosimetry in accidental radiation exposures because of its efficient application. Dosimetric results with all three methods seem closely correlated.

Since differences in dose patterns appear to exist for Nagasaki and Hiroshima and since cytogenetic dosimetry has suggested individual variations with respect to Dosimetry System 1986 (DS86) doses, perhaps related to differing shielding situations, a research project is planned to make dosimetric comparisons among subjects from Hiroshima and Nagasaki selected by DS86 dose shielding category, age ATB, and radiation symptoms. *The council favors this undertaking and hopes that the results will help clarify the differences seen, as well as enable further cross-comparisons with other biodosimetric approaches (eg, GPA and ESR/tooth enamel).* In the meantime, the statistical analyses presented concerning possible relationships among shielding, age ATB, and DS86 dose should be interpreted with caution.

Biodosimetry and cancer risk

A thought-provoking presentation by Mortimer Mendelsohn drew attention to parallel dose-risk curves for leukemia in relation to chromosome aberration dosimetry and for solid tumors in relation to GPA dosimetry. Striking slope differences between the two sets of curves suggest underlying differences in molecular mechanisms of carcinogenesis, the leukemia/chromosome model suggesting a chromosomal translocation mechanism and the solid tumor/GPA model suggesting a sequence of 5- or 6-point mutations akin to the statistical model which Armitage and Doll originally proposed to explain age patterns in cancer occurrence. It is important that RERF data be continuously and imaginatively scrutinized in search of such patterns that may well lead to new avenues of thought and to new research initiatives. *The council will be interested to learn how this particular idea evolves and the extent to which it can be further tested in RERF data sets or in information from other sources.*

Clinical Studies

AHS health surveillance

Various potential approaches are being evaluated for improving the collection of health information on older AHS participants. As the AHS cohort ages, participation in clinic visits tends to fall, while frequency of illness increases. A special workshop addressed this issue in 1993 and urged that AHS participants over age 70 be seen on an annual rather than a biennial basis. It also suggested that various alternative means for participant contact be explored. This reassessment of approaches has now reached the point where procedural changes can be adopted. The choices include, in addition to more frequent visits, the use of telephone or mail questionnaire follow-up, home visits in selected cases, and possibly computer-assisted reviews of insurance claims for health care services by persons identified by A-bomb Survivors Health Handbook identification numbers. *The council would encourage prompt implementation of whatever combination of these approaches seems most workable.* As RERF follows the lifetime health status of A-bomb survivors, it is important that AHS information be as complete and current as possible and that clinical contacts with aging survivors be especially maintained.

Medical dosimetry

Studies of the possible impact of medical radiation (diagnostic and therapeutic) have been conducted in the A-bomb survivor populations since the mid 1950s. On several occasions, surveys have been conducted to determine the numbers and types of exposures received by AHS participants both at RERF facilities and elsewhere. Updated analyses of accumulated data for diagnostic exposures show no appreciable differences among persons in different A-bomb dose categories. *Continued emphasis on detailed analyses regarding diagnostic medical exposures does not seem warranted since their potential for distorting A-bomb dosimetry and disease risk estimates is minimal.*

A non-negligible number of patients (1,670 among the whole LSS cohort) has undergone radiotherapy, one-third for treatment of benign conditions and two-thirds for malignancies. *Further studies in this area seem indicated principally in relation to the occurrence of second primaries.*

Menopause studies

Midori Soda and others have previously described a relationship between decreasing age at menopause and increasing A-bomb dose, using information obtained at periodic AHS examinations. This issue is important for understanding possible biologic changes induced by radiation in ovarian function. The nature of AHS data and a new retrospective survey do not suggest that the finding results from defects in memory recall concerning date of menopause. A prospective study is planned to examine possible hormonal mechanisms by following hormone levels (follicle-

stimulating hormone and estradiol) in premenopausal AHS participants. *The council strongly encourages this new study as a promising approach for gaining new knowledge regarding tissue-radiation interactions.* The observations reported concerning increased cholesterol levels after menopause also may be useful in this regard.

Cataracts

Radiation-induced cataracts was a topic of discussion during the informal phase of the meeting. Sixteen years have passed since studies were last conducted in this area. *It would be of interest to take up the subject again in studies of AHS participants.* Precise evaluation of cataract formation can be made by grading different degrees of nuclear, cortical, and subcapsular opacity using the lens opacities classification system and densitometry with special camera equipment.

Appendix

Some Strategic Suggestions for Genetic-Epidemiologic Studies at RERF

by Ei Matsunaga

Studies could be made at the following three levels:

1. **Pilot studies using cancer-concordant sibs** among LSS and AHS samples, as identified by *koseki* or other means and tumor/tissue registries. As controls, data from cases with no known sibs affected or from the general population may be used. Information about medical history of sibs is, because of proximity in time, usually much more reliable and comparable than about parents or other relatives.

- (1) Is the tissue-concordance rate higher among the affected sibs than randomly expected?

It is known that familial aggregation of cancer affects generally the same sites, suggesting that the presumed genes which predispose to cancer are tissue-specific. (There are, however, rare exceptions).

- (2) Does the age at first diagnosis tend to be lower among the tissue-concordant sibs as compared with controls?

Somatic mutations are essential in carcinogenesis, which is considered a multi-step and multifactorial process. If germinal mutation is involved in any one of the steps, then cancers develop earlier than otherwise in the site affected.

- (3) For a paired organ such as the breast or the thyroid, is the proportion of bilateral cases higher among concordant sibs?

Cancers involving germinal mutation usually develop bilaterally and often almost simultaneously. Conversely, bilateral cases may be assumed to involve (always) a germinal mutation.

- (4) How are the relations of the age at onset and bilaterality with the history of A-bomb exposure, dose, and age ATB? Is there any difference between those sibs who were exposed and those not exposed? For example, in the exposed concordant sibs age at onset could be lowered further as a result of the synergistic effect of genes and radiation. This is an intriguing but complicating question.

In this approach, the net effect of genes cannot be separated from those due to common familial environment such as diet and life-style. One may get, however, an approximate inference about the maximum extent to which genes could play a role in common cancers.

2. **Extension of LSS:** RERF has already estimated successfully, by means of sophisticated statistical methods and models, the relative risk (RR) or excess relative risk of various cancers for persons classified by sex, city, dose, attained age, and age ATB. It may then be possible to incorporate an additional factor, namely, information about family data. A question may be formulated as follows: is the RR of a certain cancer increased proportionally with the number of his or her sibs known to have been affected by the same kind of cancer? Using this approach, possible interaction between exposure and genetic (or familial) factors also may be checked.
3. **Molecular biologic studies:** Ultimately, however, involvement of genes has to be verified with families in which multiple cases of cancers have been observed, by means of a molecular genetic approach. Using blood samples taken from members of these families, it may be feasible to check certain predisposing genes such as *p53* or *BRCA1*. If verified, its possible interaction with specific environmental factors including irradiation may be clarified. At the same time, such a test also could serve for primary prevention of a cancer in a predisposed family.

