放影研 RERF update
Radiation Effects Research Foundation News and Views
Hiroshima and Nagasaki, Japan
Volume 16, 2005

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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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From the Editors

Sumimasen

This volume of the *RERF Update* has been a long time in coming to press. For one reason or another, time got away from us and we failed to produce a volume during the last calendar year. For this we do indeed apologize to our readers.

We plan on atoning for our lapses, and for the time lost in reporting of RERF's ongoing scientific programs and events, by publishing three volumes over the next twelve months. This volume, No. 16, will be devoted largely to RERF's activities of fiscal year 2004; whereas volumes 17 and 18 will focus on activities of fiscal years 2005 and 2006, respectively. Although the basic format of the *RERF Update* will remain the same, several new sections have been added in order to enhance the quality of the publication and to increase the pleasure of its reading. Most notably a "Human Interest Notes" section has been added, along with an expanded "Science Articles" section, including newest research findings.

Sincerely,

Thomas M. Seed
Editor-in-Chief

Yuko Ikawa
Technical Editor

Recommendations of the 31st RERF Scientific Council and Our Responses

The 31st Scientific Council meeting was held on March 17-19, 2004 at the Hiroshima Laboratory, co-chaired by Drs. Yasuhito Sasaki and Theodore L. Phillips, with the aims of reviewing the research programs of the Radiation Effects Research Foundation and of looking closely into the Statistics Department's research activities as well as its dose estimation program. On the first day, there were presentations regarding departmental activities and future plans by the Departments of Genetics, Radiobiology/Molecular Epidemiology, Clinical Studies, Epidemiology, and Information Technology as well as a report from the Chief of Research. Following these presentations, the Scientific Councilors made an inspection of a recently renovated blood sample storage facility; they were then divided into small groups to visit specific departments, and received reports directly from research scientists on recent research achievements and current problems. On the second day, the Statistics Department made an in-depth report on its research programs including its dose estimation program. Each presentation was followed by valuable, lively discussions.

The 31st Scientific Council made 12 general recommendations, of which six were the same as those of last year's Scientific Council, and detailed recommendations to each department. The following are responses to the general recommendations:

1. We again appreciate the Scientific Council's recommendation that the recruiting of replacements for senior people who are leaving within this year, especially from the Department of Statistics, should be considered as the highest possible priority. We will make more efforts to identify top candidates for the statistician positions.

2. We concur that the publication rate of many of the scientists at RERF should be higher. The chief of each department should have many opportunities to discuss plans for publication of research projects as well as to make high-level research protocols.

3. The Council again recommended that every effort be made to limit our internal review process for publications to no longer than one month. We will make greater efforts to shorten the time of this internal review process to within one month.

4. We agree with the Scientific Council that we should develop a data sharing policy and should allow RERF researchers and selected external collaborators to have more ready access.

5. As recommended by the Council, we will make efforts to have high-quality on-line access to more journals as well as ready access to journals not available on line.

6. Regarding the new dose estimation system,

DS02, as recommended by the Scientific Council, we will continue refinement of the dose assignments based on the DS02 system.

7. We also feel that there was insufficient time available for in-depth study of the department being reviewed, even though informal department meetings attended by Scientific Councilors were held. We will reconsider possible improvement to provide enough time for in-depth review of the department.

8. Regarding the number of participants in the F_1 study, it was advised that another search be done in the catchment area to find additional persons whose parents received significant doses above 1 Sv. There are about such 2,000 people, and it is estimated that about 35% of these individuals reside within the catchment area. In cooperation with the Department of Statistics, we will estimate statistical power to be obtained from the addition of these individuals, and carefully consider balancing this with matters of personal data protection.

9. We agree whole-heartedly that the review of new research protocols (RPs) and pilot studies should be speeded up. We will make more efforts to expedite the review process of these projects as soon as possible.

10. The Council again recommended that a statistician should be in principle included in every research protocol, including pilot studies. However, all of RERF's RPs and pilot studies last year involved a statistician as a co-investigator while the study was being designed and conducted.

11. Regarding the recommendation that guidelines for outside grant applications be established, we do not think that they are necessary because all grant applications approved so far in the outside grant application process are directly or indirectly related to the mission of RERF.

12. We concur that further steps should be taken to fund and attract young scientists to RERF at the postdoctoral level. We will make more efforts at recruiting such scientists.

RERF Scientific Councilors

Dr. Yasuhito Sasaki, President, National Institute of Radiological Sciences
Dr. Ohtsura Niwa, Professor, Radiation Biology Center, Kyoto University
Dr. Toshitada Takahashi, Director, Aichi Cancer Center Research Institute
Dr. Shinkan Tokudome, Professor, Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences
Dr. Teruhiko Yoshida, Chief, Genetics Division, National Cancer Center Research Institute
Dr. Theodore L. Phillips, Professor, Radiation Oncology, Cancer Center, School of Medicine, University of California, San Francisco
Dr. Gloria M. Petersen, Professor of Epidemiology, Mayo College of Medicine
Dr. Clarice Ring Weinberg, Chief, Biostatistics Branch, Environmental Diseases and Medicine Program, National Institute of Environmental Health Sciences
Dr. Joel S. Bedford, Professor, Department of Environmental and Radiological Health Sciences, and the Graduate Faculty of Cellular and Molecular Biology, Colorado State University
Dr. Roy E. Shore, Professor, Department of Environmental Medicine, New York University School of Medicine

The 39th Board of Directors Meeting in Hiroshima

The 39th Board of Directors meeting was held on June 23 and 24, 2004 in the auditorium of the Hiroshima Laboratory with 23 participants including directors, supervisors, and observers. Active discussion was held on the operations of RERF.

At the beginning of the meeting, Dr. Burton G. Bennett, in his opening remarks, paid a tribute to A-bomb survivors cooperating in RERF's research activities, emphasized the significance of the Adult Health Study and the F_1 health effects study, and referred to the efforts of RERF to call on entities concerned for cooperation in obtaining support needed for continuing RERF projects and pursuing the foundation's mission.

Subsequently, the minutes of the previous board meeting (38th, Hiroshima) were approved. The meeting agenda then proceeded to reporting on the items for information.

The session "Items for Information" was opened by Dr. Bennett presenting a status report of RERF including progress of the research projects. Subsequently, Dr. Senjun Taira reported on progress in the clinical study of survivors' children and on international collaboration work, and then Dr. Eiichi Tahara

outlined the status of current external grants. Mr. Masaharu Yoshikawa gave reports on the present personnel status, FY2003 salary revision, and Labor Union FY2004 negotiations.

In the session "Discussion of Issues Proposed by the Members of the Board," Dr. Bennett explained the current budgetary situation, referring to support from U.S. Ambassador Howard Baker in an attempt to prevent reduction of FY2005 U.S. funding as proposed by the Department of Energy (DOE), Dr. Bennett's efforts to approach U.S. lawmakers and others and actions to be taken in future. The directors had a lively exchange of views about how to secure funding for the RERF operations, and the board as a whole decided to prepare a statement opposing the U.S. planned budget cut. The board also discussed the auditing process and remuneration and salaries for directors and staff.

With respect to the "Items for Deliberation and Action," Scientific Councilor Ohtsura Niwa gave a summary report on the recommendations of the 31st meeting of the Scientific Council, and Dr. Tahara expressed his gratitude for those recommendations and presented responses. Consequently, discussion was held on such items as the FY2003 research activities report and audit, the FY2004 research activities plans, the FY2003 settlement of accounts and audit, the FY2004 working budget, and the FY2005 provisional budget plan, all of which were approved by the Board of Directors.

In the session "Election and Appointment of Directors and Others," Dr. Tomio Hirohata, who continued to fulfill his duties even after completion of his term at the end of June 2003, was unanimously reappointed as supervisor. As for the scientific councilors, Dr. Niwa, Professor of the Kyoto University Radiation Biology Center, was reappointed. Dr. Theodore L. DeWeese (Professor and Chairman, Department of Radiation Oncology and Molecular Radiation Sciences, The Johns Hopkins University School of Medicine) was elected and appointed as successor to Dr. Theodore L. Phillips. Furthermore, Mr. Eiji Akimoto (Director of the Matsuyama Finance Office, Shikoku Local Finance Bureau, Ministry of Finance) was recommended for the position of Chief of Secretariat, succeeding Mr. Yoshikawa who will leave RERF at the end of June, and the appointment of Mr. Akimoto was approved by the board. Each of them will assume his post on July 1. (As for the directors, Dr. James D. Cox [Professor, University of Texas M.D. Anderson Cancer Center] was appointed by mail ballot as successor to Dr. Samuel H. Wilson, who resigned effective June 1.) It was agreed that the next meeting of the Board of Directors be held on June 22–24, 2005.

Lastly, the board closed its annual meeting by approving the board's statement opposing the budget curtailment proposed by the U.S. government.

List of Participants

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

Visiting Directors:
Mr. Masaaki Kuniyasu, Former Ambassador Extraordinary and Plenipotentiary
Dr. Hiromichi Matsudaira, Consultant, Radiation Effects Association
Dr. Takefumi Kondo, Guest Professor, Keio University School of Medicine
Dr. Paul L. Ziemer, Professor Emeritus, Purdue University
Dr. James D. Cox, Professor, University of Texas M.D. Anderson Cancer Center
Dr. John E. Burris, President, Beloit College

Supervisors:
Dr. Tomio Hirohata, Professor Emeritus, Kyushu University Faculty of Medicine
Mr. David Williams, Senior Financial Advisor, National Academy of Sciences

Scientific Councilor:
Dr. Ohtsura Niwa, Professor, Kyoto University Radiation Biology Center

Representatives of Supporting Agencies:
Mr. Shuichi Oshige, Ministry of Health, Labour and Welfare
Mr. Takaaki Kikuta, Ministry of Health, Labour and Welfare
Mr. Kevin K. Maher, Embassy of the United States of America
Ms. Nicole Nelson-Jean, Embassy of the United States of America
Dr. Evan B. Douple, National Academy of Sciences
Ms. Catherine S. Berkley, National Academy of Sciences

RERF Secretariat:
Mr. Masaharu Yoshikawa, Chief of Secretariat
Dr. Charles A. Waldren, Chief Scientist
Dr. Gen Suzuki, Chief Scientist
Dr. Kazunori Kodama, Chief Scientist
Dr. Nori Nakamura, Chief Scientist

Staff News

The period from April 2004 to March 2005, was a busy one in terms of personnel turnover here at RERF. The "revolving-door" was moving briskly, indeed, bringing new people into the organization, and at the same time, losing its share of well-known individuals.

