放影研 RERF update
Radiation Effects Research Foundation News and Views
Hiroshima and Nagasaki, Japan
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RERF conducts research and studies—for peaceful purposes—on the medical effects of radiation on humans with a view toward contributing to the maintenance of the health and welfare of atomic-bomb survivors and to the enhancement of the health of all mankind.

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Editorial Policy

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

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The 37th Board of Directors Meeting

The 37th meeting of the Board of Directors was held at the National Academy of Sciences (NAS) in Washington, D.C., U.S.A. on June 19 and 20, 2002. Twenty-three people including directors, supervisors, and observers attended the meeting, and animated discussions took place concerning RERF management.

In his opening address, Dr. Burton G. Bennett said, "RERF's mission is to study radiation effects in A-bomb survivors. We hope to maintain the Foundation's scientific excellence and fulfill our social obligations in terms of the welfare of A-bomb survivors." The Board then approved the minutes of the previous Board meeting (36th, Hiroshima), and proceeded to report on the status of RERF. In the status report, Dr. Bennett used a slide presentation to introduce various aspects of the RERF research activities. Dr. Bennett expressed in the report his intention of continuing to work for the accomplishment of the following goals: to enhance congeniality and trust among all the staff, strengthen epidemiology, and restore a balance in the U.S.-Japanese management of RERF. A report on the health study of children of A-bomb survivors was presented by Dr. Senjun Taira, who explained the history of the expansion of sample size in the study. Dr. Taira stated that full-scale health examinations would start in July 2002.

In his report on the agreement on joint courses with Hiroshima University and results of applications for the Ministry of Education, Culture, Sports, Science and Technology (MEXT) Grant-in-Aid for Scientific Research, Dr. Eiichi Tahara noted the high standing accorded to research conducted at RERF. Other items of report included "present personnel status," "FY2001 salary revision," "FY2002 labor-management negotiations," and "international collaboration."

In the discussion of issues proposed by the members of the Board, Dr. Bennett suggested regarding the "directorship balance" that the previous number of permanent U.S. directors be restored. This issue is to be deliberated further by the governments of Japan and the U.S. In the area of "future planning," Dr. Tahara explained the results of each department's brainstorming sessions and further discussions at Future Planning Committee meetings. It was projected that the future plans would be developed and completed within two years. Concerning the issue of relocation of the Hiroshima Laboratory, Dr. Taira stated that relocation is an issue that RERF cannot avoid, and that he would like the issue, along with the future plans, to be considered.

Among the items for deliberation, a summary of "recommendations of the 29th meeting of the Scientific Council" was presented by Dr. Joe W. Gray. In the responses of RERF to the recommendations of the Scientific Council, Dr. Tahara said, "We appreciate the Scientific Council's recommendation that RERF must continue to broaden its research base beyond a strict focus on radiation effects, considering the importance of RERF as a joint institution supported by the U.S. and Japan. We will continue the brainstorming approach for the establishment of future plans." Following this, deliberations were carried out on the "FY2001 research activities report and audit," "FY2001 settlement of accounts and audit," "FY2002 working budget," and "FY2003 provisional budget plan," and all of the items were approved by the Board of Directors.

As regards the "election/appointment of directors and others," it was concluded that Mr. Kazuaki Arichi and Dr. Jonathan M. Samet would continue to serve as directors until successors are decided. Concerning Scientific Councilors, Dr. Toshitada Takahashi, Director of the Aichi Cancer Center Research Institute, and Dr. Joel S. Bedford, Professor of Colorado State University, were elected as successors to Dr. Shinichiro Ushigome and Dr. Joe W. Gray, respectively. It was decided that the next Board meeting would be held at the Hiroshima Laboratory on June 18–20, 2003.

List of Participants

Permanent Directors:
Burton G. Bennett, Chairman
Senjun Taira, Vice Chairman
Eiichi Tahara, Permanent Director and Chief of Research

Visiting Directors:
Kazuaki Arichi, Councilor, Japan Institute of International Affairs (submitted a letter of attorney for both days)
Takefumi Kondo, Professor, Department of Preventive Medicine and Public Health, Keio University School of Medicine
Hiromichi Matsudaira, Consultant, Radiation Effects Association
John E. Burris, President, Beloit College
Jonathan M. Samet, Professor and Chairman, Department of Epidemiology, School of Hygiene and

Public Health, Johns Hopkins University (submitted a letter of attorney for the 1st day)
Richard B. Setlow, Senior Biophysicist, Biology Department, Brookhaven National Laboratory, Adjunct Professor, Biochemistry and Cell Biology Department, State University of New York at Stony Brook

Supervisors:
Tomio Hirohata, Professor Emeritus, Department of Public Health, Faculty of Medicine, Kyushu University
David Williams, Senior Financial Advisor, National Academy of Sciences (NAS)

Scientific Councilor:
Joe W. Gray, Professor of Laboratory Medicine and Radiation Oncology, Program Leader, Cancer Genetics and Breast Oncology, Comprehensive Cancer Center, University of California, San Francisco

Representatives of Supporting Agencies:
Shigeki Shiiba, Deputy Director, General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare
Steven V. Cary, Deputy Assistant Secretary for Health Studies, U.S. Department of Energy (DOE)
Joseph F. Weiss, Japan Program Manager, Office of Health Studies, DOE
Libby White, Office of Health Studies, DOE
Warren R. Muir, Executive Director, Division on Earth and Life Studies, National Research Council (NRC), NAS
Evan B. Douple, Director, Board on Radiation Effects Research, Division on Earth and Life Studies, NRC, NAS
Catherine S. Berkley, Administrative Associate, Board on Radiation Effects Research, Division on Earth and Life Studies, NRC, NAS

Secretariat:
Charles A. Waldren, Chief Scientist
Masaharu Yoshikawa, Chief of Secretariat
Richard D. Sperry, Administrative Advisor, Secretariat

Observer:
Seymour Abrahamson, former RERF Vice Chairman and Chief of Research

The 29th Meeting of RERF Scientific Council

The 29th meeting of the Scientific Council was held on April 16–18, 2002, in Hiroshima. The meeting was co-chaired by Drs. Joe W. Gray and Yasuhito Sasaki. After RERF Chairman Dr. Burton G. Bennett extended greetings and introductory remarks, Chief of Research Dr. Eiichi Tahara presented a general report of RERF research. Dr. Tahara also presented a report of the Future Planning Committee of the RERF based on internal brain-storming sessions among department members and chiefs of the departments throughout the past year, listing several possibilities that were suggested as future directions. Dr. Tahara further proposed a set of policies on the use of biological samples developed by the Working Group on Ethical Policy for Biological Samples, based on recently established ethical guidelines set forth by the Japanese government for the protection of human rights and privacy of study participants. Present status and trends in the U.S. were introduced by American councilors.

Drs. Gen Suzuki and Masazumi Akahoshi presented a response to the Multinational Peer Review of the Departments of Clinical Studies. Presentations were then made by all departments. In addition to overviews given by department chiefs, the following more specific presentations were made:

- Adult Health Study (AHS) Report 8 (Michiko Yamada, Clinical Studies)
- Cataract study (Kazuo Neriishi, Clinical Studies)
- Thyroid disorders (Misa Imaizumi, Clinical Studies, Nagasaki)
- Microarray-based comparative genomic hybridization (CGH) (Norio Takahashi, Genetics)
- Epilation, chromosome aberrations, and dose bias (Yoshiaki Kodama, Genetics)
- Clonal chromosome aberrations (Nori Nakamura, Genetics)
- Cancer and noncancer mortality (Yukiko Shimizu, Epidemiology)
- F_1 mail survey (Akihiko Suyama, Epidemiology, Nagasaki)
- Projections regarding Life Span Study (LSS)/F_1 cohorts (Eric Grant, Epidemiology)
- Plan for molecular epidemiology (Hidetaka Eguchi, Epidemiology)
- Molecular basis of A-bomb induced carcinogenesis (Yuko Hirai, James Cao, Kiyohiro Hamatani, Radiobiology)
- T-cell homeostasis (Seishi Kyoizumi, Radiobiology)
- LSS cancer incidence (Dale Preston, Statistics)
- Describing and interpreting radiation effects (Donald Pierce, Statistics)

- Probability of radiation causation (John Cologne, Statistics)
- F_1 cancer and noncancer mortality (Shizue Izumi, Statistics)
- Dosimetry revision status (Shoichiro Fujita, Statistics)

The Scientific Council affirmed continued support for the core mission of RERF, but also supported expansion of this core mission in a manner based on thorough evaluation of research priorities, funding bases, and resources. The Council's general recommendations are summarized as follows:

Long term planning. The Council encourages continued departmental brainstorming on future plans, and supports the idea that RERF must broaden its research base beyond a strict focus on radiation effects. In this, continuation of RERF as a joint U.S.-Japanese effort is important. RERF is encouraged to obtain blood, serum, and tumor samples from as many LSS and F_1 members as possible, including those who have moved away. Collection should more involve representatives of local physicians and research communities. Patients should be asked for consent to use of specimens in international collaborations. The Council supports development of international and private sector collaborations. Increased involvement should be achieved with organizations representing LSS and F_1 cohorts in the development of strategic plans and molecular epidemiology studies. Efforts should be made to increase the value to cohort members of the RERF studies, in order to encourage their maximal participation. The public should be better shown that RERF work is the foundation of international radiation protection, and that refinements will come from future work. The policy on intellectual property should be reconsidered and revised to encourage collaborations with academia and the private sector.

Cohort and tissue resources. As the cohort and specimens are unique and highly valuable for research, every effort should be made to maintain the cohorts and increase the number of subjects contributing specimens. Further effort should be made to increase the F_1 study with persons whose parents were exposed to high doses, even though not living locally. A better system of prioritization and protection of specimens is needed. Production of microarrays is recommended, and immortalization of nucleic acids should be attempted.

Collaboration. Collaboration is needed both to promote high-quality work and improve the reputation of RERF in Japan. Special efforts should be made to collaborate with organizations having advanced analytical capabilities. Policies for collaboration and sharing of biosamples should be reviewed. International and private sector collaborations should be developed. Involvement in Millenium Project should be evaluated.

Organizational and management issues. Online journal access should be enhanced. External peer review is needed for projects involving highly technical methods. Scientific and fiscal policies are needed for external grants. MEXT (Ministry of Education, Culture, Sports, Science and Technology) proposals using RERF facilities should only be for projects relevant to the broadly defined mission of RERF. There needs to be more rapid review for clinical RPs, and renewal reviews should be made every 1–3 years. More publication in high-impact journals is needed. The Department of Clinical Studies should become more involved in cancer studies, integrating with the Epidemiology Department. There should be increased support for IT activities. Investigators are encouraged to seek statistical advice during study design, and to take advantage of pilot studies. The Council supports annual alternation of regular meeting and departmental/program peer review.

Extensive evaluations and recommendations were also made for each research department.

Members of the Scientific Council

Takefumi Kondo, Professor, Department of Preventive Medicine and Public Health, Keio University School of Medicine

Yusuke Nakamura, Director, Human Genome Center, Institute of Medical Science, University of Tokyo (Absent)

Ohtsura Niwa, Director and Professor, Radiation Biology Center, Kyoto University

Yasuhito Sasaki, President, National Institute of Radiological Sciences

Shinichiro Ushigome, Visiting Professor, Jikei University School of Medicine (Absent)

J. Martin Brown, Professor and Division Chairman, Division of Radiation Biology, Department of Radiation Oncology, Stanford University School of Medicine (Absent)

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

Gloria M. Petersen, Professor of Clinical Epidemiology, Mayo Medical School

Theodore L. Phillips, Professor and Chairman, Radiation Oncology, Cancer Center, School of Medicine, University of California, San Francisco

Clarice R. Weinberg, Chief, Biostatistics Branch, Environmental Diseases and Medicine Program, National Institute of Environmental Health Sciences

Staff News

Dr. Kazunori Kodama, formerly RERF Chief of Clinical Studies, rejoined RERF in July 2002 as Chief of Epidemiology. During his time away from RERF he was Professor, Institute of Health Sciences, Hiroshima University. Drs. Shuhei Nakanishi and Nobuaki Hattori joined the Department of Clinical Studies in April 2002. Dr. Nakanishi was before that a medical student at Hiroshima University and Dr. Hattori comes from the Gastroenterology Department of Oda Municipal Hospital, Shimane Prefecture. Also in April 2002 Dr. Masataka Taga joined the Department of Radiobiology, following his position as Lecturer, Kyoto University Radiation Biology Center. Dr. Asao Noda joined the Department of Genetics in September 2002, having been Lecturer, Department of Molecular and Cellular Biology, Kobe University.

Dr. Kei Nakachi moved in July 2002 from being RERF Chief of Epidemiology to Chief of the Department of Radiobiology/Molecular Epidemiology. Dr. Donald MacPhee vacated the position as Chief of Radiobiology due to mandatory retirement age, and continues at RERF as Research Advisor. Drs. Kazue Imai and Hidetaka Eguchi, of Dr. Nakachi's molecular epidemiology research group, followed him in that departmental change. Dr. Fumiyoshi Kasagi moved in August 2002 from the RERF Department of Statistics to the Department of Epidemiology.

Current Status of the New Study of Children of A-Bomb Survivors

A mail survey and clinical study of the RERF F_1 cohort was initiated in recent years; some information was provided in the Spring-Summer 2001 issue of *Update*. This is a major RERF program to supplement studies of this cohort when they were children, and the continuing surveillance of their mortality and cancer incidence. Study design resulted in a mail survey cohort to obtain lifestyle information, with the clinical study comprising those respondents expressing interest in participating. A primary aim of the clinical study is to ascertain any excess risk for multifactorial diseases such as hypertension, diabetes, and cardiovascular diseases as this cohort reaches middle age.

