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Table of Contents

From the Editors 1

RERF News

The 50th Anniversary of Commencement of the Adult Health Study, by Toshiteru Okubo 1

The 36th Scientific Council Meeting 3

Staff News 5

Honors and Awards Received by RERF Scientists 6

Conference and Workshop Reports

Workshop on Radiation Risk of Breast Cancer, by Nori Nakamura 7

Radiation Cataractogenesis Workshop, by Kazuo Neriishi 8

Science Article

What and How Large Are the Risks from Prenatal (*In Utero*) Radiation Exposure? by Roy Shore, Misa Imaizumi, Yoshimi Tatsukawa, and Nori Nakamura 9

Human Interest Notes

Taking Early Retirement, by Yukiko Shimizu 13

Recontacting Work, by Toshiko Tsukamoto 14

In Memoriam 16

Facts and Figures

RERF Research: Themes, Prioritization, 5-year Program Goals, Interdepartmental Programs, and a New Contract with the U.S. National Cancer Institute, by Roy Shore 17

Research Protocols and Publications

Research Protocol approved in October 2008–March 2009 18

Recent Publications 18

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From the Editors

Subarashii!

That word was heard a lot around RERF again as Hijiyama's sakura season finally arrived and blossoms were in full bloom. It was difficult scheduling ohanami parties this year since the cool weather delayed the opening of the buds over a long period of time—as if nature was stretching out this magnificent season. We guess that Seymour Abrahamson would have called some of them "o-ha-mi" (or "leaf parties"). But when the warm weather finally arrived, the final burst of beauty was a sight to behold—kirei! While there are many sakura trees visible from within RERF, it is actually hard to obtain a photo of the trees that includes the RERF laboratories. To solve that problem, we called upon the traffic mirror and put it to another good use.

We are pleased that you have joined us for another edition of *Update*. We want to continue last year's revival of biannual issues of *Update*. In this summer issue you will find a tribute to the 50th anniversary of the establishment of the Adult Health Study (AHS), a summary of the 36th Scientific Council meeting, a review of the studies on A-bomb survivors who were exposed *in utero*, and the announcement of the start of a new contract with the U.S. National Cancer Institute to continue our long-standing collaborative epidemiological studies of cancer among A-bomb survivors. As always, we hope that you enjoy this issue and don't hesitate to drop us a line and let us know how we might improve our reporting of RERF's many activities.

Ja, mata!

Evan B. Douple
Editor-in-Chief

Yuko Ikawa
Technical Editor

On the Occasion of the 50th Anniversary of Commencement of the Adult Health Study

Toshiteru Okubo, Chairman

Fifty years have passed since the Adult Health Study (AHS), a large-scale epidemiological study of A-bomb survivors, started in 1958. It is easy to say "50 years," but this period of time is extremely long for the loyal survivors who have participated, for the many scientists who have conducted the study, and for a binational research institution. The A-bomb radiation-exposed members of the general public in Hiroshima and Nagasaki include persons representing a wide range of ages, from the very young to the elderly. The survivor who was the youngest at the time of the A-bombings has now attained the age of 63. Furthermore, the youngest staff member of the research organization who was at the age of 20 in

1958 has attained the age of 70—well over the fixed age of retirement.

The AHS's characteristics, other than the lengthy study period and exposures to people of all ages and over a wide range of radiation doses, include a very large size of the initial cohort of about 20,000 people. The A-bombings were unprecedented events in human history and, although acute symptoms were known to a certain extent around that time, no one knew what the persistent and long-term health effects of radiation would be. Hence, it was necessary to conduct the AHS. Generally speaking, the better the quality of the data, the longer the study period or observation period, and the larger the cohort size in an epidemiological study, the more likely the chance of elucidating statistically significant effects and associations which are relatively small or rare with improved sensitivity and accuracy. Therefore, the AHS' long followup, large cohort size, and faithful contributions of its many survivor participants have been indispensable for the identification and study of the health effects of A-bomb radiation.

The AHS was started during the days of the Atomic Bomb Casualty Commission (ABCC), which was established by the U.S. government and which was the predecessor of the Radiation Effects Research Foundation (RERF). The government that had dropped the A-bombs introduced this study and that fact influenced the feelings of AHS participants around that time. I understand that some people had doubts about the objectives of the study and decided not to cooperate, and that is understandable. Today, however, 50 years later, no one has doubts about the significance of the medical findings related to the long-term effects. Thus, AHS has been contributing greatly to science and to the welfare of human beings.

It is impossible to calculate the number of all of the people who have contributed to or supported this important study in a direct and/or indirect manner. It is assumed that the number of RERF staff members who engaged in this study exceeds 1,000 or even 2,000. In light of the factors mentioned previously, it is certain that AHS is an historic and impressively large-scale accomplishment of considerable importance in the field of medical sciences.