Coming into the Foundation, the Department of Clinical Studies, Hiroshima hired two new research scientists (1 April 2004): Dr. Waka Ohishi, currently serves as the Chief of the Division of Clinical Laboratories, while Dr. Yoshimi Tatsukawa is serving as a clinical researcher at the Division of Health Examinations. Four additional staff researchers were hired as well, including: Dr. Yasunari Satoh (1 April 2004), a research scientist in the Laboratory of Biochemical Genetics, within the Department of Genetics; Dr. Reiko Ito (1 April 2004), a research scientist, in the Laboratory of Cell Biology, within the Department of Radiobiology/Molecular Epidemiology; Dr. Nobuo Nishi (1 April 2004) who is serving as the Chief of the Tumor and Tissue Registry Office within the Department of Epidemiology Hiroshima; and Dr. Kyoji Furukawa (1 October 2004) a research scientist within the Department of Statistics.

Going out, the Foundation lost several of its most prominent, senior investigators: Drs. Dale L. Preston and Donald A. Pierce of the Statistics Department resigned their posts on 31 July and 31 December 2004, respectively. Dr. Preston currently is working in California, USA, at HiroSoft International Co., while Dr. Pierce is retired and enjoying the "good life." It's good to report that both of these gentlemen are still very much engaged in RERF science and try to assist the Foundation whenever and wherever they can. In addition, Statistics lost (via resignation, 31 December 2004) the very talented, Dr. Shizue Izumi, who moved on to a university position in Engineering at Oita University, Oita, Japan. The Department of Clinical Studies was hard hit as well with the resignations of the outstanding Chief Scientist Dr. Gen Suzuki who moved on to a management position within the Department of Environmental Health, National Institute of Public Health in Saitama, and Dr. Masayuki Hakoda, the hard working Chief of the Clinical Laboratories, who assumed a faculty post in the Department of Human Ecology at Yasuda Women's University here in Hiroshima. In addition, Dr. Donald G. MacPhee, the former head of the Department of Radiobiology, and latter Research Advisor, resigned (30 September 2004), returned to his native Australia, and assumed a new post within the Department of Microbiology at La Trobe University, Melbourne, AU.

International Conference on Radiation Health Effects: Biology, Risk Estimation, and Protection

Dale L. Preston, Former Chief
Department of Statistics

On June 21st and 22nd 2004 RERF in collaboration with the Kyoto University Radiation Biology Center sponsored an international conference on Radiation Health Effects: Biology, Risk Estimation, and Protection. The conference was organized by Professor Niwa of Kyoto University and Dr. Preston of the RERF Department of Statistics. The meeting, which was held in Hiroshima at the Aster Plaza, was attended by more than 100 people. The conference highlighted the current status and future directions of radiation research. It succeeded in achieving these goals and in illustrating the continuing vitality and importance of RERF research.

The speakers included leading RERF scientists and renowned Japanese and international experts. The first half-day session focused on the current state of understanding of the biological basis for the long term effects of radiation on human health. The topics discussed included: a description of evolving ideas about the mechanisms by which radiation causes cancer and the importance of animal experiments (Prof. R. Ullrich); the importance of improved understanding of the physical interactions involved in radiation energy deposition at the cellular level for understanding these mechanisms (Dr. D. Goodhead); the need to develop a biological basis for radiation protection (Prof. O. Niwa); description of a biologically-based hypothesis that can explain the nature of the temporal patterns in radiation risks seen in the Life Span Study (LSS) leukemia risks (Dr. N. Nakamura); and an overview of current work on using animal data to understand the relative biological effectiveness of different types of radiation (Prof. M. Sasaki).

The second session focused on issues in risk estimation with talks on current challenges in conducting radiation health effect studies in human populations (Dr. K. Kopecky); an overview of current analyses of solid cancer incidence in the LSS (Dr. D. Preston); a discussion of important new approaches to describing the uncertainties in radiation risk estimates more completely (Dr. C. Land); a look at how the methods used in RERF risk estimates have evolved in recent years with some ideas for future directions (Dr. D. Pierce); and an example illustrating the application of biologically-based mathematical models to data on leukemia risks in mice exposed to radiation (Prof. M. Kai).

The second day began with a session on how data from RERF and other radiation studies are used to inform and develop radiation protection standards. The topics considered included: an overview of emerging evidence from the RERF and other populations for radiation effects on non-cancer disease (Dr. K. Mabuchi); new concepts for radiation protection being developed in Japan (Dr. T. Kosako); a description of how RERF results are used in the formulation of U.S. radiation protection standards (Dr. J. Puskin); and the current status and future direction of international radiation protection guidelines with an emphasis on the continued relevance of RERF results (Dr. A. Gonzalez).

The meeting concluded with a lively panel discussion in which the panelists and conference participants described outstanding issues while highlighting the ongoing importance of the RERF studies. The comments stressed the importance of collaboration between RERF scientists and other researchers in Japan and other countries. It was clear that many of the non-RERF participants would be interested in such collaborations.

Comments from the speakers and conference participants echoed my own view that this conference was a great success. The presentations were interesting and generated a considerable amount of discussion. A number of people noted that it would be good if RERF could host similar conferences in the future. The success of the conference owes a lot to the generous financial support provided by RERF and Kyoto University and the excellent organizational support provided by RERF staff, particularly Ms. R. Shibukawa, Ms. S. Funamoto, and Ms. S. Teranishi of the Department of Statistics.

The conference highlighted the historical importance of RERF research and demonstrated that there is much important work yet to be done by RERF. I hope that RERF researchers and staff will take pride in their contributions to our important work and be challenged to continue our research in order to realize the full potential of these studies.

Participants

[Speakers]

Dr. Abel Gonzalez, Director, Division of Radiation and Waste Safety, International Atomic Energy Agency, Austria

Dr. Dudley Goodhead, Former Director, Radiation and Genome Stability Unit, MRC Harwell, United Kingdom

Prof. Kenneth Kopecky, Fred Hutchinson Cancer Research Center Public Health Sciences Division

Prof. Robert Ullrich, Department of Environmental and Radiological Health Sciences, Colorado State University, USA

Dr. Charles Land, Senior Investigator, Radiation Epidemiology Branch, National Cancer Institute, USA

Dr. Kiyohiko Mabuchi, Expert, Radiation Epidemiology Branch, National Cancer Institute, USA

Dr. Jerome Puskin, Office of Radiation and Indoor Air, Environmental Protection Agency (EPA), USA

Prof. Michiaki Kai, Laboratory of Environmental Health Science, Oita University of Nursing and Health Sciences

Dr. Toshiso Kosako, Associate Professor, Research Center for Nuclear Science and Technology, University of Tokyo

Dr. Nori Nakamura, Chief, Department of Genetics, Radiation Effects Research Foundation

Prof. Ohtsura Niwa, Department of Late Effect Studies, Kyoto University Radiation Biology Center

Dr. Donald Pierce, Research Advisor, Radiation Effects Research Foundation

Dr. Dale Preston, Chief, Department of Statistics, Radiation Effects Research Foundation

Prof. Masao Sasaki, Professor Emeritus, Kyoto University

[Observer/Panelists]

Prof. Tomio Hirohata, Professor Emeritus, Kyushu University Faculty of Medicine

Dr. Jiro Inaba, Chief, Department of Radioecology, Institute for Environmental Sciences

Dr. Yasuhito Sasaki, President, National Institute of Radiological Sciences

Prof. Yoshisada Shibata, Department of Radiation Epidemiology, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences

International Workshop on New Horizons in Radiation Biology of Fetal and Childhood Exposure

Nori Nakamura, Chief Scientist and Chief, Department of Genetics

The above workshop was held at the RERF Auditorium on February 3, 2005. The reason for selecting fetal exposure as a topic for discussion for the workshop is that there have recently been interesting discoveries in this field.

Epidemiological studies conducted since the 1950s have shown that a fetus is highly sensitive to radiation. In general, if a pregnant woman is exposed to X rays for a pelvic examination, the mortality of her child due to leukemia (or cancer) increases by 50%. It is estimated that diagnostic X rays during the 1950s caused exposure to some 10 mGy (equivalent to several years of exposure to natural radiation), corresponding to a relative risk per Gy of 50 (mean cancer risk per Gy for all A-bomb survivors is only 2). On the other hand, most animal experiments have not demonstrated a high risk for fetuses (i.e., cancer hardly increases in exposed fetuses).

Few aberrations were identified in RERF's study of chromosome aberrations among about 300 individuals exposed *in utero* (study conducted 40 years after the bombings). Those exposed *in utero* to high levels of radiation are highly susceptible to mental retardation. It was thus considered that few chromosome aberrations were identified because it was not possible to examine such heavily exposed individuals. A study of the mothers of those exposed *in utero* was therefore conducted. This study resulted in a new finding that despite a high frequency of chromosome aberrations in the mother's lymphocytes, very few chromosome aberrations were observed in those exposed *in utero*.

It is known that various types of chromosome translocations are involved in the development of leukemia in humans. Recently, it has become clear that most translocations related to infantile leukemia are already present in the fetus. About 1% of newborns (umbilical cord blood) have cells with translocations specific to infantile leukemia (pre-leukemia cells, which do not directly bring about leukemia). This frequency is 100 times higher than the frequency of infantile leukemia (0.01%). These translocation cells can be found at a rate of one in 1,000 in the immune cells that are the origin of leukemia. Although radiation actually does increase the risk of infantile leukemia, it cannot produce translocations in a large number of cells simultaneously (in principle, radiation-induced chromosome aberrations occur at random). According to the above results, rather than assuming that radiation induces cells to have various types of translocations and that one of such cells is unfortunately affected by leukemia, it seems more reasonable to consider that there are a small number of individuals in which such translocations were already present before exposure to radiation and that radiation brings about an increase of leukemia in these individuals.