A primary aspect of progress in the past two years has been to expand the size of the initially selected mail survey and clinical study cohorts. The main point of this was to further include those for whom one parent has a positive dose estimate but there is no RERF information on the other parent (which very likely means they were unexposed). This resulted in adding 6,600 persons to the original mail survey cohort of about 18,000. Notably, the number of persons for whom at least one parent had a dose of 5–500 mSv was thereby doubled, and the corresponding number for dose >500 mSv was increased by 50%.

Exceptional care is being taken to carry out this study in a scientifically and ethically most appropriate manner, and to assure the public and F_1 population that this is being done. During 2000–2003 there were seven meetings of the Scientific Committee and six meetings of the Ethics Committee, both of these being external committees established for this study. Separate informed consent procedures were established for the clinical examination and for preservation of serum plasma, urine, and blood cells for future molecular biology studies. A pilot clinical study of 500 persons was conducted in 2002, and the full-scale clinical study began in July 2002. Approximately 10,000 F_1 cohort members are expected to participate in the clinical study over a four-year period. This is about 60% of those successfully contacted in the mail survey.

The success of this study will not hinge on whether a statistically significant radiation effect for multifactorial diseases is found. The purpose is to *estimate* whatever risk there may be, and in the initial planning of the study it was determined that the precision of such an estimate will be high enough for the study to be scientifically useful. Upper confidence limits on the true risk will be important whether or not there is found a statistically significant effect.

Current Status of Dosimetry Revision

Previous issues of *RERF Update* have reported progress towards a revised RERF dosimetry system. The new system DS02 to replace DS86 was given final approval on 15 March 2003 by the Joint U.S.-Japanese Senior Review Group, chaired by Dr. Warren Sinclair and Dr. Wataru Mori. The Final Report is essentially finished in draft form, and RERF is starting to prepare the publication of it.

As with previous systems, the implementation of DS02 to compute dose estimates for survivors in RERF cohorts is a subsequent project, which we expect to complete by about the end of May 2003. Presently, the efforts in that project involve moving from the free-in-air kerma estimates for each survivor, which have now been computed, to calculation of shielding from terrain and structures and then computation of organ doses.

An article by Drs. Harry M. Cullings and Shoichiro Fujita in this issue of *RERF Update* provides insight into the history leading up to the project, basic considerations during the development of the new system, and indications of the changes in free-in-air kerma for gamma-rays and neutrons in each city. Subsequent publications in the scientific literature and in *RERF Update* will document the changes in shielded kerma, organ doses, and risk estimates for cancer and other effects.

Following is a news release prepared by the Senior Review Group, and the impressive list of scientists involved in the dosimetry review and revision project.

A major reassessment of the system used at the Radiation Effects Research Foundation (RERF), Japan to determine radiation doses for atomic-bomb survivors has resolved the long-standing problems with the system that has been in place since 1986, and has defined the parameters for a replacement dosimetry system for survivor dose calculation. Over the past two years, a Joint U.S.-Japan Working Group, chaired by Dr. Robert Young and Dr. Hiromi Hasai, has undertaken a comprehensive evaluation of the calculations that comprise the RERF dosimetry system and the measurements that are used to verify these calculations. At a meeting in Tokyo on March 14–15, 2003, a Joint U.S.-Japanese Senior Review Group, chaired by Dr. Warren Sinclair and Dr. Wataru Mori, approved DS02 (Dosimetry System 2002), which was developed by the Joint Working Group.

The dosimetry reassessment was mandated and supported by the U.S. Department of Energy (DOE) and the Japanese Ministry of Health, Labour and Welfare (MHLW), which are jointly responsible for the RERF, in an effort to resolve the apparent discrepancy between neutron activation calculated by the existing DS86 system and as measured in material exposed to neutrons at the time of the bombing. During the course of this reassessment, the working groups, with members and associates from American, German, and Japanese universities and national laboratories, have recomputed all aspects of the Hiroshima and Nagasaki radiation calculations, made new fast-neutron and low-background thermal-neutron measurements, upgraded the calculation of the radiation shielding provided by terrain and large buildings, and conducted a comprehensive reassessment of all radiation measurements in activated material. The new calculations produced during this reassessment agree with both gamma and neutron measurements out to distances from the detonations at which sample measurements become indistinguishable from background, effectively resolving the long-standing neutron dose discrepancy. The calculations that produce this agreement are the basis for the new RERF dosimetry system, DS02.

The RERF is supported by the DOE Office of Health Studies (Environment, Safety and Health; EH-6) and the dosimetry reassessment effort in the U.S. was funded both by the DOE Office Biological and Environmental Research (SC-72) and EH-6. The current reassessment was made possible largely by the development of techniques such as accelerator mass spectrometry for the measurement of trace-amounts of neutron activation remaining from 1945, and by the availability of massively-parallel computing capacity that permits three-dimensional calculation of a problem as vast and complex as an atomic detonation.

The new calculations and measurements produced during this reassessment have confirmed the yield and epicenter for the Nagasaki detonation while refining both these values for Hiroshima. Current measurements and calculations confirm a 21-kiloton-yield for the Nagasaki bomb and a burst point to within 2 meters of previous assessments. In Hiroshima, the estimated yield has been increased from 15 kilotons to 16 kilotons and the epicenter has been repositioned 20 meters higher and 15 meters to the west. While supercomputing technology made recalculation of the nuclear explosions possible, application of current geographic information systems

technology has reconciled the exact hypocenter locations on new, more accurate maps with World War II vintage maps. The new dosimetry system will be implemented at RERF as quickly as possible. Although significant changes in risk estimates are not expected, the improved calculation and refined shielding considerations should reduce the uncertainties and provide much confidence in the validity of risk assessments.

Joint Senior Review Group:

Warren K. Sinclair, President Emeritus, National Council on Radiation Protection
Harold L. Beck, Environmental Measurements Laboratory (retired)
Richard E. Faw, Kansas State University (retired)
Nolan E. Hertel, Professor, Georgia Institute of Technology
Wataru Mori, President, Japanese Association of Medical Sciences
Tatsuji Hamada, Consultant, Japan Radioisotope Association
Hiromi Hasai, President, Hiroshima International Gakuin University
Ohtsura Niwa, Director, Kyoto University Radiobiology Center

Joint Working Group:

Robert W. Young, Defense Nuclear Agency (retired)
George D. Kerr, Oak Ridge National Laboratory (retired)
Robert F. Christy, President Emeritus, California Institute of Technology
Harry M. Cullings, Radiation Effects Research Foundation
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Alexandra R. Heath, Los Alamos National Laboratory
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Masaharu Hoshi, Hiroshima University
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Yutaka Okumura, Nagasaki University
Tokushi Shibata, High Energy Accelerator Research Organization
Kiyoshi Shizuma, Hiroshima University

Contributing Associates:

Joe V. Pace, John M. Barnes, Yousry Y. Azmy, Charles O. Slater, Richard A. Lillie, Oak Ridge National Laboratory
Alfredo A. Marchetti, Jeffrey E. McAninch, Lawrence Livermore National Laboratory
James A. Roberts, Science Applications International Corporation
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Satoru Endo, Hiroshima University
Tetsuji Imanaka, Seiichi Shibata, Kyoto University
Kazuo Iwatani, Kazuo Kato, Hiroshima Prefectural College of Health Sciences
Kazuhisa Komura, Takashi Nakanishi, Kanazawa University

Ten Thousand Days Atop Hijiyama

Part 2. Genetics Program

Akio Awa

1. Introduction

In 1927, Dr. H. J. Muller devised a way to detect mutations in germ cells of Drosophila (fruit flies), and demonstrated that ionizing radiation can induce such heritable mutations.[1] Subsequently, many scientists performed radiation experiments using various animals and plants, confirming Dr. Muller's findings. For this achievement, Dr. Muller was awarded in 1946 the Nobel Prize in Physiology and Medicine.

As evident from the above, research for elucidating the genetic effects of A-bomb radiation has become an increasingly important scientific project of our institution. Thus the genetics project was launched in early days of the Atomic Bomb Casualty Commission (ABCC) and has been continued to date at the Radiation Effects Research Foundation (RERF). Before describing our F_1 cytogenetics project, I will briefly describe below an outline of the early genetics programs at ABCC, i.e., the "Untoward Pregnancy Outcome Study" started in 1948 and "Mortality Study" in 1958.

A. Untoward Pregnancy Outcome Study—Malformations and Other Abnormalities at Birth

In 1948, Dr. James V. Neel, an internationally-known human geneticist who served as Acting Director of ABCC at the time of its inception, initiated a large-scale study of genetic effects of atomic radiation in cooperation with Dr. William J. Schull, and many U.S. and Japanese collaborators.[2] The objective of this study, that enrolled about 80,000 newborn babies, was to scrutinize from epidemiological and statistical point of view a variety of genetic endpoints, such as congenital malformations among newborns and stillbirth, and neonatal mortality rate. Medical check-ups were also performed nine months after birth to determine whether there were any abnormalities that had been either overlooked or not yet manifested at the time of physical examinations at birth.

Dr. James V. Neel [taken in 1983]

Because of a shortage of food immediately after World War II, pregnant women who registered their pregnancy at a public office were granted the privilege of having an increased ration of rice. Therefore, almost all women who were in the fifth month of pregnancy would be officially registered. This made it possible to accurately confirm the state of pregnancy. Based on this pregnancy registration, pregnant women were interviewed by the ABCC field workers regarding whether they and their spouses were exposed to A-bomb radiation. For the exposed, their distance from the hypocenter and shielding status were verified and documented.

In those days, most women in Japan delivered babies at home. It is worth strongly emphasizing that the midwives in Hiroshima and Nagasaki had played a very important role in this study.

Since there was no system for estimating radiation doses for A-bomb survivors, newborns were divided into 25 categories, five for mothers and five for fathers on the basis of their parental exposure status (distance from the hypocenter, presence or absence of shielding, etc.). Comparisons were made of the rates of malformations, stillbirth, and mortality at birth. The study was finished in 1954. As shown in the literature cited at the end of this report,[2,3] the amount of research findings was enormous and extensive. Their findings indicated that no statistical evidence of relationship with parental exposure was observed for any of the genetic markers under study.

In parallel with this investigation, the sex ratio of the children of A-bomb survivors was also studied. In the general human population, males and females are born with an equal probability. It was theoretically anticipated that the parental radiation exposure would result in a change of the sex ratio of the offspring. Although there was some expectation of a decrease of females born to exposed fathers and a decrease of males born to exposed mothers, statistical analyses of the actual findings failed to support this hypothesis.

B. Mortality Study

In 1958, Kato *et al.*[4] initiated, through the Koseki surveys, a study of the mortality of the children of A-bomb survivors. Using the F_1 cohort of A-bomb survivors who were registered in the Neel study, the

Mortality Study population was newly founded. The number of deaths and the causes of death among the F_1 children were ascertained through the Koseki checks, and comparisons of death rates were made between the exposed and control (both non-exposed and distally exposed) groups.

This study, covering about 54,000 children, also failed to demonstrate evidence of genetic effects of parental radiation exposure.[5,6] It also failed to verify any increase in the mortality rate due to congenital childhood cancer in the exposed group.[7] A follow-up mortality study has been continued to date, by expanding the sample size of up to 80,000 F_1 children.

As mentioned above, none of the early genetic study series provided any positive evidence of the genetic effects of A-bomb radiation. The results of the past genetic studies at ABCC seem in conflict with those of studies performed by Muller and his followers using various animals and plants. In particular, the mutation studies of Russell *et al*,[8] conducted in the 1950's using tens of thousands of irradiated mice at Oak Ridge National Laboratory, were not in line with the human studies at ABCC. If genetic effects of radiation in various animals and plants are real, why did the ABCC studies fail to prove the increased mutation rates in the human population? This problem has not been resolved as yet, and it still remains an important issue to be investigated.

2. F_1 Cytogenetics Study: 1967–1984

A. Initial Studies: 1967–1968

The purpose of the chromosome study, termed F_1 cytogenetics, was to evaluate genetic effects of A-bomb radiation on humans using the then novel technique of chromosome analysis. More specifically, this study was designed to answer the question of whether parental exposure to A-bomb radiation would increase the frequency of children carrying radiation-induced chromosome aberrations. In other words, if the chromosome aberrations were produced *de novo* in the germ-line cells of the exposed parents (both sperm in the male and ova in the female), then the increased genetic risk with radiation-related chromosome aberrations would be anticipated among the offspring of survivors. As already described in Part 1, there are two types of chromosome aberrations, (i) abnormalities of chromosome number (aneuploidy), and (ii) structural aberrations of chromosomes, as represented by reciprocal translocations. The former type of chromosome aberrations are in general characterized by phenotypic abnormalities of varying degree of severity. Down's syndrome, featured by the presence of an extra chromosome 21, is a typical example of this category. Structural chromosome aberrations were considered as the most suitable marker for the evaluation of genetic effects of ionizing radiation.

The structural rearrangements of chromosomes are further classified into two groups; one where there is no loss or gain of chromosome material (genetically balanced rearrangements), and the other being associated with either loss or gain of parts of certain chromosomes (genetically unbalanced rearrangements). The carriers of the former aberrations look superficially normal. In other words, the carrier's phenotype is normal, though his (or her) genotype is abnormal. Carriers of reciprocal translocations are found to predominate in this category of aberrations, so that they are often called "translocation heterozygotes." In contrast, the latter type of unbalanced rearrangements would result in the serious phenotypic impairments of the carrier, often leading to death.