The above strategy also could apply, in principle, to genetic-epidemiologic studies of various diseases other than cancer.

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Noboru Imamichi, Contacting Unit supervisor (concurrent assignment)
Nachiko Fukae, Counseling Unit supervisor

Department of Radiobiology

Takeo Honda, department chief
Yoko Urakawa, chief of technicians
Michiko Hirose, Administration Unit supervisor

Cell Biology Laboratory

Kiyohiro Hamatani, laboratory chief
Masumi Abe, research scientist
Masahiro Ito, research scientist
Hiromitsu Miki, assistant chief of technicians
Masako Edo, assistant chief of technicians

Department of Epidemiology & Biometrics

Yoshisada Shibata, department chief
Masahide Tanaka, administrative assistant department chief

Master File Section

Koji Nakamura, section chief
Yuiko Imamichi, assistant section chief
Yoshiko Ichinose, Master File Unit supervisor
Toshiko Tanaka, Records and Archives Unit supervisor
Yuiko Imamichi, Coding Unit supervisor (concurrent assignment)

Field Investigation Section

Nobuhiro Mizushima, section chief
Osamu Kusumi, assistant section chief
Osamu Kusumi, Field Investigation Unit supervisor (concurrent assignment)

Computer Management Office

Yoshisada Shibata, acting office chief

Department of Epidemiologic Pathology

Midori Soda, acting department chief
Midori Soda, assistant department chief
Seiichi Oya, administrative assistant department chief
Makiko Hamamatsu, Administration Unit supervisor

Pathology Laboratory

Midori Soda, acting laboratory chief
Masayoshi Tokunaga, visiting research scientist (concurrent assignment)
Yoko Yanagihara, chief of technicians

Tumor and Tissue Registry Office

Midori Soda, acting office chief
Tatsue Taneguchi, section chief
Kazuko Dateki, assistant section chief
Koki Sonoda, unit supervisor

Radioisotope Facility

Kazuyoshi Yamashita, assistant chief of technicians

Secretariat

Tadashi Nakaoka, chief of administration

General Affairs Section

Takaaki Hashiguchi, section chief

Kin-ichi Honda, chief of Public Relations Office (concurrent assignment)

Hiroshi Ichoda, assistant section chief

Atsuko Nakagawa, assistant section chief

Akihiro Yamauchi, General Affairs Unit supervisor

Hiroshi Ichoda, Employees Unit supervisor (concurrent assignment)

Accounting Section

Kin-ichi Honda, section chief

Mitsuo Yutaka, assistant section chief

Mitsuo Yutaka, Accounting Unit supervisor (concurrent assignment)

Yasushi Takeda, Supply and Property Unit supervisor

Shigeru Hashizume, chief of guards and maintenance staff

Summary Tables

April 1994–March 1995

Contacting Adult Health Study (AHS) participants and contacting families for permanent lymphocyte cell-line* establishment

City	AHS allocated for contacting	Appointments made	PLC family allocated for contacting	Appointments made
Hiroshima	11,354	1716	108	9 (44)
Monthly average	946.2	143	9	0.8 (3.7)
Nagasaki	5997	1180	523	34 (102)
Monthly average	499.8	98.3	43.6	2.8 (8.5)

*RP 5-85: Culture of permanent lymphocyte cell lines (PLC) as sources of biological samples for investigation of genetic effects of radiation on children of atomic-bomb survivors. The study was initiated in Hiroshima in August 1985 and commenced in Nagasaki in September 1986.

Note: The numbers of contacts made are entered in the columns "AHS allocated for contacting" and "PLC family allocated for contacting." The column "Appointments made" for PLC study gives the numbers of families. Figures in parentheses are the numbers of persons examined.

Medical clinic visits

City	Total persons	AHS		Non-AHS		Specimens only
		Scheduled	Others*	Referral	Return	
Hiroshima	2266	1716	550	84	7	95
Monthly average	188.8	143	45.8	7	0.6	7.9
Nagasaki	1537	1180	357	72	9	48
Monthly average	128.1	98.3	29.8	6	0.8	4

*Return visit, nonscheduled examination, etc.

Note: AHS = Adult Health Study. "Non-AHS" refers to the family members, friends, etc. of AHS participants. "Specimens only" refers to the collection of urine, stool, sputum, etc. from examinees who do not come to the clinic.

Cryopreservation of blood samples obtained from AHS participants

January-December 1994

DS86 (Gy)	Number of survivors by age ATB*		
	0-15 y	>15 y	Total
	Hiroshima		
0-0.5	515 (226, 289)	718 (191, 527)	1233 (417, 816)
>0.5	193 (79, 114)	281 (90, 191)	474 (169, 305)
Unknown	38 (5, 33)	112 (37, 75)	150 (42, 108)
Total	746 (310, 436)	1111 (318, 793)	1857 (628, 1229)
	Nagasaki		
0-0.5	171 (79, 92)	232 (66, 166)	403 (145, 258)
>0.5	87 (45, 42)	132 (48, 84)	219 (93, 126)
Unknown			186 (73, 113)
Total	258 (124, 134)	364 (114, 250)	808 (311, 497)

*Total number of persons: (male, female)

April 1990-December 1994

DS86 (Gy)	Number of survivors by age ATB*		
	0-15 y	>15 y	Total
	Hiroshima		
0-0.5	2236 (948, 1288)	3650 (896, 2754)	5886 (1844, 4042)
>0.5	731 (301, 430)	1313 (357, 956)	2044 (658, 1386)
Unknown	172 (31, 141)	534 (180, 354)	706 (211, 495)
Total	3139 (1280, 1859)	5497 (1433, 4064)	8636 (2713, 5923)
	Nagasaki		
0-0.5	326 (143, 183)	589 (174, 415)	915 (317, 598)
>0.5	245 (116, 129)	478 (165, 313)	723 (281, 442)
Unknown			298 (108, 190)
Total	571 (259, 312)	1067 (339, 728)	1936 (706, 1230)

*Total number of persons: (male, female)

Tumor-registry accessions (medical records for malignant tumors only)

January-December 1994

City	Total	LSS sample		F ₁ , in utero samples	Others
		Total	AHS		
Hiroshima	6301	520	138	42	5739
Monthly average	525.1	43.3	11.5	3.5	478.3
Nagasaki	4402	167	41	22	4213
Monthly average	366.8	13.9	3.4	1.8	351.1

Note: F₁ = children of atomic-bomb survivors.

Tissue-registry accessions

Year	Hiroshima	Nagasaki
1973	3249	—
1974	5735	2543
1975	4653	3287
1976	6906	3565
1977	9840	4318
1978	8219	4528
1979	10056	4633
1980	10521	6110
1981	12434	6972
1982	13440	7163
1983	13942	7567
1984	14959	8237
1985	15353	10022
1986	17542	7761
1987	20132	8458
1988	21641	8368
1989	22965	6124
1990	25507	4833
1991	26158	4888
1992	30368	5051
1993	34320	2749
1994	30312	4819

Note: Tissue registration was commenced in Hiroshima in April 1973 and in Nagasaki in September 1974 with funds provided by the US National Cancer Institute.