After my introductory presentation as mentioned above, in Session (1), Dr. M. Linet (U.S. National Cancer Institute) talked about leukemogenic factors and Dr. D. Preston (formerly of RERF) on cancer risk in those exposed *in utero*. Session (2) focused on mouse-experiment issues: First, Dr. Masao Sasaki (Kyoto University) reported that skin cells in a mouse fetus are not susceptible to chromosome aberrations, but with *in vitro* cultivation, their sensitivity reaches a level similar with that of an adult mouse. Dr. Mimako Nakano (RERF) reported that a mouse exposed to X rays in its fetal period does not have a memory of chromosome damage after reaching adulthood (as is the case with A-bomb survivors). Dr. Tetsuya Ono (Tohoku University) explained that mice deficient in a DNA repair gene (Mlh1) exhibit an accumulation of mutations especially during their fetal period. Session (3) covered abnormal chromosome numbers and their development: First, Dr. J. Chun (University of California) reported that about 30% of brain cells in mouse fetuses show abnormalities in the number of chromosomes, but that such cells are rare in adult mice. Dr. D. Kalousek (formerly of the University of British Columbia) reported that most fetuses are normal even if diagnosis prior to birth shows abnormalities in the number of chromosomes in the placenta. Dr. Shinya Matsuura (Hiroshima University) reported on hereditary diseases showing abnormal chromosome segregation, a topic recently drawing much attention.

Lastly, it should be noted that we owe much to Dr. S. Rockwell (Yale University), Dr. Toshiaki Ogiu (National Institute of Radiological Sciences), Dr. Koichi Tatsumi (Radiation Effects Association), Dr. Gen Suzuki (RERF) and Dr. C. Waldren (RERF) for their contribution to the workshop as chairpersons. I would like to express my heartfelt appreciation to these scientists, as well as to those who supported the event behind the scenes.

Fetal Exposure to Ionizing Radiation: Chromosome Aberrations Do Not Persist in Lymphocytes and Bone Marrow Cells of Mice Irradiated *In Utero* or Soon after Birth

Nori Nakamura,[1] Mimako Nakano,[1] Yoshiaki Kodama,[1] Kazuo Ohtaki,[1] Ohtsura Niwa,[2] Megumi Toyoshima[2]

[1]Department of Genetics, Radiation Effects Research Foundation; [2]Kyoto University Radiation Biology Center

Introduction

We have recently reported that atomic-bomb (A-bomb) survivors exposed *in utero* did not show translocation dose response (about 300 survivors were examined when they were about 40 years of age). Since 13 mothers did show a clear dose response as we usually observe in A-bomb survivors, we interpreted the results as indicating that the lack of a dose response is a biological response, rather than possible overestimations of individual doses assigned to the *in utero*-exposed survivors that we examined.[1] Because we found no relevant studies in animals, we conducted a mouse study to confirm the results.[2]

Methods

Male and female B6C3F1 mice (10-12 weeks old) were mated and the progeny at various ages (including 15.5-day fetuses) were exposed to 1 or 2 Gy of X rays (220 kVp, with a 0.5 mm Al and 0.3 mm Cu filter; 1.0 Gy/min). When the mice reached about 20 weeks of age, blood lymphocytes, spleen cells, and bone marrow cells were examined with fluorescence *in situ* hybridization (FISH) method using probes for chromosomes 1 and 3.[3] The observed translocation frequency was used to estimate genomic translocation frequency as described,[3] which is about four times the observed frequency under the conditions used.[2] Metaphase spreads were prepared by conventional air-drying method.[4] Generally, 800 cells were scored with FISH for each tissue sample from each animal (no less than 500 cells).

Results

In the case of fetal irradiation, the observed translocation frequencies were generally very low (genome-equivalent frequency of <3%). Similar low translocation yields were also observed in mice irradiated as newborns (3 days old). However, with time following birth and with subsequent irradiations, these translocation frequencies gradually increased and reached a plateau of 10 to 20%. This frequency plateau occurred when the mice were irradiated at approximately 6 weeks following birth or beyond (Figure 1).

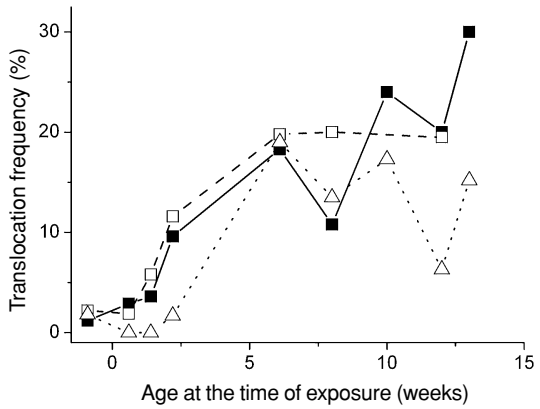

Figure 1. Translocation frequency of mice irradiated with 2 Gy of X rays at various ages and examined with FISH when the animals reached about 20 weeks of age. ■ Blood lymphocytes, □ spleen cells, and △ bone marrow cells (ref. 2). Each point represents a mean of 2 to 12 animals except for the points at 12–13 weeks which represent the results of mothers (single animal per point). The y-axis represents the genome-equivalent frequency.

The results seemed to indicate that damaged cells in fetuses and in neonates were actively eliminated. To test for the possibility, we used mutant mice bearing a knocked-out allele of the *p53* gene. Following X irradiation (2 Gy) of a pregnant dam [p53(–/–)] which was mated with a p53(+/–) sire, we found that the mean translocation frequency in blood lymphocytes and bone marrow cells in mice irradiated *in utero* was about 7% in p53(–/–) offspring and 6% in p53(+/–) littermates (examinations were done at 6 to 11 weeks of age, earlier than 20 weeks, before

onset of lymphoma in the homozygous mutant mice), and the difference was not statistically significant. In addition, these frequencies were considerably lower than 30% in the p53(–/–) mother ($p < 0.001$ when compared to the frequency in either heterozygous or homozygous offspring). Therefore, the data did not seem to support the idea the radiation-damaged cells were being eliminated by a p53-dependent apoptotic process. Although it remained possible that the damaged cells were eliminated through other apoptotic pathways, we felt that fetal irradiation probably induced chromosome damage to fetal lymphohematopoietic cells (not necessarily stem cells *per se*) but that these aberrant cells simply did not persist. To test for the possibility, we carried out another set of experiments to see if chromosome aberrations are observable *in situ* or not (i.e., without use of cell cultures *in vitro*) within spleen cells and liver cells soon after irradiation of neonates. As expected, various kinds of chromatid- and chromosome-type aberrations (both stable- and unstable-type ones) were observed, and was strikingly similar to the observations in bone marrow cells of irradiated adults (also spontaneously cycling cells). The results indicated that most of the spleen cells and liver cells of neonates (and probably fetal cells as well) entered mitosis irrespective of bearing chromosome aberrations or not. Further, the frequency of unstable aberrations rapidly declined with the increase of post-irradiation time, and approached nearly zero at 48 h after irradiation (i.e., passive elimination of cells bearing unstable-type aberrations). By contrast, translocation frequency remained at 10% at 48 h in both neonatal splenocytes and in adult bone marrow cells. However, the neonates and adults differed in a longer time scale; namely, the frequency in splenocytes following neonatal irradiation declined and approached nearly zero after 20 weeks whereas the frequency in bone marrow cells following adult exposure remained relatively stable over the same period.

Discussion

Irradiation of fetuses and neonates

The present study seems to indicate that fetal blood cells in general (excepting perhaps stem cells and primitive precursors) are sensitive for induction of various kinds of chromosome aberrations, including translocations. However, fetal cells bearing these chromosomal lesions are efficiently cleared with time following irradiation, and as such the translocation frequency declines to close to control levels as the irradiated animal grows postnatally. This is probably because hematopoietic stem cells (and the precursors as well) in fetuses are equipped with a system that makes the cells refractory to yield exchange-type aberrations. As such the progeny derived from such stem cells (blood lymphocytes, spleen cells, and bone marrow cells) are aberration-free as well, and that ultimately serve to dilute the preexisting cells that carry radiation-induced aberrations. Figure 2 shows a schematic representation of the hypothesis.

Irradiation of adults

By contrast to fetal irradiation, in the case of irradiating adult mice one fully expects to find dose-dependent frequencies of chromosome aberrations within bone marrow cells (a mixed cell population of different lineages at various levels of differentiation), and with subpopulations of persisting cells bearing translocations. For example, Xiao *et al*. reported that after irradiation of 6-week old mice, the translocation frequency remained relatively stable for 100 days, although there was a small decline in a first few days following the 3-Gy exposure (Figure 3, ref. 5). The initial decline was probably due to partial inclusion of unstable-type aberrations within the translocation-bearing cells soon after irradiation (the FISH method used here paints only a few, select sets of chromosomes, and is effective in detecting translocations between the painted and unpainted chromosomes; whereas the method used cannot

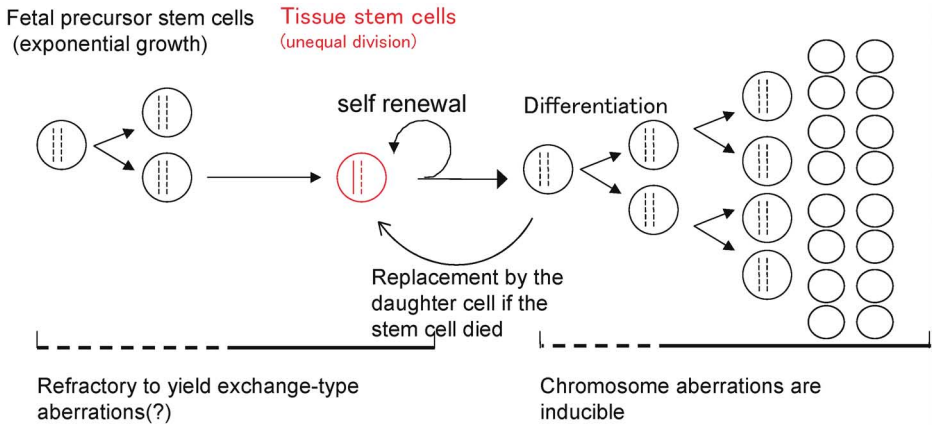

Figure 2. A schematic presentation to explain why chromosome aberrations are unlikely to remain in blood cells or bone marrow cells following fetal irradiation.

readily detect unstable-type aberrations among the unpainted chromosomes). During the 100-day post-irradiation period, substantial numbers and kinds of bone marrow cells would be produced from bone marrow stem cells, and hence the overall translocation frequency would surely decline if the stem cells of the adult mouse were refractory to translocation induction at the time of irradiation. This is not the case, however.