The proportion of persons having translocation heterozygotes in the general human population is estimated to be about 1 in 1,000. This rate does not seem to be influenced by racial or ethnic differences. Family studies have confirmed that about 80% of the translocation heterozygotes are inherited from either one of the carrier parents. The remaining one-fifth of the translocation heterozygote children was found to born to genetically normal parents due to a *de novo* mutation produced in germ-line cells in either of the parent.[9]

In our proposal, we adopted use of the frequency of translocation heterozygotes as an indicator of the genetic effects. If the increased rate of the translocation carriers is statistically significant in the exposed group as compared with the controls, then we can deduce that the increase would be ascribed to the exposure of the parents to atomic radiation. When these chromosome aberrations are detected in the children of A-bomb survivors, their parents as well as siblings must be investigated to determine the origin of the aberrations.

In the early spring of 1967, we prepared a pilot study project.[10] The study subjects were chosen from the children born to exposed women enrolled in the Fertility Study population.[11] The samples were further divided into four groups: children born before the atomic bombing (Group I), children whose mother was exposed to the bomb (Group II), children whose father was exposed (Group III), and children whose parents were both exposed (Group IV). Group I constituted as a comparison group, while Groups II–IV were the exposed. Our proposal was submitted and approved immediately by ABCC.

A pilot study started in the spring of 1967, and was completed in the fall of the same year. Somatic chromosomes analysis was performed on a total of 185 individuals in Hiroshima and Nagasaki, comprising 128 in the exposed group (born between 1946 and 1963), and 57 controls (born from 1940 through 1946). There was no instance of children with in-

born chromosome error, except for one case in the exposed group showing a sex chromosome mosaicism of 45, X / 47, XXX. Because of the small sample size, no proof of genetic effects was attained.[12]

B. Extended Study: 1969–1984

In 1968, we again started planning a full-scale F_1 cytogenetics study in cooperation with the Statistics Department staff. Study subjects under study were selected on the basis of the F_1 Mortality Study of Kato *et al*.[4] Advantages in use of this population were two-fold; (i) exposed categories are well defined, and (ii) dosimetry (T65D) information was available for some parents. After exclusion of deceased cases (about 5%) and individuals having moved away from Hiroshima and Nagasaki (35%), about 22,000 children born after 1 May 1946 were found to be eligible for study. All of these were found to reside in the two cities, whom ABCC staff members could easily contact. Young students and others who temporarily moved away from their parents' address were contacted during summer or winter school vacations. Those who lived separately from their parents because of marriage or other reasons but who lived within the cities were also included in the population. About a half of the 22,000 individuals were born to parents either one or both of whom had been exposed to the bomb within 2 km from the hypocenter, with T65D estimated dose of 1 rad or more. The remaining children were born to either non-exposed or distally exposed parents, with estimated dose of less than 0.5 rad, serving as a comparison group for the exposed.

There were some social and ethical problems we had to resolve prior to the realization of the project. The most serious issue was the dark image of words "hereditary diseases." In those days, there was a tendency to discriminate against people afflicted with such diseases and to segregate them from the society. Under these circumstances, the words "heredity" and "hereditary diseases" were taboos. Some of the human geneticists were skeptical as to whether the general public could correctly understand the meaning of the words "hereditary disease." In order to obtain agreement to our research, we decided to visit the homes of the study participants, and to fully explain them and the parents (or close relatives) the purpose of our research. Prior to the initiation of the work, it was absolutely necessary to reach mutual understandings between the examinees (study participants) and examiners (ABCC), and to obtain their cooperation. This was indeed a key to a success of our study.

Today, genetic knowledge has been widely disseminated among the public, though in a limited way, and genetic counseling provided by certified physicians or experts in human genetics has become a routine procedure. However, about 30 years ago, physicians who specialized in human genetics were rare in Japan. In addition, there were neither adequate guidelines nor manuals available for genetic counseling. Since none of us in ABCC were physicians, we needed help from experts in the Japanese Society of Human Genetics regarding this issue. Prior to the initiation of our project, we were able to obtain a great deal of knowledge on genetic counseling from the Society members. It should be noted here that we received a remarkable support from Dr. Koso Ohama, a staff member of the Department of Obstetrics and Gynecology at Hiroshima University School of Medicine, in establishing measures to carefully take when hereditary diseases were detected.

The cytogenetics study was thus launched with all involved being determined to walk a tightrope, coping with difficult problems we had never encountered before. As a first step, public health nurses and medical social workers at the Clinical Contacting Section of the Department of Medical Sociology (currently belonging to the Department of Clinical Studies) visited homes of the participants and their parents. They explained our genetics study in easy terms. When understanding was either unavailable or a more detailed explanation was requested by them, I visited their home accompanying a social worker in charge, and gave them further detailed explanations. Some of the participants hesitated about participating in our study. In this case, we were cautious not to forcibly persuade them to participate, and always followed their own judgment.

Our public health nurses, Mss. Chie Yanagawa, Miyoko Kamisako, and Midori Kamouchi, willingly committed to this program and worked very hard, helping our study to become a great success. I now can imagine how difficult it must have been for these members to perform all their duties without any previous experience. Mr. Kanjuro Hidada (former Administrative Assistant Chief of the Department of Clinical Studies) and other staff of the Clinical Contacting Section took a heavy burden of contacting the participants by home visit. The staff in the Medical Records and Coding Section of the Statistics Department (currently in the Department of Clinical Studies) provided great help with necessary backup support. We owe a debt of gratitude to these people for the smooth operation of our study. Although belatedly, I would like to express my sincere appreciation to those involved.

The citizens of Hiroshima and Nagasaki became increasingly interested in our study through coverage by the mass media. As I well knew, many of the A-bomb survivors seemed to have concerns about genetic effects of radiation in their offspring. They were also anxious about the genetics study itself. Those who opposed the study were much concerned about the possible consequences of genetic effects of radiation among the children of A-bomb survivors. None of us had any idea about what to do if any evi-

dence of genetic effects was demonstrated. For this reason, some people did not want to conduct the study. Those who supported the study wished that any genetic problems should be scientifically clarified and settled the issue as soon as possible. Two opposite opinions seemed to be well represented in the results of a large-scale public opinion poll carried out in the Chugoku Shimbun on July 31, 1972.[13]

In those days, more than 20 years had already elapsed after the atomic bombings. As the children of A-bomb survivors became older, they began moving out from Hiroshima and Nagasaki to other megalopolitan areas such as Kanto and Kansai districts. The major reasons for this move were (i) to receive better education, and (ii) to get much better job opportunities. This tendency irritated me a great deal. I believed that, as time goes by, the chance of conducting genetic studies would become smaller and smaller. It occurred to me that early 1970's would be the last opportunity for us to conduct a large-scale genetics survey.

In the course of cytogenetic study, I was deeply indebted to Dr. Hiroshi Maki, then Associate Director of ABCC (who passed away on October 23, 1998), in the realization of the genetics study. Caught between the one-sided claim of mine and the generally difficult situation that ABCC faced at that time, Dr. Maki must have worried greatly. I feel sorry for Dr. Maki now, and continue to respect him and appreciate his efforts toward this study.

For some five years from the spring of 1969 to 1974, about 4,000 cases in two cities, about 2,300 in Hiroshima (60%), and about 1,700 (40%) in Nagasaki, could be examined cytogenetically. This amounted to 720 individuals per year. This meant that the medical social workers would have met participants of approximately 3,400 in Hiroshima and 2,300 in Nagasaki in this period.

In the fall of 1974, our study was temporarily suspended. This was due in part to introduction of a new research project proposed by Dr. James V. Neel, the details of which are described in the later section of this article. In short, the existing organizational structure for routine working procedures was inadequate for the realization of a new project. It was thus urgently needed to establish a new internal structure in the ABCC. After several months of lengthy discussions by the ABCC managerial staff concerned, we could somehow settle this difficult task by sharing new working loads among all department members. Thus we were able to resume the cytogenetics survey in the summer of 1975.

The F_1 Cytogenetics Study was terminated in the fall of 1984, 15 years after its initiation. A total of 16,298 individuals in both cities, 9,828 in Hiroshima and 6,470 in Nagasaki, were cytogenetically scrutinized. Data analysis of our results was postponed until the new dosimetry reassessment system (DS86) was finalized. Even under the DS86 system, however, radiation-dose-related analyses were difficult because of the paucity of dose information with regard to parental reproductive organ doses, which remains until now unavailable for some of the parents of F_1 children.

Of the 16,298 individuals whose chromosomes were studied, autosomal structural aberrations were ascertained in 23 out of 8,322 individuals of the exposed group, and in 27 of 7,976 in the comparison group. Sex chromosome aberrations identified included 19 individuals in the exposed group and 24 in the comparison group. Thus no statistically significant difference was obtained between the proximally and distally exposed groups in terms of the frequencies of carriers having structurally rearranged chromosomes, or in terms of chromosome aneuploidy. Although the frequencies of these aberrations were lower in the exposed group than in the comparison group, no statistical significance was demonstrable between the exposed and control groups.[14]

Mention must be made that the participation rate of this study was unexpectedly high, being 74% throughout this study; 70% in Hiroshima and nearly 80% in Nagasaki. In both cities, the participation rate was slightly higher in the proximally exposed group than the distally exposed group. Among those who visited ABCC-RERF, many wanted to be given a more detailed explanation. Although my memory is now vague and inaccurate, during the entire study period I interviewed at least several hundred participants in Hiroshima at the time of their visit to our institute. This gives an idea of how the children of the exposed people positively participated in the genetics program, and how deep was their concern about their health problems.

I would like to close this chapter by citing part of the acknowledgements described in our F_1 paper [14] as follows:

"We are grateful to the Hiroshima and Nagasaki citizens for their willingness to voluntarily participate in this survey. Without their cooperation this study would not have been possible."

3. Dr. Neel and Biochemical Genetics Study: 1971–1984

Dr. Neel visited Hiroshima in the fall of 1971, with a plan of initiating a new genetics study to be conducted at ABCC. That was the time when a new technology of electrophoresis had become practically available for protein (and enzyme) analysis. Proteins that are the end-points of the gene products show differing electric charges. When a gene mutates, it may, or may not, induce an alteration of electric

charges of the same protein. Thus this method was thought useful to detect some forms of the protein variants by identifying the electric charges that are deviated from the normal pattern. A small amount of serum or plasma in the blood is required for analysis. Aliquots of sample are placed in starch gel arrays. When electric current is applied to the gel, proteins move along within the arrays. Depending on the electric charges, proteins would stop at a specific array position. The gel is stained with dye to visualize the position of proteins, and thus the mobility of proteins under study is measured. If the position of a target protein deviates from expectation, the protein is considered as a variant or a mutant. This technique is also capable of measuring a large number of samples at a time. A drawback is of this technique is that mutated proteins are not necessarily associated with changes in the electric charges.

Dr. Neel, bringing this new technology with him, came to Japan with the intention of initiating a study at ABCC for clarifying the relationship between radiation dose and gene mutation frequency using this technique. As soon as Dr. Neel arrived in Hiroshima, he started working hard by attending various meetings, to make briefings and discuss the feasibility of new electrophoretic technique with those concerned in and outside ABCC. He also worked energetically to make the general public aware of his project through the mass media. All the events and happenings in those days were described in detail in his book.[15]

ABCC had, since its inception, always received criticisms from A-bomb survivors and the mass media, insisting that the victims of the atomic bombings had been handled at ABCC as guinea pigs, and for not providing medical treatment. The same held true for Dr. Neel's research proposal; the news media were more or less bitter towards him. There was an escalated view against this plan saying that 'ABCC should know that to examine the blood of the children of A-bomb survivors is more costly than to produce an atomic bomb.' Although opinions and criticisms of this kind were publicly open, a key issue in the success of the new project depended on whether ABCC could obtain understanding and support of A-bomb survivors and the local community.

Dr. Neel and the author [taken in 1988]

Many Japanese scientists also were aware of the situation of A-bomb studies, and held views similar to those of the mass media in Japan. I regretted in those days that this unique and important genetics project had not been conducted under the initiative of Japanese scientists funded by the Japanese government. It was my belief that it was a responsibility of Japanese scientists to conduct a study of genetic effects of the atomic bombings. In fact, funds from the Japanese government were very limited regarding research of the A-bomb effects. Consequently, ABCC was the only institution that could conduct genetic studies.

Despite Dr. Neel's efforts and great excitement, his project did not easily get started. Based on discussions with those concerned at ABCC, it was decided that Dr. Neel should conduct a feasibility study as to whether the technology would be applicable. A full-scale study was indeed launched three and a half years later, after ABCC was reorganized into RERF. Thereafter, Dr. Neel visited Hiroshima at least once a year without fail, and stayed here for a month, or as long as 2–3 months, to check the progress of the project, and to put relevant research supplies in order.

The Biochemical Genetics Laboratory, abbreviated as "BGS" Lab, was established in the Department of Clinical Laboratories. Since Dr. Neel was not permanently assigned to RERF, the laboratory was placed under the administrative supervision of Dr. Howard B. Hamilton, Chief of the Department of Clinical Laboratories. To set up routine laboratory procedures, Drs. Robert Tanis and Robert Ferrell from the University of Michigan came to Hiroshima and worked hard everyday in the laboratory. Drs. Naoki Ueda (Yamaguchi University), Shinya Kishimoto (Hiroshima University), and Shigeo Akaiwa (Tokyo Medical and Dental University) were newly recruited to the laboratory. Several technicians were transferred from other sections of the department. Since then, many research associates have been recruited from time to time. This included Dr. Chiyoko Sato (former Chief of the Department of Genetics) and others such as, to name just a few, Drs. Takeshi Kageoka, Kazuaki Goriki, Norio Takahashi, Jun-ichi Asakawa, Mikio Fujita, and Keiko Hiyama.