Requests for RERF journal-article reprints by country*April 1994-March 1995*

Country	No. of requests	Country	No. of requests
USA	177	Iran	4
Germany	50	Norway	4
France	45	Switzerland	4
Japan	29	Ukraine	4
Poland	24	United Kingdom	4
India	17	Brazil	3
The Netherlands	13	Paraguay	3
Bulgaria	12	Russia	3
Hungary	11	Slovakia	3
Lithuania	11	Turkey	2
Czech Republic	10	Belarus	1
Israel	10	Chile	1
Spain	10	Colombia	1
Canada	9	Croatia	1
Cuba	9	Denmark	1
Italy	9	Finland	1
Austria	8	Ireland	1
Argentina	7	New Zealand	1
Belgium	7	Pakistan	1
Romania	5	Portugal	1
Yugoslavia	5	Sweden	1
Australia	4	Taiwan	1
Estonia	4	former USSR	1
Total: 533 from 46 countries			

Agreements on RERF International Collaborations

RERF has been conducting or participating in a number of international collaborative programs. These include the Nippon-Honolulu-San Francisco (Ni-Hon-San) Study on cardiovascular diseases, inaugurated in 1965 as an ancillary ABCC study; the Sino-Japanese friendship and exchange program; research collaboration with the Urals Research Center for Radiation Medicine (URCRM) in Chelyabinsk, Russia; cooperation with the Hiroshima International Council for Health Care of the Radiation-exposed (HICARE); and a US National Cancer Institute (NCI) collaborative study on cancer epidemiology. Following is material relevant to these collaborations.

1. Ni-Hon-San Study

Editor's note: The following brief description of the Ni-Hon-San Study was extracted from Atomic Bomb Casualty Commission Technical Report 12-71, "Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California; research plan." Providing the historical context upon which the Ni-Hon-San Study continues to collect data today, the extracted TR text is followed by a brief update of recent Ni-Hon-San activities.

Preface

The research protocol which follows is the culmination of several years of planning as well as actual field studies in Japan, Honolulu, and California. As such, it describes methods for gathering data regarding cardiovascular disease, programs for comparative analyses, definitions, controls and descriptions of the involved populations.

The protocol does not designate all investigators; these will be listed in the several reports stemming from the observations begun in 1965 in Honolulu and Japan, and in 1969 in the San Francisco area. Those responsible for proposing, planning, initiating, and directing these efforts are listed below by location of the study centers.

The Atomic Bomb Casualty Commission, Hiroshima and Nagasaki, Japan. [A list of ABCC researchers follows in the original text.]

The Honolulu Heart Study, Honolulu, Hawaii. [A list of HHS researchers follows in the original text.]

The School of Public Health, University of California at Berkeley. [A list of UC researchers follows in the original text.] *[Editor's note: Follow up of the San Francisco cohort ceased in the mid-1970s.]*

The National Heart and Lung Institute. [A list of NHLI researchers follows in the original text.]

Introduction

Since around 1950, a number of studies around the world have documented geographic differences in the mortality, pathology, prevalence, and incidence of coronary heart disease. Among others, marked differences have been reported in the coronary heart disease and cerebral vascular disease experience of populations living in Japan and in the United States. It was not clear whether the differences might be due to genetic makeup, to environmental experiences, or whether, in fact, they might be spurious and based on differences in hospitalization practices, in modes and criteria for diagnosis, and in customs and practices regarding medical certification of death.

It appeared that some answers to these questions could be sought in the fortuitous circumstance offered by the migration of a substantial number of people from Japan to Hawaii and to California during the past 100 years. Anthropologic studies showed that the majority of migrants had come from Hiroshima and two or three other nearby prefectures. It was believed that a suitable indigenous Japanese population could be studied that would be comparable in its ethnic background to that of the migrant Japanese. Thus, it would be possible to minimize genetic factors in the epidemiology of disease while exploring, in these three ethnically similar populations, those environmental and behavioral variables which might affect the risk of coronary heart disease and cerebral vascular disease (stroke). The plan was to organize the studies so that differences in mortality reporting, in autopsy, clinical, and laboratory procedures, and in criteria for diagnosis could be held to a minimum.

To carry out the objectives of this investigation, three cooperating cardiovascular disease (CVD) studies have been established in Japan, Hawaii, and California to capitalize on the existence of three population groups presumably similar genetically but differing in their environment and in their life styles.

It is of interest that while the study cohorts in Hawaii and California were selected mainly for the program outlined in this Research Plan, the ABCC investigation of cardiovascular diseases actually goes back to 1958. A comparison of initial findings in Japan with the Framingham study followed site visits to Massachusetts by ABCC researchers, efforts to enlist other supervised cohorts in Japan (viz, the Railroad Hospital in Hiroshima), and extensive biochemical comparisons with Japanese and American counterparts. Results of the continuing ABCC program were reported for 1958-64. A symposium on epidemiology of cardiovascular disease and stroke was held in Hiroshima in 1965.

With the addition of comparable questionnaires and certain anthropometric and biochemical observations, the ongoing program at ABCC was recognized as being readily adaptable into a tripartite effort. This was facilitated by agreement between the ABCC sponsors, Japan and the US (described in the ABCC Annual Report 1964-65, pp 72-77), to share the CVD data with other investigators and to permit the use of funds from the US National Heart and Lung Institute. This support was necessary for

that portion of the study expenses which were above and beyond the basic, binational mission of ABCC.

In Japan, the study is being conducted by ABCC in collaboration with JNIIH [Japanese National Institute of Health]; in Hawaii, by the Honolulu Heart Study, an arm of the National Heart and Lung Institute, established specifically to carry out this investigation; and in California, by the School of Public Health of the University of California at Berkeley with funds from the National Institute of Neurological Disease and Stroke (Grant NS06818) and from the National Heart and Lung Institute (Grant HE14783).

Update of recent Ni-Hon-San research

Background

The Ni-Hon-San Study of stroke began in 1972 and an early surveillance of stroke incidence in men was completed in 1978. Stroke cases were classified into two types: intracranial hemorrhage and thromboembolic stroke. For both types of stroke 20 years ago, the incidence in Japan was about three times greater than in Hawaii. For all strokes in Japan and Hawaii, blood pressure was the most important risk factor, followed by age. Since blood pressure levels did not significantly differ in Japan and Hawaii, the difference in stroke incidence may have resulted from differing animal protein and saturated fat intake, which is inversely associated with stroke incidence. Animal protein and saturated fat intake in Hawaii was much greater than in Japan.

Today's perspective on the CVD study

After 1978, male population cohorts in Japan and Hawaii have been continually surveyed for cardiovascular disease (CVD) incidence, facilitating cross-cultural lifestyle comparisons while pursuing the study of possible interactions between CVD and its risk factors and radiation exposure among men and women in the RERF Adult Health Study (AHS). Epidemiological methods in use have been developed in the course of the Ni-Hon-San Study.