Another example to support that exchange-type of aberrations are induced in bone marrow stem cells comes from our observation that identical translocations exist in multiple lineages of blood cells from A-bomb survivors (clonal translocation).[6]

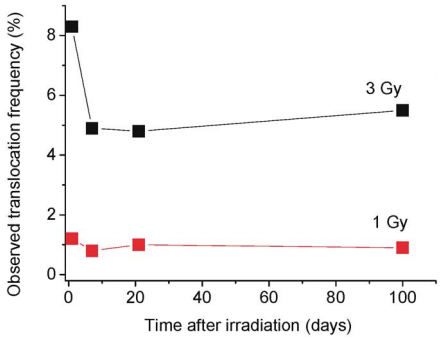

Figure 3. Translocation frequency in bone marrow cells of mice exposed to 1 or 3 Gy at 6 weeks of age (ref. 5).

Evaluation of Cairns' hypothesis and its expansion

Our data suggest that exchange-type chromosomal aberrations are *not* induced within fetally irradiated lymphohematopoietic stem cells whereas they are readily induced in bone marrow stem cells of adults. Is this really so?

After the hypothesis proposed by Cairns, tissue stem cells (defined functionally by its self-renewing, proliferative, and differentiative capacities, and operationally by its reproductive pattern in which one daughter cell remains as the stem cell, while the other daughter cell starts to differentiate) have a mechanism to maintain master strands of DNA (solid line within a tissue stem cell, Figure 2).[7] There are several reports to support the hypothesis. If the system is properly operating, both sister chromatid exchanges (SCE) and chromosomal rearrangements resulting from misrepair of DNA double strand breaks are not expected to occur. Our results here on the low frequency of translocations following fetal irradiation are compatible with Cairn's hypothesis. It does not however explain the noted constancy of the translocation frequency in bone marrow cells of irradiated adult mice for periods as long as 100 days.[5] Further, it does not explain the occasional observation of clonal translocations within various lineages of blood cells originating from bone marrow stem cells in A-bomb survivors.[6]

The apparent contradiction may be explained by assuming a tissue repair system in adult bone marrow; namely, the stem cell death, and replacement of the stem cell niche by the daughter cell. This idea was presented by Cairns[8] to explain the results of a mutation study at *Dlb* locus in mouse intestine.[9] In this study, *Dlb-1*$^{a/b}$ heterozygous mice were repeatedly treated with ethylnitrosourea (ENU) and mutant cells as a result of inactivation of *Dlb-1*^{b} allele were detected by tissue staining. Contrary to the expectation of one-hit dose response, the results showed a curvilinear response (Figure 4). Cairns interpreted the results as indicating that depletion of stem cells in the niche by cell death was the first event, and replacement by a mutant daughter (undergoes exponential growth, has to be discarded after differentiation) was the second event.[8] These daughter cells are not prohibited to acquire mutations and therefore it appears as if mutation occurred in the stem cells. It seems that the induction of clonal translocations originating from bone marrow stem cells in A-bomb survivors may also be explained by this two-hit mechanisms, although it would be difficult to distinguish from the possibility of its direct induction in stem cells.

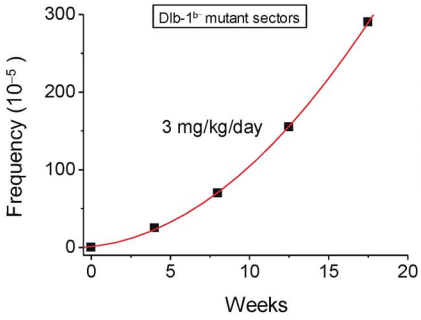

Figure 4. Dose response for induction of *Dlb* mutation in mouse intestine by daily exposure to ethylnitrosourea (ENU, 3 mg/kg body weight) (ref. 9).

How does the Cairns' hypothesis fit the results following fetal irradiation? Since hematopoietic stem cells move from fetal liver to spleen and to bone marrow along with development of animals, it seems reasonable to assume that lymphohematopoietic stem cell niche is not yet established in fetuses. This means that fetal hematopoietic stem cells are not yet established to maintain the master strand DNA, which in turn indicates that mutation induction is not prohibited in these cells. Nevertheless, translocations are not readily induced in fetal stem cells (although on occasion stem cell-derived clonal translocations have

been observed). The discrepancy may be explained by the possibility that stem cell precursors that are still undergoing exponential growth also do not generally repair DNA breaks (thus, exchange-type aberrations are difficult to be induced). Such a system might have been evolutionarily acquired in order to avoid an accumulation of somatic mutations during fetal growth, and subsequently significant pathology later in life (e.g., cancer). Alternatively, it might simply be a matter of saving time and energy by leaving the broken DNA unrepaired so that fetal development can proceed since fetuses contain a large number of stem cells (or at least cells with the potential).

If this were the case, one would expect it to be difficult to induce translocations in stem cell precursors. While no relevant studies were found in the literature, there are studies indicating that exchange-type aberrations are inducible in mouse embryonic stem (ES) cells.[10] If ES cells and multipotent embryonic stem cells (inner cell mass of an embryo) share the same characteristics (which is still to be confirmed), then, translocations might be induced by irradiation in fetuses younger than 15.5 days. We think this probability is rather low, however, because we have no evidence to suggest that gestational age affected the low yield of translocations in A-bomb survivors exposed *in utero*.[1]

Similar kinds of observations, i.e., proneness of mutagen-exposed fetal cells to die and to be cleared from tissues rather than to repair and survive with specific genomic lesions, have been made repeatedly. One such observation relates to significantly lower (~50% lower) yields of mutation in male germ cells of fetuses or newborns as compared to the yields found in adults.[11-13] A similar observation was made for the induction of translocations.[14] Likewise, in female gametes, the mutation induction rate was shown to be lower if irradiated perinatally.[15,16] Fetuses are also generally less sensitive to radiation in terms of tumor induction when compared to young animals (for example, ref. 17).

Fetal exposure, cell death, and cancer risk

Last, we would like to address a possible relation between the low yield of translocations and the low yield of cancer induction following irradiation of mouse fetuses. Studies on radiation sensitivity of human fetuses have been interesting to say the least. Epidemiologic studies in the 1950s (the first one was the famous Oxford Survey of Childhood Leukemia conducted by A. Stewart) indicated that offspring of pregnant mothers who were exposed to diagnostic, low-dose X rays (estimated dose of about 10 mSv) had an increased relative risk (RR) of dying from childhood leukemia or cancer by ~50% above the background level (ref. 18 for a good review). This corresponds to an excess RR value of 50 per Sv if a linear dose response is assumed, which might look very large but is not in fact unrealistic because leukemia risk of the survivors exposed below 10 years of age showed similar large RR values.[19] Regarding the lack of excess leukemia cases among the survivors exposed *in utero*, there had been hot arguments between Dr. Stewart and epidemiologists at the Atomic Bomb Casualty Commission (ABCC). Now we know that individual dose estimates by the Dosimetry System in 1965 (T65D) were on average nearly twice as large as the current estimates (DS86 or DS02), and gave rise to too many expected number of cases of leukemia. Further, there are only 3,600 survivors in the *in utero* cohort; a number too small to derive any firm conclusion.[19]

A puzzle still remained however; in none of the comparable *in utero* animal irradiation studies conducted were large RR values generated as one might have expected from the human epidemiologic studies at low doses. We think that the apparent contradiction might be resolved by assuming that the cancer dose response is non-linear; namely, the increased risk of childhood cancers occur only at low doses, and the lack of dose effect in animal studies occurs because the doses were too high (e.g., 1 Gy or larger) and killed excessive numbers of the target cells at risk. A non-linear (i.e., a humped shaped) dose response curve is often observed in many studies using young or adult mice (e.g., induction of cancer or germline mutation). However, the dose required to give the peak response is usually in the range of 5 Gy, whereas in fetuses, it might well be much smaller, e.g., less than 0.5 Gy. A humped dose response at <0.1 Sv was suggested in translocation dose response in blood lymphocytes from A-bomb survivors (Figure 5, ref. 1) and a similar humped response at <0.5 Gy of X rays was also reported for induction of liver tumors after irradiation of mouse fetuses (Figure 6, left panel, ref. 20). The results after irradiation of fission neutrons gave a very similar response with a peak effect at around 0.5 Gy (Figure 6, right panel),

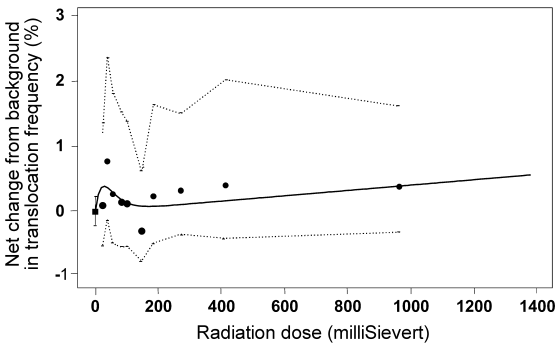

Figure 5. Fitted dose response curve for induction of translocations in blood lymphocytes of A-bomb survivors exposed *in utero* and examined at about 40 years of age (ref. 1).

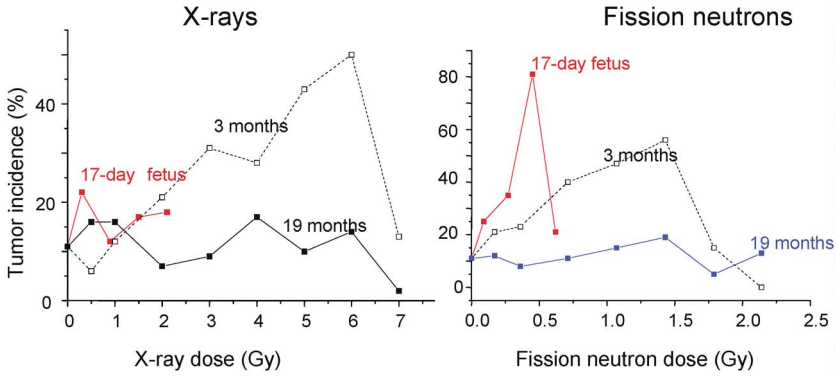

Figure 6. Dose response for induction of liver tumors in mice exposed to X rays or fission neutrons at various ages (ref. 20).