4. Beginning of Biochemical Genetics Study: 1975–1984

The years 1974 and 1975 were the time of preparation of ABCC's reorganization. The ABCC issue became a subject of diplomatic deliberations between the U.S. and Japanese governments, and ultimately the two countries reached to an agreement stipulat-

ing that ABCC would become a Japanese juridical person foundation.

On the morning of Tuesday, April 1, 1975, under a clear blue sky, the opening ceremony of the new Radiation Effects Research Foundation was held in the front yard of the main entrance. Four people were appointed as directors of the new organization: Dr. Hisao Yamashita (former professor of Keio University) as Chairman; Dr. LeRoy R. Allen (former ABCC director) as Vice Chairman; Dr. Gilbert W. Beebe as Chief of Research (formerly called Chief Researcher); and Dr. Masuo Takabe as a Permanent Director. That summer, Dr. Beebe resigned from RERF and returned to the United States. Dr. Stuart C. Finch assumed the position of Chief of Research.

The Crow Committee, which was convened just prior to the reorganization, recommended that in addition to the Life Span Study (LSS), the Adult Health Study (AHS), and the Pathology Study, RERF initiate the Biochemical Genetics Study as a top priority. Based on this recommendation, a comprehensive genetics research program was approved as the RERF Platform Protocol, and endorsed by the Board of Directors in late 1975.[16] This included the Mortality Study, Cytogenetics Study, and Biochemical Genetics Study as major genetic components of the platform protocol.

After approval of the protocol, the initiation of the Biochemical Genetics Study (BGS) was officially announced. The actual work, however, did not get underway. This was due to a lack of a research leader who could coordinate overall administrative and routine works in order. The true responsible investigator was Dr. Neel, but he was not permanently stationed at RERF. The research associates just assigned to RERF had no idea how to operate the daily work in the laboratory.

I talked with Dr. Finch, who also was a newcomer of RERF as Chief of Research, and who had been irritated by the delay of BGS program, about how to proceed with getting the BGS program in motion. We agreed the following items: (i) Current administrative and operational structures of RERF were adequate only for conducting the currently ongoing LSS, AHS, and Pathology Study projects, and thus there was no leeway for conducting the BGS project, (ii) In order to initiate the BGS program, a project leader was indispensable for the coordination of all necessary works, and (iii) The vertical organizational structure was suited only for top-down work, but not horizontal collaboration with the members in other departments.

The role of coordinator of the study fell on me. Since I brought up the issues, I guess that was what I had to deserve. After I became a coordinator of the BGS program, I solicited of all department chiefs and supervisors to support BGS research activity and to share the newly added working load caused by this program. Through more than ten weekly meetings, we could reach an agreement establishing new supporting systems for the BGS program through the lending of hands from other department members, adding to their own daily routine work. All members, key persons of RERF attending the meetings, agreed voluntarily, or somewhat reluctantly, to accept extra burden of work for this purpose. Some of the major changes in the work procedures at ABCC-RERF are as follows.

For realization of the F_1 BGS project, it was understood that support was required from members from all departments; especially from the clinical research staff, Department of Medicine (currently Department of Clinical Studies). Until that time, clinical members did not participate in the F_1 cytogenetics program, but this was successfully changed. Emphasis should be made that this arrangement was made possible by the effort of the late Dr. Hisao Sawada, then Assistant Chief of the Department of Medicine, to whom our thanks are dedicated.

Because the proposed study subjects would be expected to include young people, we decided not to draw blood for safety and health purpose from children below 12 years of age, or pupils of the primary school. For this we would better wait until they reached that age. Occasionally, the parents of the study participants visited RERF bringing all children, some of who were enrolled in our study cohort, and asked us to do medical checkups for all of them. When requested by the parents, blood was drawn even under age of 12 years for routine genetic tests.

Due to the geographical location of ABCC, which stood on the top of Hijiyama, arrangements were made to use taxis for transporting the participants. Dispatchers then played a new role in this project. An institution-wide work sharing system for genetic study was thus established. After many trials and errors, a new working system finally proved to be smoothly workable.

In those days, we had a weekly clinical night shift (from 1:00 p.m. to 8:00 p.m) on Thursdays at Hiroshima and Wednesdays at Nagasaki. We thought this arrangement would be efficient and also convenient for those participants who are unable to come to RERF clinic during daytime of the weekdays. Nearly half of the participants visited RERF to receive medical check-ups including blood drawing relied on those night clinics. When a variant was discovered, a physician or a research scientist in charge made an interview with the variant carrier to explain the result of tests in detail, and ask permission together with his (or her) parents for further family studies. After obtaining agreement from them, a family study was performed in order to verify the origin of the variant. Thanks to the devoted efforts of the entire RERF staff, the BGS project was finally in order.

The BGS project was initiated in 1975 simultaneously with the Cytogenetics program. Both programs were successfully completed in 1984. At the time of completion of the BGS study, the number of children totaled 23,661, 11,364 in the proximally exposed group and 12,297 in the distally exposed or unexposed group as control. The number of gene loci analyzed was 544,779 for the exposed and 589,506 for the comparison group, respectively. The numbers of mutated genes that were confirmed through family studies were two in the proximally exposed group, and four in the distally exposed group.[17]

None of these genetic studies have provided the basis for verifying genetic effects of atomic radiation. In order to verify the observed negative findings, a further genetic study with the aid of much refined technology would be desirable. I understand that a couple of new F_1 study projects have been approved and are currently ongoing. If further genetic research is to continue in the future, it will be associated with a human genome project that is a collaborative research involving scientists from all over the world.

5. Unforgettable People

Over my thirty years of scientific career at ABCC-RERF, I have encountered a great number of unforgettable people who have rendered an immense help to me. Not to mention the chairmen and directors of the institution, a great many colleagues have supported me in various ways. I now feel guilty that I caused a lot of troubles that influenced to a great extent a number of goodwilled people. Whenever I met troubles, I used to ask Dr. Hiroshi Maki for his help. He did help me all the time in many ways. I still remember Dr. Maki's warm face with smile, and used to say: "Don't worry. This is my job."

Mention must be made of Dr. Howard B. Hamilton, Chief of the Department of Clinical Laboratories, who would keep me under control when I started to stampede. Kanze-school Noh performance was more than just a hobby for Dr. Hamilton. In the spring of each year, he dedicated a Noh play to the Gods at Itsukushima Shrine. He also was an expert of Kabuki, and was acquainted with many famous Kabuki actors. His collection of "Kumadori (make-ups of famous Kabuki actors copied directly to the sheet of paper taken immediately after the actual performance)" is nothing but a treasure. He now lives in Virginia, in a suburb of Washington D.C.

(from left) Dr. Hiroshi Maki, Dr. William J. Schull, Mrs. Victoria Schull, Mrs. Chie Maki [taken in 1996]

Due to space limitation, I will describe below my recollections of only a few people.

Dr. Sajiro Makino (1906–1989):

Dr. Makino, my mentor, devoted his lifetime to the human and animal chromosome research, that covered all animal kingdom. He was very active and productive while working with classic techniques, using an old-fashioned Leitz microscope without any support of advanced technology that is available today. He received the Japan Genetics Society Award in 1944 for his research on mouse chromosomes. Then he turned to chromosomal research of transplantable ascites tumors of rats, such as Yoshida sarcoma. He was the first to discover what is known as the "stem-line cell theory." The theory indicated that each tumor cell line has a specific, and thus unique, karyotypic pattern, and that such a cell line plays a central role in the proliferation of tumors. For this theory he was conferred the Japan Academy of Sciences Award in 1958. In the mid-1950's, he moved into a new area of human cytogenetics, and paved the way for this research field in Japan. His name became widely known both nationally and internationally as an authority on human and mammalian cytogenetics. This was the reason why ABCC asked help from Dr. Makino in the conduct of new research on radiation cytogenetics. In 1973, he was elected as a member of the Japan Academy of Sciences. Immediately after his retirement from university, Dr. Makino received an honor as Professor Emeritus of Hokkaido University.

Dr. Makino was a very eager mentor for young researchers who eventually became active scientists. None of his disciples could escape from his loud voice in scolding. Dr. Masao Sasaki, currently Professor Emeritus of Kyoto University, who served until recently as Scientific Council of RERF, is one of the most excellent students trained by Dr. Makino. Dr. Makino always advised his disciples to write scientific papers in English. He kept saying: "That is the only means to be internationally evaluated by the scientists of the world." He himself published over 700 papers, including co-authored works, and 20 monographs and books, most of which were written in English. He practiced what he preached to his students. Despite the fact that I had long been one of his students, after all, I have been nothing but a packhorse.

For more than 40 years since I first received training from Dr. Makino in 1958, and began wandering into the world of "chromosomes," what I have learned from the microscopic works is: "Chromosomes never lie."

Dr. James V. Neel (1915–2000):

Together with Dr. Schull, Dr. James V. Neel, Professor Emeritus of the University of Michigan Medical School, was a founder of the Japan Society of Human Genetics. I am sure that many of the Japanese human geneticists never forget their names.

In the spring of 1968, annual meeting of the Japan Society of Human Genetics was held at the Hideyo Noguchi Commemorative Auditorium of Keio University in Tokyo. It was there that I first met Dr. Neel. He was invited as a guest speaker for the keynote lecture of the Society. During the conference, I had a chance to talk with him about our F_1 cytogenetics program. Dr. Neel listened intently to me with furrowed brows. I still remember vividly what he said after I finished my talk. He said; "I think you know that we did conduct a large-scale genetic study in 1948, and the subject is still extremely important for the elucidation of the genetic effects of radiation. But you must also realize that this indeed is a difficult task to perform and to interpret."

Dr. Neel and I first started working together in 1971, when Dr. Neel brought the idea of initiating the BGS program. Although he kept saying; "Research is my hobby," his attitude toward research was very strict and he never allowed any compromise.

In the years of 1968 and 1969, in the AHS study, and in 1969, in the F_1 study, we discovered an extremely rare type of cells in cultured lymphocytes from AHS and F_1 participants. It showed an uncountable number of complex chromosomal aberrations so that karyotype analysis was impossible. The discoverer of the cell was Dr. Toshio Sofuni, who was our research associate during the period between 1967 and 1979. Apparently, the aberrant cell was unrelated to any radiation exposure. We could not understand why such an incredible cell was produced and present in the body of a healthy non-irradiated person. In any case, we named it "a cell with multiple chromosome aberrations." We recorded the phenomenon in detail in our data books. Some of the results were published in our AHS paper in 1978.[18] Almost at the same time of our discovery, a research team headed by Dr. Neel carried out human genetics studies on the native Venezuelan people in South America. They also discovered the same kind of aberrant cells in Yanomama tribe residents. They reported the results in 1968.[19]

Around the mid-1980's, when Dr. Neel came to Hiroshima as his routine visit, I showed him some of cells with multiple chromosome aberrations that we had encountered in our F_1 study subject. He was surprised and extremely pleased by the conformity with his own experience in South America. We immediately conducted epidemiological analysis on the F_1 members in whom at least one or more of cells with extremely aberrant chromosomes were detected. The results of analysis were then published.[20]

Dr. Neel recommended in the report that the cell with multiple chromosome aberrations be called a "rogue cell." I learned that the term "rogue" means "scoundrel," "villain," and an expression like "a rogue elephant." In the report, the term was used in the classical biological sense of a "marked deviant from the typical observations."[15]

Since we published the report, there have been many papers that have dealt with the rogue cell phenomenon, discovered all over the world. Many cytogeneticists in European countries and, in particular, scientists from the former USSR, observed instances of rogue cells in the course of chromosome screenings on the sufferers of the Chernobyl nuclear plant accident. For this reason, a symposium on "rogue cells" was held in early 1990's in Obninsk, Russia. In a chromosomal study of those exposed in the Chernobyl accident undertaken at RERF, we also observed many rogue cells derived from the residents living in uncontaminated areas.[21] Dr. Neel's interest was shifted toward the elucidation of the mechanism by which the rogue cells are produced. Later on, he hypothesized the possibility of an interaction between host cells and tumorigenic/teratogenic viruses.[22,23]

In a very unfortunate turn of events, Dr. Neel passed away on February 1, 2000. In the Christmas card I received from him one year prior to his death he had written the words:

"The rogue cell story is getting more and more exciting."

This was to be the last message that I would receive from him in his own writing.

Dr. William Jackson Schull:

Dr. Schull and his wife, Victoria, have had a longstanding relationship with ABCC as well as RERF. He first came to Japan in 1949. Since he participated in the Child Health Study as Dr. Neel's right-hand man, so to speak, his contribution to the Japan Society of Human Genetics have been significant, starting with the initial genetic study at ABCC followed by the Hirado consanguineous marriage study.[24] He worked hard not only in research but also in the administrative operations after ABCC was reorganized into RERF. He served as Vice Chairman (from 1978 to 1981), Director (from 1990 to 1992), and again as Vice Chairman and Chief of Research (from 1996 to 1997). I always call him Jack, in a familiar manner. I still feel he is "mon oncle (my uncle)."