Analysis of RERF's Life Span Study (LSS) mortality data in recent years suggests a possible relationship between A-bomb radiation exposure and CVD, thus the continued clinical monitoring of the cohorts in Hawaii and Japan may lend broader clinical support to these epidemiological findings.

Ongoing studies

Ascertainment of new CVD cases through review of examination records, ECG records, mortality surveillance reports, and autopsy reports is ongoing in Hawaii and Japan. Analyses are underway in the Honolulu Heart Program and in RERF's AHS.

Measurements of fibrinogen are underway in the Honolulu cohort for comparison with levels in the Hiroshima cohort, for which measurements from the 1990 to 1992 examination cycle are completed. Laboratory standardization of plasma fibrinogen

measurements taken at RERF and those of the Ni-Hon-San reference laboratory at the University of Vermont are completed, confirming that the data is directly comparable. Data analysis is currently underway independently at each study site. A manuscript will be written in FY95.

Comparison of total mortality for baseline serum glucose level and history of diabetes mellitus also is underway.

In each cohort, the relationship between physical activity and CVD incidence has been analyzed, and results will be compared.

The Ni-Hon-San Study cohorts also will be compared for 1) total mortality, cancer mortality, and noncancer mortality; 2) CVD risk factor levels among the elderly; 3) longitudinal changes of ECG findings; 4) pulmonary function and the risk of subsequent mortality; 5) prevalence of senile dementia; and 6) medication use among the elderly.

Outside funding for the Ni-Hon-San Study

In December 1994, a grant proposal was submitted to the Japan Foundation on Aging and Health to support travel to Hiroshima for David Curb, principal investigator of the Honolulu Heart Program. On 14 February 1995, he received funding for a 1-month stay in Hiroshima early in FY95.

In May 1995, Katsuhiko Yano, senior scientist of the Honolulu Heart Program, is expected to visit the Hiroshima Laboratory for 1 month. He will be sponsored by the Hiroshima International Council for Health Care of the Radiation-exposed.

2. Sino-Japanese friendship and exchange

Editor's note: After the exchange of the memorandum on 16 October 1985, 15 visiting research scientists were accepted for training at RERF up until 19 September 1992.

MEMORANDUM CONCERNING SINO-JAPANESE FRIENDSHIP AND EXCHANGE

1. The Laboratory of Industrial Hygiene, China National Center for Preventive Medicine, Ministry of Public Health, People's Republic of China (hereinafter "the Chinese side") and the Radiation Effects Research Foundation, Japan (hereinafter "the Japanese side") will mutually promote exchange and cooperation in areas of research and investigation, and will endeavor jointly to promote mutual understanding and friendship in accordance with the principles of equality and reciprocity as well as mutual trust.

2. Dispatch from the Chinese side
 - (1) In accordance with precedent, dispatch of personnel for a period of one year will be continued, but dispatch of personnel for a short period (2-3 months) will also be organized.

 - (2) Roundtrip travel expenses will be borne by the Chinese side and the living expenses by the Japanese side (shared equally by Japan and the US). However, the expenses for travel within Japan will be borne by the Japanese side.

 - (3) As a rule, the same working conditions and others as provided for Japanese and American staff members will be applicable, and dispatched persons will follow the regulations and supervision of the Japanese side.

3. Dispatch from the Japanese side
 - (1) The number of persons to be dispatched, the period, etc. will be decided separately upon consideration.

 - (2) Roundtrip travel expenses will be borne by the Japanese side and living expenses will be borne as decided separately upon consideration.

 - (3) Dispatched persons will follow the regulations and supervision of the Chinese side during their stay.

4. Exchange of information

Data and scientific information, whenever released, will be mutually exchanged.

5. Close Contact

The two sides will closely contact and consult with each other for the promotion of friendly exchange and collaborative relations.

Continued on next page

Sino-Japanese friendship and exchange (continued)

6. Effective Period

This Memorandum shall be effective for a period of three years from the date of signature. It shall be renewed for periods of three years thereafter if neither party notifies the other party in writing of its intention to the contrary.

7. Custody of Memorandum

This Memorandum shall be made in Chinese, Japanese and English all of which are equally valid, and each copy of the three versions shall be kept by both parties respectively, after signing and affixing the seal.

Date: 16 Oct. 1985

Witness: Wei Luxin

Wei Luxin

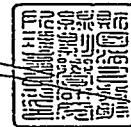
Wang, Zuo Yuan
Wang Zuo Yuan
Director
Laboratory of Industrial Hygiene
China National Center for
Preventive Medicine
Ministry of Public Health
People's Republic of China



Abraham Kagan

Witness: Abraham Kagan

Itsuzo Shigematsu
Itsuzo Shigematsu
Chairman
Radiation Effects Research Foundation
Japan



3. URCRM-RERF collaboration

Editor's note: This particular agreement has been superseded by a September 1995 contract between NCI and RERF.

AGREEMENT

for research collaboration between the Ural Research Center of Radiation
Medicine, Chelyabinsk, Russia, and the Radiation Effects
Research Foundation, Hiroshima, Japan

Introduction

The Ural Research Center of Radiation Medicine, Chelyabinsk, Russia (Director: Alexander V. Akleyev) and the Radiation Effects Research Foundation, Hiroshima and Nagasaki, Japan (Chairman: Itsuzo Shigematsu) agree to carry out a program of research collaboration in the follow-up of exposed populations and individuals following accidental radioactivity releases in the Chelyabinsk region during the nineteen fifties. Both parties consider such collaborative efforts of great scientific importance, given that both the A-bomb survivor studies and the studies on the so-called Techa River Population concern elevated exposures to large population groups, which have been carried out over extended periods of time.

These efforts, if successful, will allow a comparison between the late health effects from ionizing radiation in both acute and chronic exposure conditions, and should therefore be regarded to be extremely important from the point of view of radiation protection criteria and policies, in addition to the evident scientific and medical benefits resulting from the increase of solid data on radiation effects in humans.

Scientific research areas to be considered

Upon introductory discussions on a number of occasions, it has become clear that the following research areas promise the greatest scientific returns to both parties:

1. Epidemiology and Statistics

The collaboration will aim at a joint comparative analysis of the risk from radiation exposure in both populations. This will require a thorough evaluation of the similarities and differences between the two populations, and well-planned and executed efforts to obtain missing data wherever this is possible. Special efforts may be necessary to study subjects such as case-ascertainment and data quality (such as the quality of hematological and pathological diagnoses), in order to ensure full comparability of data among the two study populations. It will also require close liaison with other collaborative efforts, such as those under the auspices of the Nuclear Safety Research Association, Tokyo, Japan (Chairman: Eizo Tajima), the Japan Atomic Industrial Forum (Executive Managing

Continued on next page

URCRM-RERF collaboration (continued)

Director: Kazuhisa Mori), and the Ural Research Center of Radiation Medicine, covering dosimetric and related subjects.