Figure 7. Comparison of age at the time of irradiation for induction of various types of tumors (single exposure to 3.8-Gy gamma rays, ref. 17).

thus strengthening the possibility of a humped shaped dose-response curve. It needs to be pointed out, however, that since the dose range that gave the peak response is a rather narrow one, low dose experiments, with its appropriate selection of doses, would be difficult. Further, it remains to be determined why fetuses (e.g., 17 days p.c.) are more sensitive than young animals to radiation for induction of certain types of tumors (e.g., pituitary and lung), while being less sensitive for others (e.g., ovarian tumors, liver tumors, malignant lymphoma, and myeloid leukemia) (Figure 7, ref. 17). We suspect that these differences might be related to differences in modes of death within stem cell pools within these different tissues. Further studies are required to test the hypothesis however.

Conclusion

Ironically, the one clear conclusion that we draw from the present study is that we need to know more about biology of fetuses and associated effects of ionizing radiation. Preconceived notions on this subject probably should be set aside, because our concepts are often based on biological responses of adult mammals and not on fetal responses. A prime example of this is that fetuses that had undergone heart surgery and returned to *uterus* have no scar on the skin when born at full term.

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Radiation Dose-response Relationships for Thyroid Diseases of Atomic Bomb Survivors in Hiroshima and Nagasaki

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Introduction

A number of RERF studies evaluated thyroid abnormalities among atomic-bomb survivors by using the Life Span Study cohorts and Adult Health Study (AHS) cohorts at different times after bombing.[1-7] Most studies suggested a positive radiation effect on thyroid cancer confirmed by tumor registry and autopsy information.[1,3-7] This is consistent with the results of studies conducted in other irradiated populations.[8-10] The RERF studies, however, were limited by their inability to identify various thyroid diseases such as benign nodule and autoimmune thyroid diseases; therefore, dose responses for these thyroid diseases other than cancer were not fully evaluated. From 1984 through 1987, the thyroid study evaluated dose responses for thyroid nodules and autoimmune thyroid diseases in the ASH cohort.[11] However, this study was conducted only in Nagasaki but not in Hiroshima.

In this article, we describe the results of the first comprehensive thyroid disease survey using advanced methods to detect thyroid nodules (malignant and benign) and autoimmune thyroid diseases. This clinical survey was conducted in both Hiroshima and Nagasaki AHS cohort members between 2000 and 2003.

Participants and Methods

A total of 4,552 AHS cohort members visited RERF for biennial health examinations between March 2000 and February 2003. We asked them to participate in the thyroid disease study at the time of the examinations, and 4,091 subjects (89.9%) agreed and completed the thyroid examination.

A trained nurse recorded information on current and past thyroid disease and thyroid medication by using a questionnaire. A blood sample was drawn to measure free thyroxine, thyrotropin levels, antithyroid peroxidase antibody (TPOAb), and antithyroglobulin antibody (TgAb). All participants underwent thyroid ultrasonography. Ultrasound-guided fine needle aspiration biopsy was performed in participants with solid nodules 1 cm or larger in diameter. Aspirates were examined microscopically and assessed for pathology. Analyses were performed in 3,185 participants specifically excluding individuals who were *in utero* at the time of atomic bombings, or not in city, or had unknown radiation doses (mean age: 71 years, 1,023 men and 2,162 women, mean and median radiation doses of 0.449 Sv and 0.087 Sv, respectively). A dose response for each thyroid disease was analyzed by using linear excess odds ratio (EOR) models.[12]

Results

In the 3,185 participants, the prevalence of all solid nodule, malignant tumor, benign nodule and cyst was 14.6%, 2.2%, 4.9%, and 7.7%, respectively. The prevalence of positive thyroid antibodies, antithyroid antibody-positive hypothyroidism, and Graves' disease was 28.2%, 3.2%, and 1.2%, respectively.

Significant linear dose-response relationships were observed for the prevalence of all solid nodules, malignant tumors, benign nodules, and cysts ($P < 0.001$, Figure 1). We estimate that about 28% of all solid nodules, 37% of malignant tumors, 31% of benign nodules, and 25% of cysts were associated with the radiation exposure. The interaction of age at exposure with dose was significant for the prevalence of all solid nodules ($P < 0.001$, Figure 2) and benign nodules ($P = 0.002$, Figure 2) showing that the dose effects were significantly higher in those exposed when young. It was not, however, statistically significant for the prevalence of malignant tumors ($P = 0.10$, Figure 2). For malignant tumors,

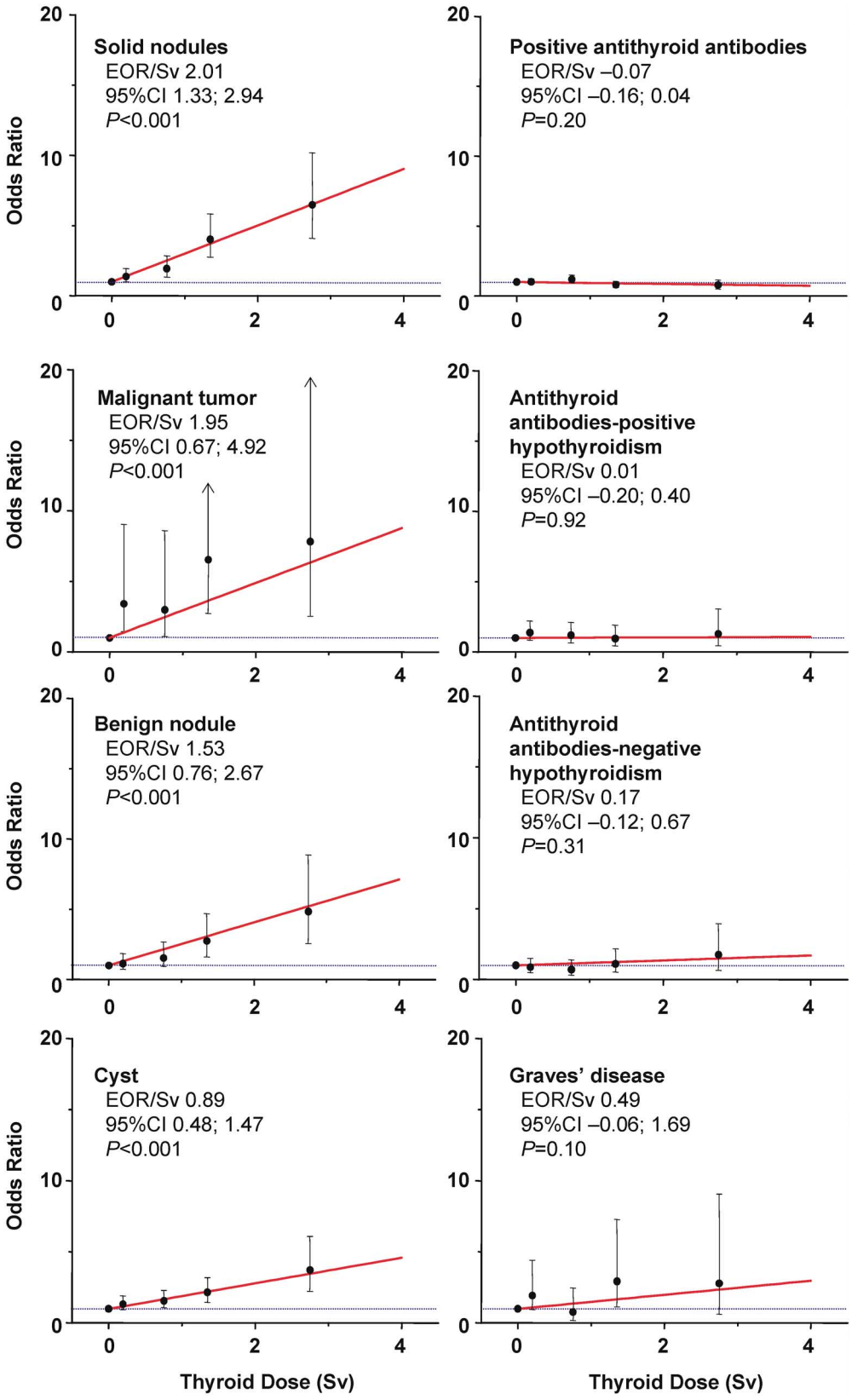

Figure 1. Dose response for thyroid diseases. The red straight line displays the odds ratio from the best-fitting linear excess odds ratio model at 10 years of age at exposure. The points are dose category-specific odds ratio with 95% confidence intervals. *P*-values are calculated by likelihood ratio test.

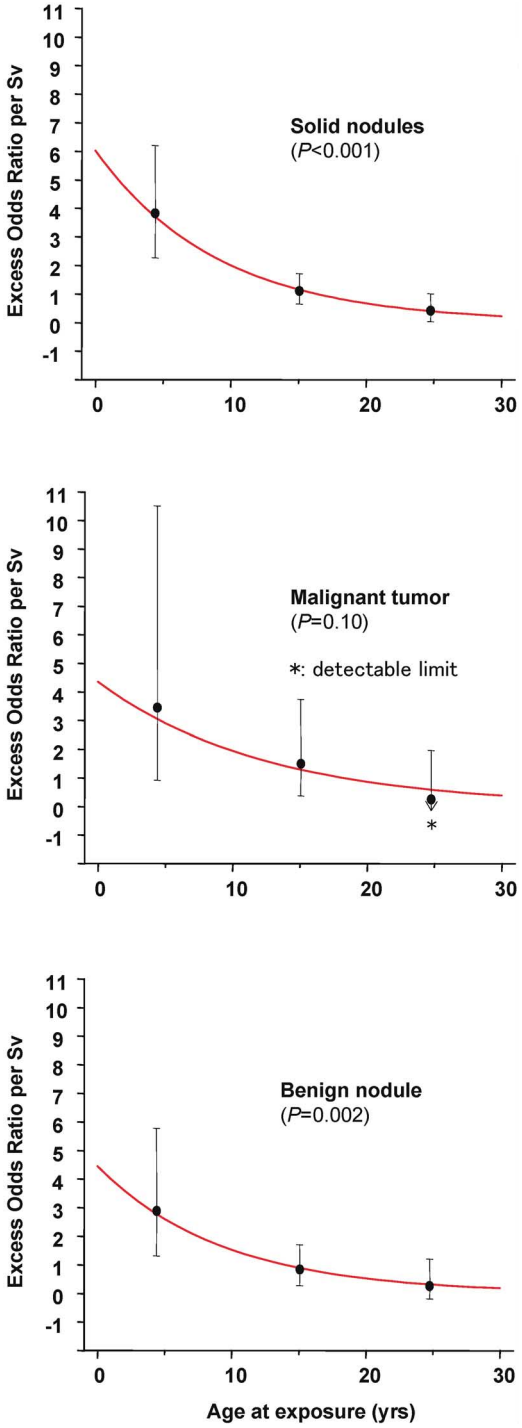

Figure 2. Trend for age at exposure in radiation dose response for thyroid diseases. The curve displays the trend for age at exposure in excess odds ratio per Sv based on the best fitting model. The points are excess odds ratio per Sv in each age at exposure category with 95% confidence intervals. *P*-values are calculated by likelihood ratio test.

however, there was a model with better fit in terms of AIC (Akaike Information Criterion) than the linear EOR model; i.e., a nonlinear model in which the square root of dose replaced dose in the linear EOR model equation. With this model, EOR at 1 Sv at 10 years of age at exposure was 3.96 (95% CI: 1.31, 12.86, $P < 0.001$), with significant effect modification by age at exposure ($P = 0.04$) and 36 (52%) cases associated with radiation exposure. However, in terms of the prevalence of cysts, there appeared to be no interaction of age at exposure with dose ($P = 0.49$). Further, there was no interaction of sex or city with dose in the prevalence of any thyroid nodules ($P > 0.30$).