When Jack came to Japan as the Vice Chairman of RERF in 1996, he was in the office next to me. When 5:00 p.m. rolled around, Jack asked me to walk home together, since our destinations were more or less the same. We walked down Hijiyama together,

crossed the Tsurumi Bridge, rambled on the western bank of the Kyobashi River, and then headed north. There was always a flavor of the four seasons around the bank of the river. While strolling along, we would talk on various topics. Jack was truly erudite. Even being a Japanese, I was in the position of being taught from him things about the history of Japan, such as hidden Japanese Christians in western part of Japan, various habits in the consanguineous area, and so on. We would sometimes drop in at a hotel standing near the river's bank, and enjoy one or two drinks of whisky and water. However, due to a lack of enzyme, aldehyde dehydrogenase, my face would quickly turn bright red even after one drink of weak whiskey and water. It was always an enjoyable end of the day's work.

Our Staff:

My long story now comes to an end. During the 10,000 or more days of research life on top of the hill, I welcomed here many scientists from overseas to receive training at RERF. In the summer of 1980, Dr. Jin Cuizhen from the Chinese Institute of Radiation Medicine in Beijing came to Japan for a period of one year, and her passion for work really left a strong impression on me. Even after the retirement, she still is active as a leader of the chromosome aberration research in China.

At the end of December 1993, before reaching mandatory retirement age, I resigned from the post of Chief of the Genetics Department. As I wrote in Part 1, Dr. Nori Nakamura, who had served as the Assistant Chief of the Radiobiology Department, was appointed as my successor. I find Dr. Nakamura's efforts highly respectable as he and his colleagues have published many papers amid the harsh research environment, and he holds a strong scientific leadership position both in and out of RERF. I want to take this opportunity to express my sincere gratitude to him.

Whatever words I choose, it is beyond my ability to express my feeling of gratitude to my colleagues at ABCC-RERF who have worked together with me. All I can do now is to document all of their names listed below in the chronological order without honorific. These people worked with us between 1967 and 1994.

Hiroshima:

Professional staff

Nanao Kamada, Hiromu Okada, Takeo Honda (transferred to Nagasaki), Toshio Sofuni, Hachiro Shimba, Kazuo Ohtaki, Richard A. King, Mimako Nakano, Yoshiaki Kodama, Sadayuki Ban, Nori Nakamura.

Technical staff

Shozo Iida, Kazumi Tanabe, Setsuko Furubayashi, Tatsuo Mandai, Sumie Murata, Akiko Kido, Takeshi Abe, Sadamaru Ichiyama (deceased in 1975), Masashi Hiramoto, Junso Naruto, Junko Takabayashi (deceased), Junso Takayama, Kyoko Ozaki, Mayumi Utaka, Mieko Nakamura, Yoshiko Watanabe, Miwa Miura, Kaori Muramoto, Miyuki Tsuchiyama, Hiroyuki Ryukaku, Tomoko Matsumoto.

Nagasaki:

Professional staff

Shotaro Neriishi (deceased in 2002), Tetsuya Iseki, Michihiro Yoshida, Masahiro Itoh (transferred to Hiroshima), Sei Okimoto.

Technical staff

Keiichi Ohki (deceased), Yoko Urakawa, Nobuko Okazaki, Nobuaki Taira, Mankichi Tagami, Hiroyuki Miyaji, Osamu Kusumi, Fukiko Kondo, Mikiko Mizogoshi, Yukihiro Inada, Kazuhiko Tagawa.

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The Way to DS02: Resolving the Neutron Discrepancy

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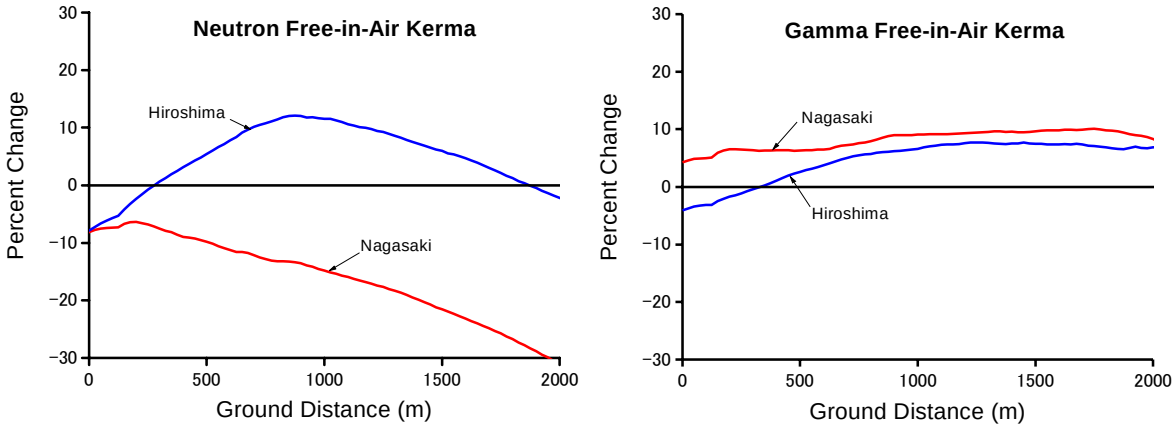
In 1987, RERF published the final report on DS86, which was a new and fundamentally different type of dosimetry system for the A-bomb survivors. DS86 used detailed calculations of the interactions of neutrons and gamma rays, rather than an adaptation of empirical results of atomic weapons tests and associated measurements. This gave DS86 more power and flexibility than its predecessors, which suffered from difficulties when trying to generalize from results of specific bombs, test conditions, and shielding experiments.

However, an issue still unresolved when DS86 was published was a discrepancy between some measured neutron activation levels, e.g. in building materials, and levels calculated from DS86. After publication of the DS86 Final Report (RERF 1987), various committees and individual investigators continued to examine the problems identified in that report. By the mid-1990's, further measurements and discussion greatly raised the level of interest in what popularly became known as the "neutron discrepancy." The story of DS02 is in many ways a story of the neutron discrepancy and its resolution.

In May 2001, a committee of the National Research Council Board on Radiation Effects Research, that was formed in 1996, published a report (NRC 2001) with specific recommendations about how DS86 should be updated and revised. At about the same time the U.S. Department of Energy formed a working group of scientists that collaborated with a pre-existing Japanese group on an intensive new program of calculations and measurements, culminating in the forthcoming publication of a report recommending a new dosimetry system, DS02.

Contrary to expectations, DS02 does not produce very large changes from its predecessor DS86 in either the free-in-air neutron or gamma-ray doses at distances relevant to survivors, even though its development addressed in a cogent manner the motivating neutron discrepancy. As will be discussed elsewhere, DS02 will result in some important changes in shielded survivor doses, because of improved capabilities to address terrain and structural shielding. But the more central part of the story, relating to the neutron discrepancy and affecting all survivor doses, concerns the free-in-air gamma ray and neutron fluences and kerma that are calculated by the dosimetry system as a function of distance from the hypocenter. The changes in free-in-air kerma produced by DS02 are shown in the figure. In the remainder of this communication a discussion is given of the causes of these changes and their significance, including their relationship to the neutron discrepancy.

Percent Changes from DS86 to DS02 as a Function of Ground Distance



All retrospective measurements of neutron dose-related quantities in Hiroshima and Nagasaki involve activation products in materials that were present at the time of the bombings. These are traces of radioactive isotopes produced by neutrons from the bombs, in nuclear reactions with normal isotopes of various elements in rocks and other building materials. The strategy of such measurements is to find an element that had a high probability of interacting with bomb neutrons to create a radioisotope with a reasonably long half-life. That is, long enough to be still present years later at the time of measurement but short enough to emit sufficient radiations per unit time to be detected. The investigator uses physical and chemical techniques to enrich a sample in the activation product radioisotope. Then, radiation emission counting, using techniques that detect only the characteristic radiations emitted by the particular radioisotope of interest, is used to make very sensitive measurements.

Japanese investigators made the first measurements of neutron activation products in 1945, within a few weeks of the bombings. They realized that "fast," i.e. high energy, neutrons react with sulfur to create a radioisotope of phosphorous, P-32, and that the porcelain insulators on electrical power lines contained a paste of pure elemental sulfur. They made a number of such measurements, although the detection technology available at the time allowed measurements with useful precision only at locations very close to the hypocenter. These measurements could not be repeated in later years because P-32 has a half-life of 14.3 days and was gone within a few months after the bombings. It would not be until the time leading up to DS02, some 50 years later, that a new technique would be devised to make retrospective measurements of fast neutrons, which are the portion of the neutron spectrum most closely related to survivor neutron doses. In the meantime, a different type of measurement would have to be made.

Because of the difficulty of finding suitable activation products for fast neutrons, investigators turned to the activation products associated with "slow" or "thermal," i.e. low energy, neutrons. Thermal neutrons have only the minimal energy associated with random thermal motion at the temperature of their surroundings: they started out as faster neutrons but lost their energy and directionality in scattering interactions with air and ground materials before they reached the sample. Thus the thermal neutrons that created activation in a sample were not neutrons that traveled straight from the bomb, and the shielding considerations that affect levels of thermal neutrons in a measured sample are not the same as those that affect the fast neutrons that delivered most of the survivor dose. As a consequence, measurements of thermal neutrons activation products are subject to difficulties of interpretation and depend on detailed calculations to establish a proportionality between the numbers of fast and thermal neutrons at a sample's location.

Japanese investigators made the first measurements of thermal neutron activation in the 1960's, using the cobalt radioisotope Co-60, which was produced by the interaction of thermal neutrons with small amounts of cobalt typically present in iron and steel. As noted, the notion of a neutron discrepancy had its beginnings in the DS86 Final Report, in the time period when neutron measurement of this type was still a relatively developing field. Although investigators in the mid-1980's had recently begun making a new type of thermal neutron activation measurement with an isotope of the rare earth element europium, the main results available for DS86 were the measurements of Co-60 that had been made some twenty years earlier by investigators of the Japanese National Institute of Radiological Sciences (JNIRS) (Hashizume 1967). The chapter on Measurements of Neutron Fluences in the DS86 Final Report began its Summary and Conclusions with this paragraph:

The sulfur activation by neutrons above 3 MeV and the europium activation by thermal neutrons show no important discrepancy with calculations. Cobalt activation, however, contradicts the calculated values by an ever-increasing factor that is five at 1000 m. If the measured cobalt activations were accepted as correct representations of thermal fluences and the assumption is then made that the calculated fluences on the ground are low by a factor that applies to all energies, then the proportion of neutron kerma in the mixed radiation field beyond 1000 m at Hiroshima would change from insignificant to significant.

This chapter of the DS86 Final Report further emphasized that the europium measurements available at the time were insufficient to either confirm or deny the cobalt discrepancy.

The cobalt discrepancy thus defined in DS86 itself contained all the essential elements of the neutron discrepancy that would give rise to the dosimetry re-evaluation and the DS02 system. The measured values suggested an obvious trend: calculated values appeared substantially above measured values near the hypocenter and below measured values at longer distances.

In the ten years following the publication of DS86, Japanese and U.S. investigators made many more thermal neutron activation measurements. Additional cobalt measurements were published in 1990 (Kerr *et al*, Kimura *et al*), 1992 (Shizuma *et al*), and 1993 (Kimura and Hamada, Shizuma *et al*). Even larger numbers of measurements were made using europium, which is present in all rocks at very low concentrations, typically on the order of a few parts

per million, but has a great affinity for activation by thermal neutrons. Due to europium's ubiquity, samples that were in known locations at the time of the bombing, e.g., in structural materials, were easier to find than iron or steel samples necessary for cobalt. By 1993 Japanese investigators had made europium measurements at dozens of additional locations, extending to ground distances as far as 1370 m in Hiroshima (Hoshi *et al* 1989, Nakanishi *et al* 1991, Shizuma *et al* 1993).

In addition to europium, the new technique of accelerator mass spectrometry (AMS) was applied to measuring neutron activation products (Straume *et al* 1990). Because AMS counts atoms of a particular isotope by ballistically separating them as ions by their charge-to-mass ratio, rather than by waiting for them to decay and counting their characteristic radiations, it opened the door to low level measurements of activation products with very slow radioactive decay. It was applied to the chlorine isotope Cl-36, and was extended down to concentrations approaching the order of one Cl-36 atom per 10^{15} atoms of chlorine.

In 1992 (Straume *et al*), an influential paper based on Cl-36 measurements and summarizing other measurements of thermal neutron activation suggested that measured values were "a factor of two to ten, or more" higher than calculated values at distances beyond 1 km in Hiroshima. The extensive series of Eu-152 measurements published in 1993 (Shizuma *et al*) appeared to add further support to this trend.

Meanwhile, work was being done in the realm of calculations, including re-calculation in 1993 of the delayed radiations from the bombs, using new physical constants and adjustments to the energy groupings, to try to resolve the discrepancy. At a conference on the Hiroshima Dosimetry Discrepancy Study in1994, papers were presented that reported on the updating of DS86 to include newer interaction probabilities between neutrons and air (Hale *et al*), on the DS86 source term (Whalen), and on efforts to explain the measurements by devising *ad hoc* sources to replace those from the calculations based on physical principles of nuclear explosions (Rhoades *et al*). An influential paper (Kaul *et al*) made a multivariate analysis of the problem and asserted that no reasonable bomb source term could simultaneously explain all of the available measurements.

A major assumption underlying much of the debate in the 1990's relating to the neutron discrepancy was that the problem was the Hiroshima *source term* of DS86, as opposed to its *transport* calculations. The models for calculating the transport of radiations over distances of hundreds of meters through air had been proven elsewhere in atomic weapons tests. These models establish the quantitative relationship between the fluences in the source term and those at the location of interest. Moreover, the Hiroshima bomb was a unique type of design not measured elsewhere in such tests, as the Nagasaki bomb had been. Hence the most logical cause of the discrepancy seemed to be the calculation of the types and numbers of radiations emitted in various directions at various energies by the Hiroshima bomb: the Hiroshima source term.