2. Dosimetry

This area includes two parts: dose reconstruction and biological dosimetry.

a. Dose Reconstruction

The main objective of this project is the reconstruction of individual radiation doses, both internal and external, for the exposed population in the Southern Urals. This will be done by special field studies, using existing information as far as possible and feasible. Special emphasis will also be placed on assessing the accuracy and precision of dosimetric data obtained. The project will be coordinated with the Dosimetry Assessment efforts agreed upon between the Nuclear Safety Research Association (NSRA), Tokyo, Japan, the Japan Atomic Industrial Forum, Tokyo, Japan, and the Ural Research Center of Radiation Medicine.

b. Biological Dosimetry

This project concerns the comparison of cytogenetic, immunological, and other biological dosimetry data, and may also involve training of Russian scientists in the particular techniques employed at RERF, and transfer of these techniques for use in Chelyabinsk.

3. Medical Follow-up Studies

The emphasis in this study area will be more on exchange of knowledge, training and advice than on actual research collaboration (epidemiological aspects of the Adult Health Studies to be covered under 1, above). Areas of particular interest will be: population characteristics, dosimetric aspects, participation rate, examination schedules and contents, quality control, medical records and data handling, and analysis of data. Actual involvement in medical examinations will be minimal, given the legal limitations on both sides.

4. Future Studies

At a joint meeting, to be organized after completion of the feasibility stage of this project (see item 1, below), the planning of future research programs will be discussed, including studies in such areas as genetics and molecular epidemiology.

Continued on next page

URCRM-RERF collaboration (continued)Phases of the collaborative research

It is agreed that initial activities will be directed towards further evaluation of the feasibility of common studies and training programs, with development of detailed protocols in a later stage. This initial phase will include, as necessary, visits by RERF staff to Chelyabinsk, and of Russian scientists to RERF, as proposed in more detail below. In later phases, RERF will consider making available for use in Chelyabinsk computer hardware support, so as to allow identical computer analyses to be performed in both places.

The following measures are proposed for each of the three research areas specified above:

1. Epidemiology and Statistics

Two scientists from RERF will visit Chelyabinsk for a period of two weeks to develop a better understanding of the data available, and to determine the specific items that would be necessary for a successful collaboration. This will be followed by a visit to RERF by two Chelyabinsk scientists, thoroughly familiar with the Chelyabinsk data, available dosimetry, and statistical methods for analysis of these data. Some familiarity with the RERF data set would be very helpful. The duration of this visit would be approximately three months, during which a plan for collaborative efforts in risk assessment and additional data collection can be developed, and knowledge of techniques for this can be transferred. During the last two weeks of this period, a joint meeting will be held in Japan (preferably at RERF) with representatives of all parties involved to define the contents and to determine the schedule for future collaboration.

2. Dosimetry**a. Dose Reconstruction**

For this project, a dosimetry project coordinator from Russia will be identified. The coordinator will develop the draft proposal for dose reconstruction. This proposal will be initially mailed to Japan. This will be followed, if necessary, by the visit of one or two Chelyabinsk expert(s) who is (are) responsible for the proposal. Based on discussion, a final protocol will be prepared and the project will proceed as agreed upon then.

Continued on next page

URCRM-RERF collaboration (continued)

b. Biological Dosimetry

This project will, in the first phase, require the visit to RERF of two or three Russian scientists to become thoroughly familiar with the methods used at RERF for the quantitative measurement of radiation-induced damage in chromosomes and with respect to immunological competence. Discussions on the timing and funding of these visits are already underway. It may be appropriate, however, to have two scientists from RERF visit Chelyabinsk, to investigate the facilities, equipment, and human resources available for this study, in order to be better able to match the training at RERF to the resources present locally. In a later stage, it might be necessary to consider equipment support to be provided to the Chelyabinsk group to ensure full comparability of the data collected by both parties.

3. Medical Follow-up Studies

This study area will require a visit to RERF by a Russian medical scientist involved in the Chelyabinsk medical follow-up program. The main emphasis will be on training and information transfer as indicated in 2 above, and to discuss possible items for collaboration in the future. A duration of between two to four weeks appears to be most appropriate. The timing of this visit should be such that the Russian visitor will be able to attend the joint meeting discussed in the previous paragraph.

Funding Arrangements

It is planned that the Japanese parties involved will provide financial support, to the greatest extent possible, for the activities described above. Details on this will be decided based upon further discussion. Assistance for the housing and feeding of participants from Japan while on Russian territory is requested to be provided by Russian authorities.

Requirements for Participating Scientists

The language in all communications concerning this project will be English. Consequently, all participants should have a reasonable working knowledge of that language. Given the serious interference in scientific work and discussions created by the need for translation, use of interpreters should be avoided if at all possible. In addition, all participants should be thoroughly familiar with the available data on their study populations in their field of involvement.

Continued on next page

URCRM-RERF collaboration (continued)Further Particulars

Upon approval by both sides of the above described proposal, details will be arranged through correspondence, and the agreed upon arrangements will be confirmed by letter agreement between both parties. Given previously committed activities, RERF will be ready to start active collaboration in the sense described above from July 1992 onward. Some visitors to RERF, however, may be arranged -- and some already have been -- before that date.

It is proposed that the different fields of collaboration described above will proceed independently, so that no further synchronization should be necessary.

It is understood that no other participants in the projects covered by this proposal shall be included without written agreement by the undersigned, before actual involvement of such participants shall commence.

This agreement resulted from the discussion between A.V. Akleyev and I. Shigematsu in consultation with E. Tajima and K. Mori. Signed copies of the agreement will be sent to E. Tajima and K. Mori.

Approved:

For the Ural Research Center of
Radiation Medicine,

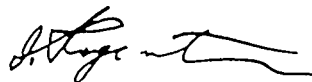


A.V. Akleyev, Director

Date:

12 May 1992

For the Radiation Effects
Research Foundation,



I. Shigematsu, Chairman

Date:

12 May 1992

Continued on next page

URCRM-RERF collaboration (continued)

ADDENDUM TO
AGREEMENT

for research collaboration between the Ural Research Center of Radiation
Medicine, Chelyabinsk, Russia, and the Radiation Effects
Research Foundation, Hiroshima, Japan

(Signed 12 May 1992)

This addendum provides clarification of the penultimate paragraph of the Agreement, concerned with the participation of other parties in the projects covered by the proposal. It is understood that the objective of this paragraph is to enable the participation of third parties in a well-coordinated manner. It is agreed that once specific RERF/URCRM research programs are defined and developed, the enrollment of third parties will be realized with the written consent of both RERF and URCRM. It is also agreed that, prior to the establishment of specific research programs, both RERF and URCRM will inform each other of its discussion with third parties regarding research in areas for which joint RERF/URCRM research is planned.

Approved:

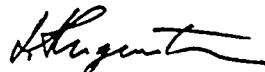
For the Ural Research Center of
Radiation Medicine,



A.V. Akleyev, Director

Date: 30 Oct. 1992

For the Radiation Effects
Research Foundation



I. Shigematsu, Chairman

Date: 27 October 1992

Copies to: Dr. Eizo Tajima
Mr. Kazuhisa Mori

4. US NCI-RERF epidemiologic studies of cancer among atomic-bomb survivors

AGREEMENT NO.
NCI-4896-93-001

A G R E E M E N T

THIS AGREEMENT is entered into by and between the National Academy of Sciences, hereinafter called the Academy, a corporation organized and existing under the laws of the United States and having its principal office at 2101 Constitution Avenue, N.W., Washington, D.C. and the Radiation Effects Research Foundation, a non-profit foundation organized under the laws of Japan and having its principal office in Hiroshima, Hiroshima Prefecture, Japan.