The achievements of the AHS as a medical study have been disseminated world-wide through a large number of papers published in scientific journals. However, it is said that with regard to epidemiological research, the results of the research which can be quantified, generalized, and expressed as conclusions in a scientific paper usually account for less than 10% of the total information collected which is available for future research and discoveries. And there is also a humanitarian aspect to the AHS. For example, when one takes into account the difficult situation under which the A-bomb survivors were placed during the early years often called a "decade-long hiatus," medical staff who were engaged in AHS worked very diligently and must have met a large number of A-bomb survivors in the course of starting and conducting the study during difficult times, and they shared the A-bomb survivors' joys and sorrows. Furthermore, the staff members must have seen changes in lifestyles, aging of the A-bomb survivors, and the passage of time as the two cities were reconstructed from the ashes of the A-bombings. This required patience, dedicated hard work, and understanding.

Toshiteru Okubo, Chairman

In epidemiological research, the importance of such social and medical observational findings that are brought about through relationships of the researchers among people in the course of interviews and/or health consultations cannot be adequately described in scientific papers and should not be ignored. This is different from experiments involving cultured cells or from animal experiments in that epidemiological data are often generated through interpersonal relationships. The strength of those relationships which accompanies the acquisition of data is said to be a secondary gain for the researchers and often contributes to the success of the study and the reliability and quality of the scientific research. Thus, rich and historical observational data exist behind statistically quantified, scientific achievements, and the resource remaining for future scientists of the AHS is no exception. And unless all information is taken into account in epidemiological research, false conclusions can be drawn.

Since many ABCC and RERF staff members who were involved with the AHS have left RERF, the number of people who can testify about the past days is limited. We would like to introduce a memoir (as one of the "Human Interest Notes" on page 14 of this issue of *Update*) of a former ABCC employee who served for many years as a contactor and who talked directly to A-bomb survivors to ask for their cooperation and who was intimately involved in obtaining and preserving the valuable records of the humanitarian or so-called "secondary research achievements."

Report on the 36th Scientific Council Meeting

The 36th Scientific Council (SC) meeting to review research progress and plans at RERF was held on March 2–4, 2009 at RERF in Hiroshima. It was co-chaired by Drs. Katsushi Tokunaga and David Hoel. Two new members joined the SC, Dr. Sally Amundson (Columbia University) and Dr. Kiyoshi Miyagawa (The University of Tokyo). The pattern begun the previous year of augmenting the intensive review of selected departments by adding several *ad hoc* Special SC members was again followed, with the addition of Drs. Ranajit Chakraborty, Yoshiya Shimada, and Gen Suzuki to enhance the review of the Genetics and Radiobiology/Molecular Epidemiology Departments.

Dr. Toshiteru Okubo, Chairman of RERF, expressed his appreciation for the SC members' willingness to come and provide a review of our research program, and emphasized how important SC's work is to the scientific staff of RERF. He reported that the Senior Review Panel had issued its final report which expressed strong support for the continuance of RERF for the mission of assessing the health risks to atomic-bomb survivors. He emphasized the need to follow up the key cohorts, the Life Span Study, Adult Health Study, *in utero*, and F_1 generation cohorts, for at least the next 20 years, and to use the data obtained through them to the best scientific advantage.

Dr. Roy E. Shore, Vice Chairman and Chief of Research, expressed gratitude for the previous year's SC review, which has been very helpful to RERF. In responding to last year's recommendation that we better articulate the long-term goals and research directions of RERF, he indicated that we have now defined six major research themes and developed a five-year plan oriented toward those themes. Briefly stated, the research themes are: cancer, cardiovascular disease, other radiation-related health outcomes, genetic effects, immunologic effects, and dosimetry. In response to other recommendations, he mentioned that we have worked with the respective departments to develop and refine research priorities; that we now have several examples of programmatic, interdisciplinary research and will continue to move further in that direction; that we have been strengthening our relationships with local and regional research universities; that we are giving increasing attention to study design and analysis issues to assure appropriate research methodology; and that we have devoted considerable attention to international collaborative research and to international education and training.

Next, detailed presentations were made by members of the Department of Radiobiology/Molecular Epidemiology and the Department of Genetics of their research activities and plans, followed by brief overviews of the activities of the Departments of Clinical Studies, Epidemiology, and Statistics, as well as the Public Relations program. Subgroups of SC members then spent several hours in informal meetings with the various department research staffs.