The ongoing debate about the neutron discrepancy in the 1990's was hampered by a lack of an agreed-upon quantitative definition of the trend in the discrepancy as a function of distance. This was particularly problematic at longer distances, where the measurements become increasingly imprecise as they approach natural or "background" levels, i.e., all measurements have finite levels unrelated to the bomb radiations, whose natural variability is a limiting factor in measurement precision. In general, a model with neutron fluences lower than DS86 near the hypocenter and higher than DS86 at longer distances required a more penetrating neutron spectrum. To explain such a difference from DS86, concomitantly with the increasing concern created by the neutron discrepancy, some investigators suggested theories based on an unplanned sequence of events in the explosion of the Hiroshima bomb. They suggested that the bomb might have had breaches in its heavy metal case before the fission chain reaction of the nuclear material occurred, which would have allowed the escape of unattenuated neutrons in certain directions, resulting in larger numbers of neutrons at further distances than calculated by DS86.

Many of the models proposed to explain the discrepancy attempted only to explain a trend vs. distance in thermal neutron activation that was more like the apparent trend in the thermal neutron measurements than that in DS86, and did not address other radiations and their measurements completely. One of the major theoretical concerns about attempts to make any such alternative model was the question of how much of a departure from the trend in DS86 was physically obtainable from any feasible source term, even one with a totally unshielded "bare fission" neutrons escaping in some directions, if it were constrained to originate from a localized source at the height above ground of the Hiroshima bomb. Despite the complexities involved, it seems fair to say that, in general, the observation made in 1994 had merit: the physically plausible models under consideration prior to the reassessment effort were not able to satisfactorily and simultaneously explain all of the measurements, including the 1945 sulfur measurements of fast neutrons and the gamma ray thermoluminescent dosimetry (TLD) measurements.

This was the general situation when the National Research Council's Board on Radiation Effects Research charged its committee on RERF dosimetry, beginning in 1996, to prepare a report on the prob-

lem, which was published in 2001. In 2000, the U.S. Department of Energy formed a U.S. working group to work in concert with the existing Japanese working group on the dosimetry reassessment that resulted in DS02. The U.S. funding allocated for DS02 focused strongly on the re-evaluation of both the source term and the transport calculations of DS86 and the resulting free-in-air (i.e., unshielded) kerma values. Complete new calculations were performed using the latest weapon simulation codes available at Los Alamos National Laboratory. Relative to DS86, the new calculation made many improvements:

- the newest data on physical constants were used,
- the entire bomb up to and including the tail fins was modeled,
- a finer time and spatial resolution was used,
- finer discrete subdivisions of energy and angle were used, and
- the calculation, which must consider events that occur at times well below the microsecond level, was carried out to a full second, much longer than the DS86 calculation.

In addition to the source term calculation, which fully and dynamically models the transmission of neutrons through the bomb casing as the bomb is exploding, the Little Boy replica, made of unused parts identical to the Hiroshima bomb, was subjected to new experimental measurements of transmission of neutrons through the case. These measurements, using a wide-energy-spectrum, accelerator-based neutron source at Los Alamos, provided new empirical verification of the source term.

New transport calculations were performed using two complementary methods, Monte Carlo and discrete ordinates, and were found to agree. The latest values for physical constants, particularly the interaction probabilities for neutrons of various energies colliding with atomic nuclei of the nitrogen and oxygen in air, were used. Again, as with the source term, no major surprises emerged.

None of these efforts led to results that could provide a satisfactory explanation of the neutron discrepancy. Furthermore, although many details of the Hiroshima bomb's design specifications remain classified, the Los Alamos group provided cogent assurances that the bomb could not have exploded with a lack of integrity in the case, because if it had done so the yield of the explosion would not have been in the range that clearly occurred.

How, then, has the neutron discrepancy been resolved?

The resolution resulted primarily from

- reconsideration of and changes to the estimated height of burst and yield of the Hiroshima bomb,
- better calculations of the relationship between free-in-air quantities and the quantities existing in samples *in situ*,
- better understanding of the natural variability among measurements at different sites due to physical irregularities in the real city that are not practical to model, and
- a better understanding of the limitations of distal measurements.

One of the troubling aspects of the neutron discrepancy was the disagreement near the hypocenter, where measurements are at their best due to the strong signal, and calculated values exceeded measured values for most types of measurements. When it became clear that neither the new source term calculations nor the new transport calculations were likely to explain this aspect of the discrepancy, the working groups were compelled to consider the "bomb parameters," particularly the interrelated quantities of bomb yield and height of burst.

To tackle this problem, all known measurements made to date were assembled in a large spreadsheet and the calculated activation for each measured sample was specified as a function of the burst height and yield. These calculated values include corrections such as the "transmission factor" relating the calculated free-in-air value at a sample's distance to the calculated *in situ* value in the sample based on its size, composition, and geometrical configuration. In many cases, this involved new, detailed, Monte Carlo calculations using a model of the entire building in which the sample resided at the time of the bombing. Such calculations are also the best way to address the question discussed earlier, of establishing the relationship between numbers of fast and thermal neutrons at a given location. Because thermal neutrons are more like a diffusing cloud of gas and do not have the directionality of fast neutrons, the things such as shielding that affect the relationship between the free-in-air fluence and the fluence in the sample are different for thermal than for fast neutrons. The entire ensemble of measurements was combined with appropriate statistical weighting in a calculation to determine the yield and height of burst that would best fit the totality of available measurements. The yield and height-of burst values implied by the measurements were carefully considered in light of all of the other lines of evidence bearing on those parameters, such as the yield range implied by the new source term calculations, and all of the older data relating to sightings, shadows of thermal burns, blast canisters, and so on. A change was made, and was a key improvement in the agreement of measurements and calculations at short distances.

In Hiroshima, the yield was increased from 15 kt to 16 kt, producing an essentially uniform, proportional increase of about 6.7% in all fluences, all other things being equal. In addition, the height of burst was raised from 580 m to 600 m, which tends to decrease the fluences near the hypocenter but has a

diminishing effect at longer distances. The most important other factor affecting the unshielded gamma kerma in Hiroshima is an increase in the "prompt" portion of the gamma ray fluence in the source term, which increase is due to the newer values for physical constants ("cross-sections") that were used in the DS02 calculations The total prompt gamma ray fluence per kiloton of yield in the source term increased by 31% in Hiroshima, but the effect on kerma is much smaller because only a small fraction (about 4%) of the total kerma is due to prompt gamma rays. (The remainder is delayed gamma rays emitted by the radioactive materials in the fireball and by the capture of neutrons by nitrogen in the air near the fireball.) The overall effect of these changes, along with others due to the newer cross-sections and improvements in computational capability, is that the gamma ray kerma, shown in the right panel of the figure for Hiroshima, is slightly reduced near the hypocenter, where the effect of the increased height of burst predominates. At distances beyond about 500 m the other effects begin to predominate, and the kerma is increased by a factor approaching 10% at longer distances.

After careful consideration of the available evidence in Nagasaki, the working groups concluded that the yield and height of burst should remain unchanged. The predominant factor affecting gamma ray kerma is an increase of about 37% in prompt gamma rays per kiloton of yield, similar in proportion and for the same reasons as the increase in prompt gamma rays in Hiroshima. The kerma values are more uniformly increased because the height of burst is unchanged, and the effect is more pronounced than in Hiroshima because prompt gamma rays produce a larger proportion (about 25%) of the total gamma ray kerma in Nagasaki. This factor, combined with others related to the newer cross-sections and improvements in computational capability, results in the relatively uniform increase in gamma kerma over the entire distance range shown in the figure.

In Hiroshima the DS02 neutron kerma is lower than DS86 near the hypocenter, increases to values slightly more than 10% above DS86 at distances on the order of 1 km slant range, and falls off to values less than DS86 at distances beyond about 2 km. The trend in thermal neutron activation vs. distance is similar but not identical to what is shown here for kerma. As with gamma rays, the change in fluence is essentially proportional to yield. The effect of the increased height of burst is similar but somewhat stronger than for gamma rays because neutrons are more strongly attenuated by the same distance through air. The other features seen in the plotted curve are due to changes in cross-sections and improvements in computational capability. The reduction near the hypocenter is more important to improving the agreement with measurements than the slight increase at somewhat longer distances.

The most marked change arising from the new calculations is the substantial overall reduction in neutron kerma in Nagasaki, although the effect on survivor doses is negligible because the neutron kerma there was already so small in relation to gamma kerma. This is primarily attributable to carrying out the source calculation to much longer times than were feasible in DS86, which results in more down-moderation of the neutrons by the hydrogenous materials in the high explosive of the Nagasaki bomb. This down-moderation, a reduction overall in the energy of neutrons leaving the nuclear explosion, results in fewer neutrons at distances relevant for survivors.

In summary, the primary effect on total kerma and hence on survivor doses in contrast to DS86 is a very modest increase of 5 to 10% in both cities, which is primarily due to gamma rays and is thus illustrated by the gamma ray kerma values in the plots beyond about 1000 m ground distance, where most survivors are located. But what of the more important aspect of the neutron discrepancy, particularly with respect to survivor dose—the trend at longer distances by which the measurements appeared to increasingly exceed the calculated values? It is clear from the figure that DS02 calculated values of neutron kerma in Hiroshima do not greatly exceed DS86 estimates at longer distances, although there is some minor increase at distances from about 700 to 1500 m, where most of the discrepant measurements were located.

The range from about 700 to 1500 m is the portion of the discrepancy whose resolution has more to do with the understanding of the measurements, and their relationship to the calculated "free in air" values of the dosimetry system, than does the discrepancy close to the hypocenter. Investigators in this realm have long understood the difficulties of interpreting measurements that begin at some point to approach limits of detection because the signal of interest is too weak to reliably separate from "noise" or "background." And there is genuine room for disagreement about matters such as, for instance, the acceptable, statistically defined error rates that one will agree to tolerate in distinguishing signal from noise.

But the most important understandings relate to peculiar, technical aspects of the measurements. These measurements require special methods to detect levels much lower than similar measurements made for routine purposes, such as radiation protection in the vicinity of an operating nuclear facility. Furthermore, the investigators in this case are not only compelled to peer back in time over several decades or more, but are forced to find ways to use natural materials rather than designed and specially prepared dosimeters.

One example is the measurement of Eu-152, which is detected and quantified by the characteristic gamma

rays that it emits at certain discrete energies. Rocks and building materials contain many other, naturally occurring radioactive isotopes that emit gamma rays at energies too close to the Eu-152 gammas to be completely distinguished by even the most modern detectors. Extremely low-level measurements rely upon both sophisticated chemical processing and spectral methods to reduce the natural interferences. They also require a very careful quantitative assessment of the "non-bomb-related counts" from the interferences that remain, and from the spectral continuum of ambient x rays and system noise. The working group held workshops on the special statistical and quantitative methods needed for such problems. Other related topics were addressed in detail, such as the properties of samples themselves (e.g., content of hydrogen and other elements with strong neutron interaction probabilities) that affect the amount of activation for a given number of bomb neutrons impinging on the sample.

Another example relates to chlorine 36. New understanding emerged from differences between measurements in granite vs. those in concrete. Reports of measurements in granite became important in working group meetings circa 2000, whereas those in concrete had been reported since about 1990. Because of the 300,000-year half-life of Cl-36, natural levels in rock were produced as it sat in the earth for times on the order of a million years or more before being quarried by humans, by neutrons from cosmic rays and spontaneous fissions of natural uranium and thorium in the rock. Much of the chlorine in concrete, on the other hand, has been in the hydrosphere, particularly the earth's oceans, where there is typically less shielding of the cosmic ray fluence but also less natural uranium and thorium, for much of its "recent" history on the geological time scale. Thus the natural Cl-36 levels that affect measurements at medium to long distances are determined differently in concrete and in various types of rocks, including the pebbles that are often present in concrete.

Another consideration is that chloride ion, in contrast to the chemical forms of cobalt or europium in measured samples, is substantially mobile in some materials, and much more so in concrete than granite. Some advances related to understanding potential sources of misleading results in concrete samples taken near the surface of a wall or other structure. Artifacts can result from infiltration of rainwater with a Cl-36 level different from the level in the surface concrete, or from the existence of surface concrete that was added to exterior walls after the war, among other causes.

One useful endeavor of the current work has been an organized program of chemical processing of eight large samples of granite from various distances, by a specialized, contracted laboratory at the Japan Chemical Analysis Center, followed by measurements of Eu-152 in a special, low-background counting facility located in a deep underground tunnel in Japan. The same samples were also measured for Cl-36 by three different laboratories, in Japan, Germany, and the United States, as part of a designed intercomparison among different activations products, laboratories, and methods.

In another development, new techniques for measuring the isotope nickel 63 were developed in the years leading up to DS02, which allowed the first measurements of fast neutrons since 1945. Nickel 63 atoms are produced by the interaction of fast neutrons with copper. A new and very sensitive method uses special chemical processing to completely separate nickel from the copper, followed by accelerator mass spectrometry with (AMS) a special gas-filled magnet detector in Munich, Germany. Japanese investigators have also shown that radiation counting methods based on beta emissions of nickel 63 may also be feasible with special sample preparation, in cases where large enough samples of copper are available. The capability of making direct, new measurements of the numbers of fast neutrons produced by the bombs is a major development, and the AMS measurements of nickel 63 have added confidence to the dosimetry assessment.