W I T N E S S E T H:

WHEREAS, the Academy has received specified funds from the National Cancer Institute through Contract No. NO-CP-21028, which provides for epidemiologic studies of cancer among Japanese atomic bomb survivors,

NOW, THEREFORE, the parties hereby agree and covenant as follows:

ARTICLE 1. This Agreement shall be effective as of September 30, 1992 and shall extend through September 29, 1993 unless otherwise amended by the mutual agreement of both parties.

ARTICLE 2. The Foundation shall furnish necessary personnel, services and materials and do all other things necessary to perform satisfactorily the work described herein and to report upon such work. The Foundation will perform the following tasks:

(1) Conduct epidemiological and multi-disciplinary studies of cancer risk, radiation dose, and other factors among members of the Life Span Study (LSS) sample (extended) as agreed upon by NCI and other collaborating investigators. For each such study, in collaboration with NCI investigators, prepare research protocols (RP) for these studies and submit them for approval by appropriate review committees of the NCI and the Radiation Effects Research Foundation (RERF).

(2) As specified by the appropriate approved RP, identify cancer cases among members of the LSS sample. Sources of case ascertainment may include tumor and tissue registries, autopsy files, hospital and clinic records, death certificates, and existing RERF data files.

(3) Identify members of the LSS sample not known to have cancer (or cancer of a particular site or group of sites) who are otherwise similar to selected sample members known to have a particular kind of cancer. Similarity here pertains to date of birth, sex, city of exposure, vital status, and other properties as specified in the appropriate RP.

(4) Determine the whereabouts of living cancer cases and non-cases (controls), and the whereabouts of the next of kin of those who have died.

Continued on next page

NCI-RERF studies (*continued*)

(5) Design and pretest questionnaires, in collaboration with NCI and other investigators, to be administered to cancer cases and controls or their next of kin. Questionnaires shall be developed in both English and Japanese, with a sufficient number of Japanese questionnaires copied to be used for interviews of the selected cases and control or their surrogates. The English language version should be submitted to the appropriate NCI review committee in ample time for that committee's recommendations to be incorporated in the final version, and to allow time for obtaining clearance by the U.S. Office of Management and Budget (OMB).

(6) Provide and train interviewers experienced in field survey investigations to administer the questionnaires in personal interviews.

(7) Conduct person-to-person interviews with the cases and controls or their next of kin, as appropriate. It is anticipated that most interviews will be conducted at the subjects' homes. Field edit each questionnaire for completeness. Verify sample questions from 10% of all interviews to assure quality control.

(8) Obtain diagnostic materials, sera, and stored tissues from cancer cases and non-cases, as specified in an approved RP, from RERF repositories or by negotiation with other institutions such as universities, hospitals, or clinics, for pathological and/or laboratory analysis. Conduct such examinations and analyses pertaining to comparisons of cancer cases and suspected cancer cases in the LSS sample and in selected comparison populations.

(9) Abstract and record data required for each collaborative study conducted in connection with this statement of work. Provide the data to NCI in a format and on a storage medium that will facilitate easy transfer to NCI computer systems, and in sufficient detail to permit parallel analyses at NCI and RERF. The appropriate level of detail will be determined by mutual agreement between NCI and RERF on a study-by-study basis, in accordance with (1) the scientific requirements of the research, and (2) RERF policy restricting the transfer of individual dosimetry data.

ARTICLE 3. By no later than (a) September 29, 1993, (b) the end of each succeeding 12-month period, and (c) September 29, 1997, the Foundation shall submit to the Academy 25 copies of a report, that will describe the progress of work conducted during the period reported, projections for the following period, and problems encountered, if any. Such reports will be written in English.

Continued on next page

NCI-RERF studies (continued)

ARTICLE 4. Funds currently available and allotted to this Agreement total \$315,000 which is estimated will cover performance under this agreement from September 30, 1992 through September 29, 1993. The Foundation shall submit monthly financial reports which shall include a breakdown of expenditures in forms shown as attachments A, B and C. Reports are to be submitted not more often than 15 days after the end of the period covered by the report.

The Foundation shall maintain adequate books and records as provided in Act 35 of the Foundation's Act of Endowment. The Foundation agrees to make such books and records available for an audit which may be made during the period of this agreement either by the Academy or by an independent firm of auditors which is acceptable to the Academy.

ARTICLE 5. Expenditure of funds provided by this Agreement shall be made as appropriate for a juristic person in Japan and in accordance with the terms of this Agreement, as well as with policies and procedures approved by the Board of Directors of the Foundation. Notwithstanding the above, under the terms of the Academy's prime contract with the National Cancer Institute, this subcontract is subject to written authorization by the Government's Contracting Officer for those items as set forth below. The subcontractor agrees to enter into such further negotiations and execute such further instruments as may be necessary to effect such approval. Authorizations will be passed from the U.S. government via written approval from the Director, Office of Contracts and Grants, National Academy of Sciences. Unless authorized in writing, no expenditures shall be made for the following purposes:

- a. Acquisition, by purchase or lease, of any interest in real property;
- b. Special rearrangement or alteration of facilities;
- c. Purchase or lease of any item of general purpose office furniture or office equipment regardless of dollar value (General purpose equipment is defined as any items of personal property which are usable for purposes other than research, such as office equipment and furnishings, pocket calculators, etc.);
- d. Travel to attend scientific meetings
- e. Patient Care Costs.
- f. Capitalized non-expendable equipment (defined as having an acquisition cost of \$500 or more and a life expectancy of two years or more.
- g. Foreign Travel - Request for foreign travel must be submitted at least eight weeks in advance, and shall contain the following: (a) Meeting(s) and place(s) to be visited, with costs and dates; (b) names and titles of personnel to travel, their functions in the project; (c) contract purposes to be served by the travel; (d) how travel of the personnel will benefit and contribute to accomplishing the project; and (f) what additional

Continued on next page

NCI-RERF studies (continued)

functions may be performed by the travelers to accomplish other purposes of the contract and thus further benefit the project.

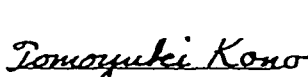
ARTICLE 6. This Agreement may be terminated for convenience in whole or in part, if both parties agree that the continuation of this Agreement will not produce beneficial results commensurate with the further expenditure of funds. Both parties shall agree upon termination conditions including the effective date, and in the case of partial termination, the portion to be terminated. The Agreement to terminate shall be set forth in a letter from the Academy to the Foundation. This Agreement also may be terminated for convenience unilaterally by the Academy if the prime contract under which this Agreement is issued should be terminated by the National Cancer Institute.

IN WITNESS WHEREOF, the parties have caused this Agreement to be signed and sealed, intending to be legally bound thereby.