The prevalence of positive cases for antithyroid antibodies was not associated with thyroid radiation dose ($P = 0.20$, Figure 1). The separate analyses for TPOAb and TgAb showed that neither the prevalence of TPOAb-positivity ($P = 0.91$) nor TgAb-positivity were associated with dose ($P = 0.52$). Neither antithyroid antibody-positive hypothyroidism nor -negative hypothyroidism were associated with dose ($P = 0.92$ and $P = 0.31$, respectively, Figure 1). An association between the prevalence of Graves' disease and radiation dose was suggested but did not reach the level of statistical significance ($P = 0.10$, Figure 1).

Discussion

It is well substantiated that thyroid cancer increases with radiation exposure[8-10]; our results here are consistent with those of the reports. There have been several previous studies that have reported on the association between benign thyroid nodule formation and thyroid radiation dose,[10,13] but this relationship has not been well documented in atomic-bomb survivors.[5] Our results clearly demonstrated that benign nodule formation increased with radiation dose. While it is well known that sufficient doses of ionizing radiation can induce DNA strand breaks, along with a host of other types of genomic lesions, the mechanisms by which those molecular lesions evolve into thyroid neoplasms are at best ill-defined. Recent studies have suggested that rearrangements of the *ret* proto-oncogene are in someway associated with post-Chernobyl thyroid cancer.[14] However, in contrast to earlier suggestions that specific rearrangements of the *ret* proto-oncogene are directly associated with radiation exposure have not been substantiated.[15]

The present study indicated that individuals who were exposed when young were at higher risk of developing thyroid nodules. This result is consistent with previous studies on children in the Chernobyl accident,[16] medical irradiation,[10] and atomic-bomb survivors.[7,11] The reason why radiation elicits this response at younger ages is unknown. The fact that not only solid thyroid nodules but also other solid

cancers in various organs were observed more frequently in subjects exposed at younger ages[6] indicates that organs in children may be more radiation sensitive to the carcinogenic effects of radiation than those in adults.

Reports on effects of radiation on autoimmune thyroid diseases have been inconsistent; largely because of methodological differences of sample selection, and the varied diagnostic techniques and criteria used in these studies.[5,11,17] Eheman *et al*. pointed out that some studies had limitations due to small subject number, absence of thyroid radiation dose, or uncertain diagnostic methods.[18] Therefore, we diagnosed autoimmune thyroid diseases using technologically advanced methods and clear diagnostic criteria in a large cohort with known radiation doses. In the dose-response analyses, we did not observe significant radiation dose-response relationships between either antithyroid antibody positivity or antithyroid antibody-positive hypothyroidism. This is consistent with the results of a recent publication evaluating people exposed as young children to iodine 131 from the Hanford Nuclear Site[19] and previous epidemiological studies on atomic-bomb survivors.[5,20,21] However, the study conducted in Nagasaki AHS subjects from 1984 through 1987 demonstrated a convex dose-response relationship in antithyroid antibody-positive hypothyroidism, with maximum prevalence at a dose of 0.7 Sv.[11] This discrepancy may be the result of (1) the present study's increased study population, which includes both Hiroshima and Nagasaki atomic-bomb survivors, (2) the different diagnostic techniques used for measurements of thyroid antibodies and thyroid stimulating hormone (TSH), and (3) change of dose distribution of the cohort members over time because mortality and cancer risks are partially dependent on radiation dose.[22] Furthermore, we made diagnoses on the basis of serum tests at one point in time in both studies, but the results of serum tests sometimes vary over time.

There are some limitations in this study. First, people with previously diagnosed nodular thyroid diseases might have been motivated in agreeing to participate by their preexisting medical condition, thus creating a specific study bias. Second, a survival bias clearly exists in this study: median life expectancy decreases with increasing radiation dose at rate of about 1.3 years per Gy,[23] thus reducing the proportion of high-dose atomic-bomb survivors in the present study, relative to the larger proportion of the original 1958 cohort. Furthermore, not only is mortality risk radiation dose dependent, but cancer risks are radiation dose dependent as well. Severe thyroid cancer patients may have been excluded from this study due to early death. Therefore, we realize that a survival bias exists in the present population, especially in the high-dose exposed atomic-bomb survivors. Third, we were not able to clarify the earlier effects of radiation and how long the effects of radiation on thyroid nodule formation persisted after exposure, because the present cross-sectional study was conducted 55-58 years after the atomic bombings.

In conclusion, the present study revealed that 55-58 years after radiation exposure, a significant linear dose-response relationship exists not only for malignant thyroid tumors but also for benign thyroid nodule formation as well. This relationship was significantly higher, i.e., the unit effectiveness of radiation was greater, in those exposed at younger ages. Autoimmune thyroid diseases, by contrast, were not found to be significantly associated with radiation exposure.

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Memories of My Father, Paul Henshaw

Robert E. Henshaw, Ph.D.

My father began his career with a post-doctoral program with Gioacchino Failla at the Biophysics Laboratory, Memorial Hospital, New York City. Their pioneering studies on the effects of radiation on cell functions, and on use of radiation to both cause and cure cancer were classics and were cited for many years afterward. He moved on to the National Institute of Health (NIH) and continued his studies of the effects of radiation on cells. When the war started he joined the Manhattan Project, first in Chicago in 1942 for five months, then at the Oak Ridge National Laboratory in Tennessee as a staff biophysicist. His wartime attempts to predict the possible effects of the bomb's radiation led to his later work at the Atomic Bomb Casualty Commission (ABCC).

Like nearly all the scientists involved in the Manhattan Project early on, he surely was initially convinced of the need for such a weapon, though his particular work was not in production, but in analysis of effects. I am convinced that he, like many—perhaps most—of the Manhattan Project scientists, developed increasing unease with the certainty of the potential for devastation and for causing future world arms races.

I know that he became convinced by at least spring of 1945 that the bomb should not be dropped on a population center because he hosted a meeting of his fellow Oak Ridge scientists in our living room seeking a way to head off the expected carnage. In the course of their deliberations, the assembled scientists decided to send two emissaries to the White House to appeal directly to President Truman not to drop the bomb on a population center. On 17 July 1945 two scientists did go to the White House, and were shown into a front room where they sat for about two hours. Finally Secretary of War Stimson entered to inform them that the President was detained and that he (Mr. Stimson) would relay the scientists' message to the President. Within weeks the bomb was indeed dropped on Hiroshima and Nagasaki. Only years later when official records were declassified was it divulged that President Truman had not been informed of the scientists' plea, and in fact that Mr. Stimson did not even mention the Manhattan Project while meeting with the military Joint Chiefs of Staff on the day following the scientists' visit.

I sat on the floor in the corner of our living room watching. I, at age eleven, did not appreciate the significance of the meeting, nor even the actual topic discussed since my father and other scientists did not share details of their work at home. I remember that there was no levity and there was great consternation. I understood only that the meeting was very important. Shortly after the bomb was dropped, my father divulged to me the topic of the meeting in our living room, and the story about their delegation having gone to the White House. My father and I discussed that meeting many times in the 1950s and 1960s—years before other accounts were published of Dr. Leo Szilard appealing to Mr. Truman on behalf of Manhattan Project scientists. I have recently reviewed many accounts of the "Decision to Drop the Atomic Bomb" published on the web. I have reviewed the documents produced by the Manhattan Project scientists that were delivered to the White House. My father's name is not among the signatories. I wish he were alive to discuss the reasons for his absence.

My father's attempt to influence the President's decision, together with his scientific interest in the actual effects of the bomb, might have been contributing factors in his decision to be a part of the ABCC at its inception. He was assigned by the National Academy of Sciences (NAS) as a head of the field survey team for the establishment of ABCC and came to Japan in 1946 with Austin Brues, another civilian consultant selected by NAS. My father was shaken by the devastation he saw in Japan. He also came to respect and to love the people of Japan while there, and following ABCC, he took a position with the Supreme Commander for the Allied Powers (SCAP) in 1947 so that he could bring his family to Japan for

At the meeting held in Tokyo in 1946. (First row from left) Dr. Nakahara, Dr. Henshaw, Dr. Sasaki, Dr. Brues, (second row from left) Dr. Neel, Dr. Murachi, Dr. Tsuzuki, Dr. Higashi, Dr. Ulrich (photo courtesy of Dr. James Neel)

a year. That year with ABCC and the subsequent two and half years with SCAP living in Tokyo changed my father in fundamental ways, I believe. He became a life-long anti-war activist, always voting and campaigning for a peaceful solution to all conflicts.

I am certain that he felt complicity in the tragedy and that he had been betrayed, but he went on with his career. While he retained life-long interest in the work of ABCC and kept close ties with Austin Brues and Jim Neel throughout his life, his later work did not stay close to his earlier interests. In the 1950s he worked at the Atomic Energy Commission in the Medical and Biological Division handing out research grants to others, and then turned to world population growth studies. By the l950s he was talking of world peace, and by the 1970s of the futility of war. Late in his life he would support nearly any organization thinking of running a peace candidate for president of the United States. Two years before his death, he prepared a talk and slide show which he entitled "Holocaust," clearly demonstrating his beliefs late in life. His last slide was labeled "Monument in the Hiroshima Peace Park: 'Rest in Peace, These Errors Shall Not Be Repeated.'"