All available measurements made since 1945, including the original Japanese measurements of fast neutron activation in sulfur, were re-evaluated for DS02. This included a re-evaluation of sample map coordinates and hypocenter locations. Map work was done with modern geographical information system software, using both war-era maps and newer, more accurate maps in conjunction with war-era aerial photographs and other sources of information. TLD measurements of gamma ray dose as well as the neutron activation measurements were re-evaluated, including all of the newer TLD measurements made since DS86. Bounding calculations were done as part of the transport calculations to evaluate the effect on radiation transport of assumptions differing from the idealized DS86 assumption that the radiations were transported over an earth surface consisting of flat, level ground of uniform composition and moisture content. All of these improvements and many more contributed to the new understanding of calculations and measurements that emerged in DS02.

The above descriptions, of course, cover only some of the more salient aspects in which DS02 represents substantial improvements in both calculations and measurements. In the final analysis, the working groups concluded that the existing body of measurements is consistent with DS02 calculations, from the hypocenters out to distances at which individual types of measurements become insufficiently reliable for validation of the calculations, due to their technical limitations. This is a very important improvement over the situation that existed with DS86.

In addition to what has been discussed here, substantial improvements have been made in the area of shielding calculations. This includes shielding by terrain and neighboring structures not accounted for in DS86, and what should be substantial improvements for Nagasaki factory workers where shielding by buildings and equipment have long been problematical. These further issues will be discussed in subsequent publications.

The discussion given here represents only the personal views of the authors and not those of the Joint U.S.-Japan working group, the RERF, the U.S. Department of Energy, or the Japanese Ministry of Health, Labour and Welfare. The authors gratefully acknowledge the assistance of the Update Editor and Dale Preston, which was invaluable in preparing a readable discussion.

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Facts and Figures

Department of Statistics

Projections of Radiation-Related Mortality in the LSS

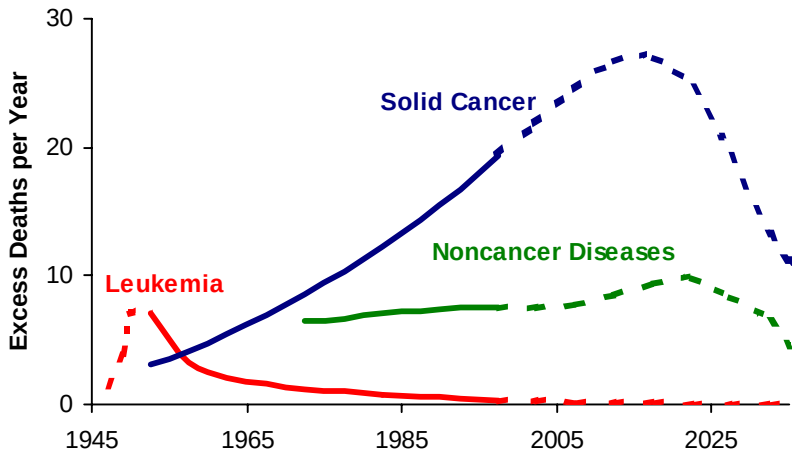
RERF reports clearly indicate that atomic bomb radiation exposure has a significant and continuing impact on cancer and noncancer death rates in the Life Span Study (LSS). It is generally well known that slightly more than half of the members of the RERF LSS cohort had died by the late 1990's. However, it is less well known that most of the radiation-related deaths in the LSS are expected to occur in the future. The figure presents estimates of the annual number of radiation-associated cancer and noncancer deaths in the LSS for the follow-up to date and projections for the future. The meaning of "excess deaths" here is the same as in LSS reports, both for the current follow-up and projected lifetime risks. In particular, for a specific cause this includes those hastened by radiation exposure even though they might have occurred later in the absence of exposure.

We estimate that between 1950 and 1997 there were about 450 excess solid cancer deaths, 100 excess leukemia deaths, and 250 excess noncancer deaths in the LSS. Our projections suggest that these numbers will increase to well over 1,000 for solid cancers and 500 for noncancer diseases, with little increase in the number of radiation associated leukemia deaths. The large projected increase in solid cancer deaths reflects the observation that excess risks are highest for those exposed as children or young adults, and about half of the cohort was under age 25 at the exposure. There is of course some uncertainty in the future projections, and also for the past since the excess deaths are not directly observable. Estimates of the number of radiation-related noncancer deaths are considerably less precise than those for solid cancer or leukemia, since the nature of both the low dose noncancer risks and age-time patterns in the noncancer are poorly characterized.

These calculations are based on the current age-specific risk estimates for solid cancer and noncancer disease mortality of LSS Report 13, which will appear shortly. The leukemia risk estimates were described in the previous LSS Report 12. For cancer, age-specific excess risks depend on both attained age and exposure age, and as noted these are highest for those exposed as children. For noncancer diseases, the exposure-age variation is presently less clear and none is used for calculations here.

The remaining follow-up will provide better understanding of the crucially important age-time patterns of radiation-related risk for both solid cancer and noncancer mortality. It is difficult with even the current 50 years of follow-up to distinguish between variations with exposure age and attained age. For noncancer mortality important further information will be obtained regarding risk at under about 0.5 Sv, which is at this time rather unclear.

Past and Projected Radiation-Related Mortality in the LSS



In Memoriam: Gilbert W. Beebe, 1912–2003

After a long a productive life, Dr. Gilbert W. Beebe, who played a central role in the organization and continuing success of the Atomic Bomb Casualty Commission (ABCC) and the Radiation Effects Research Foundation (RERF), died on March 3rd in Washington, D.C. He was 90 years old. Dr. Beebe is survived by his wife, Ruth, four children, and five grandchildren.

As all of those who knew him can attest, Dr. Beebe was an outstanding scientist and an excellent manager. Prior to World War II, Dr. Beebe, who was trained as a sociologist and statistician, worked on studies of contraception and family planning. From 1942 through 1946 he managed the Statistical Analysis Branch in the Office of the Surgeon General for the US Army. Following the war, Dr. Beebe, together with the famous heart surgeon Dr. Michael DeBakey, led the efforts to organize a large-scale follow-up study of the health US war veterans. Their efforts resulted in the creation of the National Academy of Sciences (NAS) Medical Follow-up Agency (MFUA) in 1946. Under Dr. Beebe's leadership the MFUA, which is still active today, carried out many important studies.

As the MFUA was being created, U.S. President Truman directed the NAS to organize and manage health effects studies of the atomic bomb survivors. Dr. Beebe played a key role in recruiting scientists and overseeing research at ABCC. By the mid-1950's there was a feeling that, with the decline in the rates of radiation-induced leukemia and the lack of apparent effects on children born to the survivors, further studies of the atomic bomb survivor studies were not necessary. To counter this misconception and improve the quality of ABCC research, Dr. Beebe, together with Seymour Jablon, organized the Francis Committee to review the ABCC program and make recommendations regarding its future. The committee's 1955 report laid the foundation for the creation and follow-up of the Life Span Study (LSS), Adult Health Study, and F_1 cohort. The first of Dr. Beebe's three terms as Chief of the Department of Statistics at ABCC lasted from 1958 through 1960. During this crucial period he organized the Department of Statistics, guided the creation of the LSS and F_1 cohorts, helped organize the Hiroshima and Nagasaki Tumor Registries, and established the basic mortality and incidence follow-up methods that are still in use today. Dr. Beebe returned to ABCC for two years from 1966, the period during which the T65D dosimetry was introduced. Dr. Beebe's third term of service at ABCC began in 1973. He stayed at RERF through 1975 serving as the last Chief of the Department of Statistics at ABCC and as a Director and the first Chief of Research at RERF. Following his return to the U.S., Dr. Beebe continued to oversee RERF and direct the MFUA until 1977.

After leaving NAS, Dr. Beebe went to work in the Clinical Epidemiology Branch of the U.S. National Cancer Institute (NCI). Following the Russian Chernobyl accident in 1986, he organized and managed the successful efforts to establish follow-up studies of clean-up workers and children exposed to radiation as a result of the accident. He was actively involved in this work until the time of his death. He also continued to take an active interest in RERF research, most recently working on the analysis and reporting of our liver cancer incidence studies with Dr. John Cologne, Dr. Shoji Tokuoka, and other RERF scientists.

Over the years, Dr. Beebe arranged for many young Japanese researchers to obtain training and experience in the U.S. through fellowships at NCI and other research institutions. Dr. Beebe's legacy at RERF will continue in many ways, including the newly created Gilbert W. Beebe Fellowship. This program, which is being managed by NAS, provides support for visiting researchers (including Japanese scientists) to work on joint NCI-RERF research projects.

When I came to RERF in 1981 six years had passed since Dr. Beebe worked at RERF, however his impact on the scientists and staff was still readily apparent as hardly a day went by without several references to the near-legendary Dr. Beebe. Over the last 15 years as I had the chance to meet and work with him I developed an even greater appreciation

Dr. Gilbert W. Beebe in 1966 (photo courtesy of Archives Office, Department of Information Technology)

for his kind, insightful, though sometimes demanding, advice and support. Last year, as I prepared a talk for a special symposium in Dr. Beebe's honor, I asked former RERF staff members for recollections and remembrances and received a surprisingly large number of heartfelt comments. As expected, I again heard the tales of Gil's tireless and hard-driven work habits, especially his ability to produce an amazing amount of well-written reports and memos (easily keeping a small group of secretaries fully engaged in preparing manuscripts). However, without exception, those who worked with Dr. Beebe also noted how they were inspired and encouraged by his actions, support, and example.

Dr. Beebe was a conscientious and energetic scientist with a unique talent for the organization of important, large-scale, research projects and a special ability to guide and inspire others. Dr. Beebe was motivated by a desire to advance knowledge and, despite his numerous major accomplishments, never sought to focus attention on his own crucial contributions.

Though few people at RERF today worked with, or even knew, Dr. Beebe, I hope that all of us will be inspired by Dr. Beebe's quiet but effective style and will work to keep his spirit alive through the conduct of ethical, innovative research that benefits the atomic bomb survivors and all of humanity. All of us at RERF should be proud to play a role in Dr. Beebe's continuing legacy.

Dale L. Preston

In Memoriam: Abraham Kagan, 1922–2003

Dr. Abraham Kagan, our mentor and one of the world's pioneers in epidemiology research on circulatory diseases, passed away on February 1 this year. I take this opportunity to express my regret over his death.

Dr. Kagan played a central role in the NI-HON-SAN Study, which was initiated in 1965. This renowned international collaborative study has proven epidemiologically that, among Japanese descendents spending many years in the West in Hawaii and San Francisco, the rate of cerebral stroke has decreased whereas that of heart diseases has increased. This study therefore pointed out that improvement of lifestyle is essential for the prevention of heart diseases and stroke. Because the Japanese organization responsible for this study was ABCC, the Department of Epidemiology and Statistics and the Department of Medicine were actively engaged in the study around 1974, when I first joined ABCC. I was naturally involved, as I was aiming to become a physician specializing in circulatory diseases. Dr. Kagan, who was responsible for this study in Honolulu, was the organizer of the Honolulu Heart Program and lived there. I visited Honolulu several times because of my involvement in the study, and I vividly remember his warm hospitality as if it were yesterday. Also, when I organized the 30th anniversary symposium of the NI-HON-SAN Study held in Hiroshima in September 1996, he visited Hiroshima with his colleagues, including Drs. Katsuhiko Yano, David Curb, and Beatriz Rodriguez, and participated in fruitful discussion over a span of two days.

Dr. Abraham Kagan in 1984 (photo courtesy of Archives Office, Department of Information Technology)

My specialty has somehow changed from internal medicine of circulatory diseases to epidemiology on circulatory diseases, but over these 30 years since I graduated from medical school, Dr. Kagan has been my model, on whom I have tried to pattern myself.

Currently in Japan, prevention and care of lifestyle diseases such as heart diseases and stroke is one of the most important issues in health management. We should cope with health problems in the 21st century on the basis of Dr. Kagan's many achievements including the NI-HON-SAN Study.

In closing, I offer my prayers for the soul of Dr. Kagan.

Kazunori Kodama

Research Protocols Approved 2002

RP 1-02 Health Effects Study of the Children of A-bomb Survivors: Clinical Health Study

Fujiwara S, Suzuki G, Yamada M, Takahashi N, Akahoshi M, Hakoda M, Neriishi K, Soda M, Hida A, Imaizumi M, Suyama A, Koyama K, Nakachi K, Katayama H, Pierce DA, Preston DL, Taira S

The objectives of the clinical health study on the children of A-bomb survivors (F_1 Clinical Study [FOCS]) are (1) to elucidate epidemiologically the effects of parental exposure to A-bomb radiation on the development of multifactorial diseases among the children of A-bomb survivors, (2) to preserve blood samples for the future molecular biological studies, and (3) to contribute to the health and welfare of the F_1 population via health examinations and health guidance.

The F_1 Clinical Study will be carried out over four years. A study cohort of about 17,500 has been identified, and each year one-fourth of those will be invited to participate. This will be done by including them each year in a mail survey, which will explain the study and determine their willingness to participate. There was a pilot mail survey of 300 persons in which about 50% of 300 persons (75% of the pilot mail survey respondents) expressed willingness to participate in a clinical study. Thus it can be expected that around 9,000 of the mail survey cohort of 17,500 will agree to participate.

There will be a pilot clinical study involving about 500 people, both cities together, chosen from those expressing willingness to participate in the pilot mail survey and first year of the full mail survey. The objectives of the pilot clinical study are to evaluate the usefulness and validity of the study forms and procedures, method of contacting subjects, and to review the organizational structure and costs of the health examination.