NATIONAL ACADEMY OF SCIENCES

RADIATION EFFECTS RESEARCH FOUNDATION

Signature: 

Signature: 

Name: GARY E. DWOSKIN, Director
Office of Contracts and Grants

Name: Tomoyuki Kono

Title: _____

Title: Permanent Director
Chief of Secretariat

Date: DEC 09 1992

Date: 25 December 1992

Continued on next page

NCI-RERF studies (continued)

NATIONAL ACADEMY OF SCIENCES

AGREEMENT NO.: NCI-4896-93-001

AMENDMENT NO.: 1

Subcontract Parties: The Radiation Effects Research Foundation
and the National Academy of Sciences

Pursuant to the mutual agreement of both parties, Agreement No. NCI-4896-93-001 is amended as follows:

In Article 1:

(a) Delete the date "September 29, 1993" and substitute in lieu thereof the date "September 29, 1994".

In Article 4:

(a) Delete the amount "\$315,000" and substitute in lieu thereof the amount "\$615,191".

(b) Delete the date "September 29, 1993" and substitute in lieu thereof the date "September 29, 1994".

Except as modified herein, all terms and conditions of the agreement remain the same.

ACCEPTED FOR:

RADIATION EFFECTS RESEARCH
FOUNDATION

NATIONAL ACADEMY OF SCIENCES

Signature Tomoyuki Kono
Name Tomoyuki Kono

Signature Robert Kelley
Name Robert Kelley

Director &
Title Chief of Secretariat

Title Manager, Federal Contracts

Date 25 January 1994

Date JAN 12 1994

5. Hiroshima International Council for Health Care of the Radiation-exposed

Editor's note: Since HICARE's establishment on 1 April 1991, RERF Chairman Itsuzo Shigematsu has chaired this Hiroshima-based organization of institutions involved in international efforts to share knowledge of radiation-related research and health care. RERF staff support various HICARE activities, as deemed consistent with RERF's primary research goals. See pp 103-107 for activities related to HICARE. Following is an outline of HICARE's mission and programs, as extracted from a HICARE publication.

Purpose of HICARE

The Hiroshima International Council for Health Care of the Radiation-exposed (HICARE) was established to effectively make available, for the benefit of radiation-exposed populations in various parts of the world, the expertise that has accumulated in Hiroshima from the health care of A-bomb survivors and research on A-bomb radiation effects, and, by doing so, to contribute to the world and the promotion of international cooperation.

HICARE programs

Acceptance of trainees and dispatch of medical and other specialists

To provide the necessary health guidance, support, and information to medical and other personnel engaged in health care at radiation disaster areas throughout the world, the following programs will be implemented.

1. HICARE will coordinate the efforts of the institutions concerned in Hiroshima to respond to requests from abroad for acceptance of trainees and for dispatch of Japanese medical and other specialists.
2. HICARE will accept trainees and dispatch medical and other specialists in its own programs.
3. HICARE will accept trainees and dispatch medical and other specialists in cooperation with the national government, etc.

HICARE training courses

- a. Course on radiation dosimetry
 1. Physical dosimetry
 2. Biological dosimetry (chromosome aberrations and somatic cell mutation)Training period: 1-3 months
- b. Course on assessment of biological effects of radiation
 1. Cytogenetics
 2. Molecular biology
 3. Teratology

4. Oncology
Training period: 1-3 months
- c. Course on diagnosis of radiation disorders
General internal medicine and surgery, with special reference to hematology, thyroid gland, breast gland, respiratory organs, digestive organs, endocrinology and dermatology.
Training period: 1-3 months
- d. Course on epidemiological and statistical methods
Training period: 1-3 months
- e. Course on clinical laboratory techniques
 1. Image diagnosis (X-ray, computerized tomography, scintigraphy, ultrasonography)
 2. Hematology (peripheral blood tests, bone marrow aspiration and/or biopsy tests, blood biochemistry tests)
 3. Thyroid function (serological test, ^{131}I uptake test)
 4. Respiratory function (pulmonary function tests)Training period: 1 month
- f. Course on nursing techniques
 1. Acute diseases
 2. Chronic diseases
 3. Hematological disorders
 4. Pediatric diseases
 5. Intensive care unit
 6. Terminal careTraining period: 2 weeks
- g. Briefings at radiation-related institutions
Training period: 1 week

Preparation of a reference book on the health effects of the radiation-exposed

A HICARE publication, *Health Effects of A-bomb Radiation—1992*, which was prepared for medical and other relevant specialists, was translated into English. In addition, its abridged editions in Japanese and English were prepared.

Health Effects of A-bomb Radiation—1992 is a commentary book which may be called a "white paper on the effects of A-bomb radiation." It is hoped that the publication will contribute to the promotion of the health care of radiation-exposed persons as well as to the strengthening of international cooperation.

Educational projects to promote international cooperation in the health care of the radiation-exposed

To enhance the understanding of the residents of Hiroshima in regard to the importance and necessity of promoting international cooperation in the health care of the radiation-exposed, lectures, conferences, and other educational projects will be implemented.

Research projects

To ensure that the contributions made by Hiroshima will effectively assist the promotion of international health cooperation, the following issues will be investigated:

1. Functions of training facilities
2. Functions of an information center
3. Preparation of training curricula
4. Preparation of a reference book on the effects on health of the radiation-exposed

Participating institutions and organizations

- *Radiation Effects Research Foundation*
- *Hiroshima University Medical School*
- *Hiroshima University Medical School Hospital*
- *Hiroshima University Research Institute for Nuclear Medicine and Biology*
- *Hiroshima A-bomb Survivors' Welfare Center, Hiroshima Atomic Bomb Casualty Council*
- *Red Cross Hospital and A-bomb Survivors Hospital*

Inquiries should be directed to HICARE, c/o Atomic Bomb Victims' Affairs Division, Department of Health and Welfare, Hiroshima Prefectural Government, 10-52 Motomachi, Naka-ku, Hiroshima, 730 Japan.

Chronology of Events

1 April 1994-31 March 1995

Editor's note: Unless otherwise indicated, events listed were held at the Hiroshima Laboratory.