My father's professional interests in cell function surely influenced my own decision to go into animal physiology. Being old enough to remember life in the Manhattan Project, I have always felt some sort of complicity-by-extension. I early-on adopted my father's desires for peace and his view of the futility of war. These surely explain why I will attend the 60th anniversary Peace Ceremony on 6 August 2005. My father and I had planned to attend the 50th anniversary, but he died in 1992. They may also explain why I have related to the story of Sadako Sasaki and the 1,000 paper crane to such an extent that I am bringing about a thousand paper cranes which I will hang at the Peace Shrine. In July I sent the above story of my father's work in the Manhattan Project and in the ABCC to many persons on my email list. The letter took on wings of its own. I have received paper cranes folded by dozens of people, many of whom are not known to me, but who wish to be represented at the Peace Shrine this year. My sister, who was just young enough to not remember the meeting of scientists nor even the bombing, nevertheless was heavily influenced by my father's evolution into a peace activist. She indulged in many discussions with my father through the years, and today reads voraciously on related topics. My daughter knew her grandfather before he died, and greatly valued his wisdom and values.

I would very much appreciate the opportunity to visit the Radiation Effects Research Foundation (RERF) and see some of the work that has taken place since the ABCC days. I plan to donate to RERF these slides taken by my father while he was in Japan, believing that they belong to history rather than to our family personally. I do hope that people in Japan will see these photographs and share with my father what he thought about world peace and futility of war.

(Written in July 2005)

(Editor's note: The comments and views expressed are solely those of the author and do not necessarily reflect the views or opinions of RERF and its supporting U.S. and Japanese agencies.)

The A-bomb Dome around 1946-1948. The devastated town seems to be undergoing reconstruction. (photographed by Dr. Paul Henshaw and donated by Dr. Robert Henshaw)

Dr. and Mrs. Robert Henshaw donating the photographs to RERF Chairman Okubo on August 5, 2005. (From left to right) Dr. Katayama, Mrs. Henshaw, Dr. Okubo, Dr. Waldren, Dr. Henshaw, and Dr. Cologne

Thanks for RERF Home Page Conventional Giemsa Staining and Automated Karyotyping to Detect Chromosome Aberrations

Gordon K. Livingston, Ph.D.
Cincinnati, Ohio, U.S.A.

We now consider it commonplace, even a daily practice to communicate with individuals in distant lands whom we have never met, do not know (except through the literature), likely will never meet and yet are still able to achieve worthwhile scientific goals by utilizing the internet and working as a team. I am a cytogeneticist and briefly describe in this article a fruitful collaboration with Drs. Akio Awa and Nori Nakamura at RERF in Hiroshima, Japan that culminated in obtaining research grant support within one year, which was quite unexpected. This support now makes it possible to conduct further cytogenetic evaluations of former U.S. nuclear workers with known intakes of plutonium in lung, bone and liver and known individual external and internal doses of radiation.

This rewarding collaboration can be traced to the RERF publication authored by Dr. Nakano and coworkers (Int. J. Radiat. Biol. 77:971-977, 2001) that compared cytogenetic data based on solid Giemsa staining with FISH-based staining for a large cohort of 230 A-bomb survivors. I found that this paper provided the RERF website and also a link to Dr. Awa's manual entitled, "Biodosimetry of Human Exposure to Radiation: A Manual for Detecting Stable Chromosome Aberrations by the Conventional Giemsa Staining Method."

My initial attempts to contact Dr. Awa by e-mail were handled by Dr. Nakamura but I eventually gained direct access to Dr. Awa, which led to a productive exchange devoted to radiation cytogenetics. When I read Dr. Awa's manual on the RERF website, my waning enthusiasm (associated with lack of gainful employment) received a much needed boost, and it renewed hope that my plutonium research material (which cannot be duplicated) was still a valuable resource. I felt it a privilege to be able to talk with him about a subject of mutual interest over the internet.

The method, based on conventional Giemsa staining of chromosomes and subsequent karyotyping, has merit for the reasons enumerated by Dr. Awa: 1) simplicity and low cost (no expensive DNA probes or fluorescence microscopy are necessary), 2) complete coverage of all chromosome pairs, 3) ability to detect upwards of 70% of stable aberrations, and 4) that archived slides have value as long as the staining quality is not affected. The most difficult challenge using this approach, however, is the daunting task of screening the karyotypes of at least 100 metaphase cells per examinee. The task, however, has been largely solved with the advent of computers, digital cameras and specialized software capable of counting and recognizing distinctive morphologic features of chromosomes and arranging standardized karyotypes in less than five minutes. This technology allows the chromosomes to be arranged automatically then manually edited as the karyotype is scrutinized on the computer monitor. The method links the microscope and computer as research tools and helps to reduce the fatigue of working on the microscope. Cells are screened for chromosome aberrations using the International System for Chromosome Nomenclature (ISCN, 2005), which assigns the chromosome pairs into the standard seven groups (A-G) of autosomes and the XY sex chromosomes. Although the method cannot detect all chromosome aberrations (i.e., translocations involving equivalent segments) it can detect a reasonable fraction of stable aberrations as shown by RERF scientists.

Following communication with Dr. Awa, I was invited to present a seminar at the Health-Related Energy Research Branch (HERB) at the National Institute for Occupational Safety and Health in Cincinnati, Ohio, U.S.A. The seminar title was "FISH-based Chromosome Aberrations: A Dose-related Biomarker of Historical Radiation Exposure" presented in March of 2004. Shortly afterwards, I was encouraged to submit a grant application to the National Research Council. The application was prepared, evaluated, and ultimately selected for funding. Dr. Awa kindly submitted one of the letters of recommendation in behalf of the application, which no doubt carried considerable weight given his reputation.

I am pleased that the research study is now underway with the involvement, assistance and encouragement of many individuals and organizations. I would especially like to take this opportunity to thank individuals for the effort to present Dr. Awa's manual on the RERF home page, and Dr. Awa for his encouragement and support to my research investigation.

(Editor's note: This article was originally written for the July 2005 issue of the in-house *RERF Newsletter*. A sequel will follow in the next issue of the *RERF Update*.)

Facts and Figures

When treasures are mentioned, our first thought generally turns toward the treasures of the Realm the crown jewels of the empire and all of that. However, here at RERF we speak in terms of another type of "crown jewels"—the vast *Biosample Archive* derived from the various study cohorts. Much like the Emperor's jewels, RERF's carefully collected, preserved, and archived biosamples have incalculable wealth; not monetary value *per se*, but rather extraordinary value in terms of the research and development resource for long-term health effects analyses associated with radiation exposure, aging, and general life-style issues.

There are few biosample repositories that can match the size, scope and shear potential of RERF's collection. As one can glean from the table, the collection is sizable one, with large numbers of individuals donating various types of biosamples (blood, urine, tissues, etc.) over extended periods.

The archived materials have been extensively used to date, and have added nicely not only to our basic understanding of late arising health consequences of prior acute radiation exposures, but also in helping establish risk assessment standards for radiation hygiene programs throughout the world, as well as allowing researchers to address a number of very basic radiobiological questions.

With evolving analytic technologies, these samples will gain appreciable value in the coming years. Therefore, full and proper additions, maintenance, safeguarding, and research use of RERF's *Biosample Archives* become critically important missions in their own right. In this regard, RERF welcomes any and all constructive input from the outside scientific community on the nature and use of this unique biosample repository.

Biosample Archive

Class	Subclass	Type	Number	Cohort source description
Blood	Whole[1]	Freeze-dried	5,700	AHS 1997 to present (20-53 discs per blood subject-sample)
	Cell[1]	Cryo-mnc fractions	6,900	AHS 1990 to present (4-5 vials per blood subject-sample)
	Cell[1]	Cryo-mnc fractions	11,000	F_1 subjects 2002 to present (4-5 vials per subject-sample)
	Cell[2]	Cryo-ebv lymphs	2,603	AHS 1987 to present (~2-4 vials per sample/9,504 vials in total)
	Cell[3]	Cryo-ebv lymphs	3,310	F_1/AHS 1985 to present (1,403/1,928 child/parent cells)
	Cell	Blood smears	nd[6]	LSS/AHS 1952 to present (Nagasaki); 1961 to present (Hiroshima)
	Sera/plasma[1]	Cryo/freeze-dried	15,000	AHS 1969-present (1-8 vials per subject-sample; multiple samplings)
			11,000	F_1 2002-2006 (1-8 vials per subject-sample; single samplings)
Urine	Whole[1]	Cryopreserve	4,600	AHS 1999 to present (4-1 ml vials per urine subject-sample)
		Cryopreserve	11,000	F_1 2002 to 2006 (4-1 ml vials per urine subject-sample)
Tissues	Surgery[4]	Cases	130,000	LSS/AHS and others
		Embedded tissues	173,000	LSS/AHS and others
		Stained slides	308,000	LSS/AHS and others
	Autopsy[4]	Cases	13,000	LSS/AHS and others
		Embedded tissues	472,000	LSS/AHS and others
		Stained slides	633,000	LSS/AHS and others
	Dental[5]	Teeth	1,394	AHS 1987-present (1,387/7 Hiroshima/Nagasaki AHS subjects)

Notes

[1] Yamada, M. Personal communication to RERF Archives Unit and to Update editors, 2006

[2] Hayashi et al. X-ray radiosensitivity of lymphocytes in vitro from A-bomb survivors. Part 3: Transformation of B-cell by Epstein Barr virus and their cryopreservation (RP 7-87, Addendum to RP 3-86) *In*: Program-Project Report, 1 April 2005-31 March 2006, pp 219, Radiation Effects Research Foundation, Hiroshima, Japan, 2006.

[3] Takahashi et al. Culture of lymphoblastoid cell lines as sources of biological samples for investigation of genetic effects of radiation on children of atomic bomb survivors (RP 5-85). *In*: Program-Project Report, 1 April 2005-31 March 2006, pp 142, Radiation Effects Research Foundation, Hiroshima, Japan, 2006.

[4] Submitted from the Department of Epidemiology, October 31, 2005.

[5] Nakamura et al. Radiation dose estimates of A-bomb exposed people by using teeth. Part 1. Collection of teeth from A-bomb exposed people in Hiroshima and Nagasaki (RP 10-86). *In*: Program-Project Report, 1 April 2005-31 March 2006, pp 147, Radiation Effects Research Foundation, Hiroshima, Japan, 2006.