In the F_1 Clinical Study, upon obtaining informed consent from the participants, the health examination including interviews, medical examinations, anthropometric measurements, blood pressure measurements, urinalysis, hematological tests, occult stool blood reaction tests, electrocardiogram (ECG), abdominal ultrasonography, and radiological examination for stomach and so on will be conducted. Also, gynecological examinations, and detailed examinations will be conducted if necessary. Multifactorial diseases detected via these examinations and various measurements will be analyzed in relation to radiation exposure of their parents, taking into consideration confounding factors. Blood drawn from those who gave their consent will be preserved for future molecular biological studies.

The F_1 Clinical Study will contribute to the health management of the children of A-bomb survivors by feeding back the clinical results of the health examination to them and by giving them appropriate guidance.

As a rule, the procedure and contents of the health examination, the ethical issues, data management, and so on are the same in the pilot and full-scale clinical studies. However, when some additions and modifications are indicated by the pilot clinical study, an addendum to this research protocol will be submitted for the full-scale clinical study. Molecular biological studies will be conducted after a separate detailed research protocol is prepared and approved following the institutional procedures of RERF.

RP 2-02 Studies on Skin Cancer Incidence among the RERF Life Span Study Cohort, Hiroshima and Nagasaki (Addendum to RP 2-91)

Kishikawa M, Koyama K, Iseki M, Yonehara S, Tokuoka S, Soda M, Mabuchi K, Ron E, Preston DL, Suyama A, Nakachi K

The aim of this study is to describe and quantify the risk of skin cancer in the Life Span Study cohort. The findings obtained from the previous skin cancer study (RP 2-91) completed during the study period from 1950 to 1987 suggest an increase of skin cancer risk by radiation, but for further assessment of radiation effect on skin cancer, this study proposes to review, together with previously obtained data, skin cancer cases newly developed in 1988 and after.

RP 3-02 Health Effects Study of the Children of A-bomb Survivors: Mail Survey

Koyama K, Suyama A, Grant EJ, Nakachi K, Watanabe T, Fujiwara S, Suzuki G, Preston DL, Taira S

A mail survey is being planned in the RERF F_1 cohort to obtain baseline epidemiological information that will be used for ongoing mortality and cancer incidence studies at RERF and the establishment of a sub-cohort for a clinical health examination program.

The mail survey will be sent to approximately 24,000 people. This includes 17,698 surviving members of the F_1 mortality cohort whose koseki is in Hiroshima or Nagasaki and whose current address is in or near the cities. In addition, we expect 6,000–7,000 members whose *koseki* is in either city or surrounding areas but whose current address information is not available will be subjects of the mail survey cohort. In order to minimize the time between the receipt of the survey and the scheduling of the clinical examinations conducted at the Department of Clinical Studies, RERF, the survey will be carried out over four years with the questionnaire being sent to one-quarter of the sample subjects per year.

The questionnaire and associated documents are virtually identical to those used in the "Pilot Mail Survey of the Children of Atomic Bomb Survivors"

(RP 4-00) that were sent to 300 members of the mail survey sample between May and July 2000. The material included in this survey will also include an additional brochure that provides a detailed description of the planned health examination.

The results of the pilot study suggest that we can expect a 70% response rate with about 8% of the non-responses resulting from outdated addresses. About 75% of the respondents indicate some willingness to participate in the clinical examination. This suggests that the mail survey will identify 12,000–12,500 potential clinical program participants.

Scientific and ethical issues related to the design and conduct of this study have been reviewed by the third-party committees established by RERF specifically for consideration of this survey and the related clinical examination program. These committees have indicated their support of the plans for the mail survey.

RP 4-02 Perturbation of T-cell Homeostasis in Atomic-bomb Survivors

Kusunoki Y, Kyoizumi S, Hayashi T, Hakoda M, Suzuki G, Kasagi F, Fujita S, Kodama Y, MacPhee DG

We wish to examine the proposition that radiation exposure can seriously perturb one or more of the mechanisms responsible for T-cell homeostasis in man. Our approach leans heavily on a number of recently-developed techniques which we believe will help us to learn a great deal about the history of the T-lymphocyte populations which are of vital importance to the immunological defense activities of atomic-bomb (A-bomb) survivors. The nature and extent of any substantial impairment (or in some situations unbalancing) of their immunological defense systems may well be an important element in their excessive (and ongoing) cancer and non-cancer disease histories.

Our basic strategy involves studying the blood leukocytes of about one thousand A-bomb survivors who are current or recent participants in the Adult Health Study (AHS) population to determine (1) the numbers of T lymphocytes that contain T-cell receptor-rearrangement excision circles (TRECs) and (2) the average lengths of telomere repeats in T lymphocytes and other immunity-determining cell populations.

TRECs are circular DNA molecules generated in thymocytes during the T-cell receptor (*TCR*) gene rearrangement process in the thymus, and an individual's ability to produce T lymphocytes in the thymus can be evaluated by determining how many of his or her T cells contain TRECs as a fraction of the total T-cell population. Assuming that A-bomb radiation is almost certain to have increased the rate at which age-dependent thymus dysfunction occurs (as has been suggested by several previous studies), we can expect to find that the numbers of T cells with TRECs will be somewhat lower in A-bomb exposed survivors than in age-matched but non-exposed controls.

The lengths of telomere repeats in peripheral blood memory and naïve T lymphocytes will also be measured to provide us with an indication of how many cycles of cell division these T-cell populations have undergone prior to being sampled. If it is supposed that T lymphocytes are required to divide more frequently during the recovery process from A-bomb radiation-induced cell loss than are the T lymphocytes of the appropriate unexposed controls, it ought to be possible to detect greater reductions in telomere lengths in cells from both the naïve and memory T-lymphocyte populations of exposed individuals than are seen in concurrent T lymphocyte populations from unexposed controls. Moreover, given that the recovery to near normal of the peripheral T-cell pool from A-bomb damage is thought to result in large part from an expansion in the population of memory T cells that survived exposure to A-bomb irradiation, we ought to be able to detect a more pronounced shortening of telomere length in the memory T-cell population of any given exposed survivor than in his or her naïve T-cell population.

We believe that the results of these types of measurement will provide us with a reasonable indication of the extent to which abnormalities of the immune functions (including, but not exclusively, the defense functions) of A-bomb survivors have been causal in certain of the diseases that appear to be more common in A-bomb exposed survivors. We will therefore carry out a detailed investigation of any possible relationships between the perturbations in lymphocyte-dependent immune function we have described under RPs 3-87 and 1-93 and the inferences concerning mechanism(s) that we hope to be able to draw from our measurements of TREC-bearing CD4 T-cell numbers and T-lymphocyte telomere lengths. Clinical laboratory data including blood test results and records of inflammatory disease(s) will be assessed to determine how they relate to TREC-bearing CD4 T-cell numbers and telomere lengths. From these analyses, we hope to be in a position to determine whether A-bomb radiation has perturbed the normal processes of T-cell homeostasis, as well as whether any such perturbations are directly involved in disease development or disease status in A-bomb survivors.

To gain a better understanding of the mechanisms involved in radiation-induced perturbation of T-cell homeostasis, we also plan to investigate the processes of T-cell reconstitution following radiation-induced damage using a number of potentially valuable animal models. By reconstituting irradiated mice with a population of mouse T cells that carry a stable genet-

ic marker along with functional TCRs that differ from those of the irradiated mice, we intend to examine many of the parameters that help to restore and maintain T-cell production and memory in irradiated hosts. Once we have made solid progress in the mouse/mouse system, we are planning to reconstitute the immune systems of immunodeficient mice with human rather than mouse T cells, and to investigate whether we can use such a system to better characterize some of the mechanisms involved in the control of human T-cell memory in both control and irradiated animals.

RP 5-02 Papillary Thyroid Carcinomas in Residents of Hiroshima and Nagasaki Who Were Exposed to A-bomb Radiation as Children: A Study of *RET* Gene Rearrangements and Other DNA Changes Potentially Responsible for the Origins and/or Development of These Tumors

Hamatani K, Hirai Y, MacPhee DG, Koyama K, Soda M, Katayama H, Preston DL, Tokuoka S, Fukuhara T, Hayashi Y, Fujihara M, Tsuda N, Mabuchi K, Ron E

Rearrangements of the *RET* proto-oncogene have been found to occur in the thyroid tumors of a considerable number of patients with histories of radiotherapy as well as in children who lived in the Chernobyl contaminated area. Radiation-associated thyroid cancers with relatively short latencies and/or the histological pattern of a solid variant mainly seem to contain rearrangements of the *RET/PTC3* type and rather fewer of the *RET/PTC1* type. By contrast, tumors with relatively long latencies and/or morphologically typical papillary features seem to contain predominantly *RET/PTC1*-type rearrangements. The elevated risk of papillary thyroid carcinoma that is known to have occurred among people who were exposed to the Hiroshima/Nagasaki atomic bombs (A-bombs) as children is also believed to be due in the main to the induction of *RET* gene rearrangements, and in particular to the induction of *RET/PTC1* rearrangements, by A-bomb radiation. We now plan to use the reverse transcription-polymerase chain reaction (RT-PCR) technique together with RNA samples derived from paraffin-embedded blocks of tumor tissue to determine which of several possible rearranged *RET* gene transcripts can be detected in the thyroid tumors of a carefully-selected group of A-bomb survivors. Our aim is to determine which of the known gene-activating rearrangements of the *RET* proto-oncogene are most likely to have been involved in the development of papillary thyroid carcinomas in those A-bomb survivors with an exceptionally high excess relative risk (ERR) who were still very young at the time of the bombing. However, we do not expect to be able to explain all thyroid tumors among A-bomb survivors on the basis of rearrangement-induced *RET* gene expression. We are therefore planning to carry out a later-stage screen of all otherwise uncharacterized tumor tissues for DNA sequence-based evidence of putatively causative mutant genes, and to do so with the best techniques that are available at the time.

RP 6-02 A Nested Case-Control Study of Breast and Endometrial Cancer in the Cohort of Japanese Atomic Bomb Survivors

Sharp GB, Neriishi K, Hakoda M, Suzuki G, Akahoshi M, Cologne JB, Imai K, Eguchi H, Nakachi K, Key TJ, Stevens RG, Kabuto M, Land CE

A nested case-control study of breast and endometrial cancer in the Adult Health Study (AHS) is proposed which builds upon the results of the Kabuto and associates study which was recently published. The initial study provided evidence for an association of free estradiol level in serum prior to diagnosis and subsequent risk of breast cancer. Although originally designed to examine a possible interaction of radiation and hormones, the number of cases was too small to address this question. The Kabuto and associates study included breast cancer cases diagnosed in the AHS cohort through 1983. The proposed new study will additionally include cases diagnosed since this time, resulting in a combined study group that will be more than four times larger than that used in the original study. Because risk factors for endometrial and breast cancer are similar, this research project will also investigate the etiology of endometrial cancer. Controls will be matched to breast cancer cases, and endometrial cancer cases will be compared to the pool of breast cancer controls. The proposed study will examine a series of hormone-related serum measurements, including total estradiol, bioavailable estradiol, testosterone, sex hormone binding globulin (SHBG), progesterone, insulin-like growth factors 1, 2, and binding protein-3 (IGF-1, IGF-2, and IGFBP-3), and prolactin. The study will also investigate the role played by phytoestrogen in the etiology of these diseases and, based on data available from the AHS interviews, will also take into account confounders and other risk factors. Because elevated body burden of iron may increase susceptibility to breast or endometrial cancer and because of evidence of biologic interaction between iron and estrogen, we will also measure serum ferritin, as an indication of body iron level, and protein-carbonyl, as an indicator of oxidative stress. Estrogen burden is believed to be closely related to lifetime risk of breast and endometrial cancer, and there is reason to hypothesize that the effect of estrogen varies with ferritin level in the etiology of these diseases. A diet rich in phytoestrogens may reduce risk.

RP 7-02 Measurement of Thyroid Autoantibodies in Atomic-bomb Survivors (Addendum to RP 2-99)

Imaizumi M, Neriishi K, Akahoshi M, Maeda R, Soda

M, Suzuki G, Fujiwara S, Yamada M, Nakashima E

This research protocol is an addendum to RP 2-99. The primary objective of RP 2-99 is to study the effect of atomic-bomb radiation on thyroid disease incidence. With this addendum protocol, diagnosis of autoimmune thyroid disease among the subjects of the thyroid study (RP 2-99) will be made by a newly developed thyroid autoantibody measurement method, which enables diagnosis of autoimmune thyroid disease with increased sensitivity. This project is indispensable for studying the relationship between autoimmune thyroid disease incidence and radiation dose.

RP 8-02 Ophthalmologic Study of Children of Atomic Bomb Survivors (Addendum to RP 1-02)

Minamoto A, Kumagami T, Yoshitani N, Mishima HK, Amemiya T, Nakashima E, Neriishi K, Hida A, Fujiwara S, Suzuki G, Akahoshi M

Cataracts are a multifactorial disease that stems from a combination of environmental and genetic factors. Animal experiments have suggested the possibility of an increase in the incidence of congenital cataracts in the offspring of A-bomb survivors. However, the number of cases is expected to be too small for this purpose in this study. For congenital cataract cases, if found, its relationship with radiation will be investigated as a case report. Our research will quantitatively investigate the opacity of eye lenses and retinal arteriolosclerosis in the offspring of such survivors who are at least 50 years of age at the time of examination. It is designed to investigate the association of lens opacity with multifactorial diseases and the radiation dose to which the parents were exposed. Lens opacity and retinal arteriolosclerosis are to be graded with the Lens Opacity Classification System II (LOCS II) and Scheie classification, respectively, and regression analysis conducted after incorporating a variety of risk factors. Lens and retina photographs will be stored permanently in our computers as digital images.

Recent Publications

(Japanese): the original article is in Japanese.
(Russian): the original article is in Russian.
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