1994

- April**
- 8 Long Service Award ceremony, Nagasaki
 - 12 Executive Committee meeting
 - 12 Long Service Award ceremony
 - 26 Executive Committee meeting, Operating Committee meeting, staff liaison meeting
 - 28 Laboratory liaison meeting, Nagasaki
- May**
- 10 Executive Committee meeting
 - 11-12 Research audit
 - 13 Research audit, Nagasaki
 - 23 Research Protocol Review Committee meeting
 - 23 Meeting of research department chiefs and assistant department chiefs
 - 23-24 Meeting of Ministry of Health and Welfare (MHW) and US Department of Energy (DOE) representatives at the MHW and at the US Embassy in Tokyo
 - 25 Staff liaison meeting
 - 26 Executive Committee meeting, Operating Committee meeting
 - 26 Laboratory liaison meeting, Nagasaki
- June**
- 7 Executive Committee meeting
 - 13-15 21st meeting of RERF Scientific Council
 - 16 Meeting of MHW and DOE representatives
 - 22-24 28th meeting of the RERF Board of Directors
 - 27 Research Protocol Review Committee meeting
 - 27 Meeting of research department chiefs and assistant department chiefs
 - 28 Executive Committee meeting, Operating Committee meeting, staff liaison meeting
 - 28 Retirement ceremony for the first half of Fiscal Year 1994
 - 29 Retirement ceremony for the first half of Fiscal Year 1994, Nagasaki
 - 30 Laboratory liaison meeting, Nagasaki

- June**
- 30 11th exchange seminar among National Institute of Radiological Sciences, RERF and Research Institute for Nuclear Medicine and Biology
 - 30 Permanent Director and Chief of Secretariat Tomoyuki Kono resigned.
 - 30 Permanent Director and Chief of Research Seymour Abrahamson resigned.
- July**
- 1 Permanent Director Donald R Harkness appointed chief of research.
 - 1 Operations Administrator Yasukiyo Hirano appointed chief of Secretariat.
 - 11 Hiroshima Mayor Takashi Hiraoka visited DOE and NAS in Washington, DC, to request early relocation of RERF.
 - 12 Executive Committee meeting
 - 26 Executive Committee meeting, Operating Committee meeting, staff liaison meeting
 - 28 Research Protocol Review Committee meeting
 - 28 Meeting of research department chiefs and assistant department chiefs
 - 28 Laboratory liaison meeting, Nagasaki
- August**
- 5 The film "When the Wind Blows" was shown, and an essay about his A-bomb experiences written by Secretariat staff member Tadataka Kuribayashi was distributed in commemoration of the anniversary of the atomic bombing of Hiroshima.
 - 6 Chairman Itsuzo Shigematsu, Vice Chairman Mortimer L Mendelsohn, and Chief of Research Donald R Harkness attended Atomic Bomb Peace Memorial Ceremony.
 - 6 Chairman Itsuzo Shigematsu and Permanent Director Yutaka Hasegawa attended memorial ceremony held by the Hiroshima City Medical Association for its members and medical workers who fell victim to the atomic bombing.
 - 9 Permanent Director Yutaka Hasegawa and Chief of Administration Tadashi Nakaoka attended Nagasaki City Atomic Bomb Peace Memorial Ceremony.
 - 9 Department of Clinical Studies Assistant Chief Giichi Ota attended memorial ceremony sponsored by Nagasaki University School of Medicine.

- August**
- 9 The film "Records of Atomic Bombing in Nagasaki" shown at the Nagasaki Laboratory to commemorate the atomic bombing of Nagasaki.
 - 22 Research Protocol Review Committee meeting
 - 22 Meeting of research department chiefs and assistant department chiefs
 - 23 Executive Committee meeting, Operating Committee meeting, staff liaison meeting
 - 23 Chairman Itsuzo Shigematsu awarded the Timofeev Medal by the science committee of the Medical Radiological Research Center of the Russian Academy of Medical Sciences.
 - 29 Laboratory liaison meeting, Nagasaki
- September**
- 6 Executive Committee meeting
 - 21 Department of Epidemiology Chief Kiyohiko Mabuchi chaired the third research meeting of the National Association of Community-based Tumor Registries (Hiroshima Medical Association Hall).
 - 26 Research Protocol Review Committee meeting
 - 26 Meeting of research department chiefs and assistant department chiefs
 - 27 Executive Committee meeting, Operating Committee meeting, staff liaison meeting
 - 29 Laboratory liaison meeting, Nagasaki
- October**
- 5 A film on labor health shown as part of the 45th National Labor Health Week events.
 - 7-8 Meeting of MHW and DOE representatives, Honolulu
 - 12 Executive Committee meeting, Operating Committee meeting, staff liaison meeting
 - 13 Laboratory liaison meeting, Nagasaki
 - 25 Lecture on health as part of the 45th National Labor Health Week events
 - 29-30 Hiroshima and Nagasaki staff joint recreational overnight trip to Sujiyu Spa, Oita
- November**
- 1 Executive Committee meeting
 - 3 Vice Chairman Mortimer L Mendelsohn conferred the Third Order of the Sacred Treasure.
 - 7 Research Protocol Review Committee meeting

- November**
- 8 8th general meeting of ABCC-RERF former employees at Hiroshima Century City Hotel
 - 11 NAS President Bruce M Alberts visited the Hiroshima Laboratory and made a courtesy call on Hiroshima Mayor Takashi Hiraoka.
 - 22 Executive Committee meeting, Operating Committee meeting, staff liaison meeting
 - 24 Laboratory liaison meeting, Nagasaki
 - 24 Department of Epidemiologic Pathology Acting Chief Midori Soda attended Nagasaki University Medical School's Autopsy Memorial Service.
- December**
- 6 Executive Committee meeting.
 - 9 The A-bomb Survivors Relief Law was enacted. Article 40 of the law stipulates that financial support can be provided for the operation of RERF. In the supplementary resolution, it is also set forth that the government should endeavor to provide financial support for the operation and relocation of RERF. The A-bomb Survivors Relief Law will be put into effect on 1 July 1995.
 - 14 Executive Committee meeting, Operating Committee meeting, staff liaison meeting
 - 14 Retirement ceremony for the latter half of Fiscal Year 1994
 - 15 Retirement ceremony for the latter half of Fiscal Year 1994, Nagasaki
 - 22 Laboratory liaison meeting, Nagasaki
- 1995**
- January** 9-13 Chiefs of the departments of statistics, epidemiology, genetics and radiobiology attended the First International Symposium on the Late Effects of Chronic Radiation Exposure, Urals Research Center for Radiation Medicine, Chelyabinsk. An agreement was reached on the conduct of RERF-US National Cancer Institute-Chelyabinsk joint epidemiological study.
- 10 Executive Committee meeting
 - 17 NEC ACOS mainframe computer removed.
 - 23 Research Protocol Review Committee meeting
 - 23 NAS-RERF discussions
 - 24 Executive Committee meeting, Operating Committee meeting, staff liaison meeting
 - 26 Laboratory liaison meeting, Nagasaki

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- January** 27 Contributions for the relief of victims of the Great Hanshin Earthquake sent to the Hiroshima Prefectural Chapter of the Japanese Red Cross Society.
- 30-31 Meeting of MHW and DOE representatives
- February** 1 Meeting of MHW, DOE, NAS, and RERF representatives, US Embassy, Tokyo
- 7 Executive Committee meeting
- 20 Research Protocol Review Committee meeting
- 21 Executive Committee meeting, Operating Committee meeting, staff liaison meeting
- 23 Laboratory liaison meeting, Nagasaki
- March** 7 Executive Committee meeting
- 17 Fire drills as part of the spring fire-prevention campaign
- 24 Executive Committee meeting, Operating Committee meeting, staff liaison meeting
- 27 Laboratory liaison meeting, Nagasaki
- 28 DOE-RERF meeting
- 30 George B Darling, former director of ABCC, 1957-1972, died in Hamden, Connecticut.