[6] nd = not determined

Research Protocols Approved 2004

RP 1-04 A Nested Case-Control Study of Hepatocellular Carcinoma among Atomic-bomb Survivors Using Stored Sera

Fujiwara S, Ohishi W, Suzuki G, Cologne JB, Akahoshi M, Hakoda M, Chayama K

Hepatitis C virus (HCV) or hepatitis B virus (HBV) infections are a major cause of hepatocellular carcinoma (HCC). Increased liver cancer and cirrhosis among atomic-bomb survivors have been reported based on mortality studies or tumor registries, but virus infection status was not taken account in the analyses. The previous studies at RERF demonstrated no increase in prevalence of anti-HCV antibody with radiation dose, but reported supermultiplicative effects between radiation exposure and chronic HCV infection in the etiology of HCC without concurrent cirrhosis. However, the precise mechanism of the synergy has not been elucidated.

The determinants of a progressive course for chronic HCV infection are likely to include both viral factors and aspects of host immune function. To epidemiologically test a hypothesis that radiation exposure accelerated HCC occurrence among atomic-bomb survivors in the early stage of liver fibrosis after HCV infection, in this research protocol we will plan a nested case-control study of HCC using stored serum.

The proposed study will examine sero-positivity of HBV and HCV, serum levels of the two viruses, viral genotype and subtype of HBV and HCV in core, E2-HVR-1, and NS5A of HCV, hyaluronic acid, and type IV collagen using stored serum in the HCC patients and their controls in the Adult Health Study. Presently, stored serum is available for 207 HCC patients. We will select three age- and sex-matched at-risk controls for each HCC case. We will analyze the relationship between HCC and these variables in serum, after taking account of potential predictors of progression toward HCC, such as body mass index, platelet counts, smoking, alcohol drinking, diabetes mellitus and others.

In 10 selected subjects who are positive for HCV-RNA, viral genotype and subtype of HCV will be examined in three samples that were serially collected, and the natural history of virus mutation after infection will be analyzed by a phylogenetic tree analysis with divergence time in collaboration with Dr. Kazuaki Chayama's laboratory at Hiroshima University.

RP 2-04 A Case-Control Study of Atrophic Gastritis and Gastric Cancer Using Frozen Sera and Genomic DNA: Identification of New Biomarkers for Chronic Gastritis Associated with Gastric Cancer

Suzuki G, Hattori N, Hakoda M, Fujiwara S, Akahoshi M, Kodama K, Hayashi T, Nakachi K, Cullings HM, Ito M, Hatakeyama M, Tahara E

The risk for development of atrophic gastritis and gastric cancer is known to vary depending on a host factor (*Helicobacter pylori* [*H. pylori*] infection) and genetic factors that regulate inflammatory-response. Bacterial toxicity is dependent on binding sites for SHP-2 in the CagA sequences of *H. pylori*, which would be evaluated by antibody titer in sera specific for sequences containing the SHP-2 binding site. The *IL1B* allele and the *LTA*/*NFKBIL1*/*BAT1* haplotype are thought to direct the magnitude and nature of inflammatory response to *H. pylori*. Since radiation exposure has an additive effect on the multi-step process of human stomach carcinogenesis, we will include "dose" as a potential variable in the analyses. The main purpose is to determine whether serum antibody against the binding site for SHP-2 of the *H. pylori* CagA sequences and genetic factors, namely the *IL1B* allele and the *LTA*/*NFKBIL1*/*BAT1* haplotype, would provide new biomarkers for chronic gastritis associated with gastric cancer.

A nested case-control study will be conducted using the stored sera of about 500 Adult Health Study (AHS) participants who developed gastric cancer with histological diagnosis between 1970 and 2001. Of these, only one serum sample collected 2 to 4 years before diagnosis is available in 160 cases, while two serum samples collected 2 to 4 and 8 to 12 years before diagnosis are available in 340 cases. The primary endpoint of the study is to examine the relationship between infection with virulent strains of *H. pylori* and the development of gastric cancer. The secondary endpoint is to analyze the association between infection with virulent strains of *H. pylori* and the development of chronic atrophic gastritis among the portion of the controls for the cancer study who are free of gastritis at the beginning of the study period. The cancer registries and tissue registries in Hiroshima and Nagasaki will be used for the determination of gastric cancer cases. To evaluate atrophic gastritis, pepsinogen I and II will be measured using sera collected 2 to 4 years and 8 to 12 years before diagnosis of cancer, and diagnosis will be carried out based on Miki's criteria for atrophic gastritis. Two control cases (about 1,000), matched for sex, age, city, and year of blood drawing, per case will be selected from among the AHS participants. Using serum samples collected 8 to 12 years before cancer diagnosis, IgG antibodies against *H. pylori* will be measured via a conventional method, while antibodies against the binding sites for SHP-2 of the

CagA sequences of *H. pylori* in sera of the patients will be measured using a new ELISA (enzyme linked immunosorbent assay) kit now being developed. The incidence of atrophic gastritis increased at the rate of 8%/5 years in *H. pylori*-infected individuals. Thus, it is expected that about 10% of the study subjects (16% of infected subjects [60%]) are incident cases of atrophic gastritis. We suspect that the risk for atrophic gastritis and gastric cancer varies depending on the presence or absence of CagA, and the type of CagA sequences, i.e., European/American or East Asian.

H. pylori induces a chronic inflammatory reaction that causes intestinal metaplasia, which plays an important role in the multi-step process of human gastric carcinogenesis. Therefore, it is of interest to note whether A-bomb exposure is implicated in the development of chronic gastritis associated with gastric cancer.

For genetic factors, in addition to the *IL1B* genetic polymorphism, which has already been reported as a risk factor for hypochlorhydria and gastric cancer, haplotype polymorphisms of the *LTA-NFKBIL1-BAT1* genome region will be studied. The latter is in the spotlight as a gene locus that regulates the expression of many pro-inflammatory cytokines and inflammatory cytokines.

This is a novel study for several reasons; the case-control epidemiological study's observation period is over 10 years; the study will be conducted with special reference to CagA toxicity; and it will investigate the polymorphisms of the *IL1B* and *LTA-NFKBIL1-BAT1* genome region as a genetic factor.

RP 3-04 ESR Measurements of Tooth Samples from Nagasaki Survivors (Addendum to RP 1-92)

Nakamura N, Kodama Y, Tomonaga M, Iijima Y, Mine M, Okumura Y, Kodama K, Cullings HM, Akahoshi M

The purpose of the study is to measure tooth enamel from Nagasaki survivors by means of electron spin resonance (ESR) technique to evaluate radiation dose under the same conditions specified for tooth enamel obtained from Hiroshima survivors. Frequency of chromosome aberrations will also be examined in blood lymphocytes from the tooth donors if they are Adult Health Study (AHS) members. The present study is a collaborative work between RERF and a group at Nagasaki University who collected the tooth samples. After the measurements, the enamel samples are returned to Nagasaki University in due time.

RP 4-04 Relationship between Cancer Development and Genetic Polymorphisms among A-bomb Survivors, Focusing on Immune-related Genes

Hayashi T, Kusunoki Y, Kyoizumi S, Imai K, Hakoda M, Eguchi H, Cologne JB, Tsugane S, Yoshida T, Tahara E, Fujiwara S, Suzuki G, Akahoshi M, Nakachi K

This research project will study the A-bomb survivor cohort to assess whether individual genetic background affects individual susceptibility to cancer development. This study focuses on polymorphisms of genes encoding molecules that are possibly involved in immunological defense against cancer development. The immune system can distinguish between self and non-self, and cancer development can be immunologically prevented when cancer (or pre-cancerous) cells themselves, or cancer-associated molecules, are recognized by the system as non-self, a process referred as cancer immune surveillance. In innate immunity, self and non-self recognition is mediated by natural-killer (NK) and toll-like receptors, and in acquired immunity, by the interaction between T-cell receptor and major histocompatibility complex (MHC: human leukocyte antigen [HLA] in humans) molecules. Persistent inflammation occurs as a consequence of immunological host response to xenobiotics, which involves activation of a number of genes including relevant cytokines, chemokines and their receptors. Reactive oxygen species (ROS) generated by persistent inflammation are thought to cause cancer in some cases by damaging DNA. The major defence mechanism for DNA damage is the DNA repair system, and polymorphisms of DNA repair genes may be important in analyzing genetic susceptibility to cancer. Drug-metabolizing enzymes, a counterpart of DNA repair enzymes, are involved in generating certain types of DNA damage—specifically, DNA-adducts—and polymorphisms of these genes may also be important. In this study, we will use stored biological materials (lymphocytes and paper discs) that have been collected from about 2,900 individuals including 1,444 cancer cases, a subcohort of the Adult Health Study (AHS) cohort. Genome analyses of immune-related genes, inflammation-related genes, and other cancer-associated genes, such as DNA repair genes and drug-metabolizing enzyme genes, will be conducted to identify individuals at high risk of cancer, and to determine whether the risk is related to radiation exposure or not, based on polymorphisms of these genes.

RP 5-04 Identification of Cancer-related Gene Polymorphisms and Immunological Markers (Addendum to RP 4-04)

Hayashi T, Kusunoki Y, Imai K, Cologne JB, Tahara E, Nakachi K

This research project aims to elucidate the association between cancer-related gene polymorphisms and immunological phenotypes, supplementing RP 4-04, which is a study of the A-bomb survivor cohort to assess whether radiation exposure affects individual susceptibility to cancer development. The present project will examine the association between individual genetic background and individual susceptibility to cancer development, using samples obtained from the Saitama cohort. This study focuses on gene polymorphisms encoding molecules believed to involve immunological defense against cancer development. With the aim of elucidating the association between cancer-related gene polymorphisms and immunological phenotypes, this study will examine biological samples obtained from 2,479 individuals examined in the Saitama cohort study. The immunogenome study includes the investigation of genetic background, which influences various immunological phenotype markers. Some immunological phenotype markers measured in the Saitama cohort are the same as those measured in the RERF cohort, and other markers were measured only in the Saitama cohort. The statistical power in the genome analysis with common phenotype markers can be increased by analyzing the Saitama cohort subjects. In addition, the results from the phenotype-genotype analyses in the Saitama cohort study will allow genotyping-based analyses even for phenotype markers that were not measured in the RERF cohort, including natural-killer (NK) activity.

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