The SC's written review began by again noting that "RERF is the pre-eminent leader in radiation risk research in the world and has the expertise, populations, and data sets to conduct investigations that cannot be carried out elsewhere. The support and assistance of the Japanese Ministry of Health, Labour and Welfare and the United States Department of Energy, as well as scientific guidance of the National Academy of Sciences, continue to be crucial to the mission of RERF. Without such support and the assistance of the survivors and their families, the ability of RERF to conduct superb and substantial research that has great impact around the world would not be possible. The mission of RERF has recently become all the more critical with the increased international concerns over radiation health risks due to: a) the nuclear power option, b) the increased use of radiation in medical screening and treatment, and c) the threat of nuclear terrorism." They also emphasized that "the world radiation protection bodies have relied heavily on the risk values produced by RERF" and noted several recent examples of this.

A brief summary of their general recommendations is:

- The SC commended RERF for the increased collaboration among researchers through the establishment of interdepartmental working groups organized around research themes. They recommended developing further working groups, defining comparative study priorities, and implementing study milestones and timelines. Integration and efficiency could be facilitated by developing a structure of core facilities. They also suggested that more thought be given to additional integration of departments.
- The SC recommended that a working group be established to develop plans to better integrate both data and biospecimen management.
- The SC noted that changes in the nature of science indicate the need to give high priority to the development and incorporation of bioinformatics expertise at RERF.
- The SC recommended increased communication with the A-bomb survivors and community about the collaborative sharing of data and biospecimens. They suggested that the Public

Relations unit conduct an "augmented program of interacting with cohort members and relatives of victims" and engage "global broadcast and print media in the mission and story of RERF."
- The SC noted the importance of increasing the rate of first-author publications by the research staff.

To highlight a few of the notes and recommendations for departments:
- Chromosome aberration analyses applied to *in utero* exposure are shedding light on the stability of mutations and the dynamics of stem cells, with mechanistic implications regarding the age-dependency of radiation carcinogenesis.
- The study on the immature oocytes of female rats is important, since it may provide a scientific foundation for male versus female differences in spontaneous and induced rates of mutations. Moreover, the general public is very sensitive to radiation risks regarding female reproduction.
- The SC recommended that radiation-related genomic deletions be studied in F_1 animal models with comparative genomic hybridization using high-density arrays, after which similar studies could be considered in the offspring of A-bomb survivors.
- It is recommended that the F_1 clinical study examine not only common multi-factorial diseases, but also the frequency and associated family histories of rare dominant Mendelian diseases, since a *de novo* occurrence might indicate a radiation-associated germ cell mutation.
- Immunological senescence as a mechanism for radiation-related cancer and non-cancer diseases is an attractive hypothesis. It is recommended that the Department of Radiobiology/Molecular Epidemiology more fully examine newly defined T-cell subsets that may play regulatory roles in autoimmune or inflammatory diseases, that they also consider innate immunity, and that, in collaboration with the Clinical Studies Department, they examine clinical cases of immune disease regarding this hypothesis.
- The SC was pleased that a new Chief of Epidemiology, Dr. Kotaro Ozasa, has been recruited, and believes that his leadership will provide an excellent opportunity for the department to advance.

RERF Scientific Councilors

Dr. David G. Hoel, Co-chairperson, Distinguished University Professor, Department of Biostatistics, Bioinformatics and Epidemiology, Medical University of South Carolina

Dr. Katsushi Tokunaga, Co-chairperson, Professor, Department of Human Genetics, Division of International Health, Graduate School of Medicine, The University of Tokyo

Dr. Ohtsura Niwa, Deputy Director, Research Center for Charged Particle Therapy, National Institute of Radiological Sciences

Dr. Yoshiharu Yonekura, President, National Institute of Radiological Sciences

Dr. Takashi Yanagawa, Professor, The Biostatistics Center, Kurume University

Dr. Kiyoshi Miyagawa, Professor, Laboratory of Molecular Radiology, Center for Disease Biology and Medicine, Graduate School of Medicine, The University of Tokyo

Dr. Marianne Berwick, Professor and Chief, Division of Epidemiology, Associate Director, Cancer Research and Treatment Center, University of New Mexico

Dr. John J. Mulvihill, Professor of Pediatrics, Uni-

Participants of the 36th Scientific Council meeting held at the Hiroshima Laboratory

versity of Oklahoma Health Sciences Center

Dr. Michael N. Cornforth, Professor and Director of Biology Division, Department of Radiation Oncology, University of Texas Medical Branch

Dr. Sally A. Amundson, Associate Professor of Radiation Oncology, College of Physicians and Surgeons of Columbia University

Special Scientific Councilors

Dr. Gen Suzuki, Chief, Department of Environmental Health, National Institute of Public Health (until March, 2009); currently, Professor, Clinic, International University of Health and Welfare

Dr. Yoshiya Shimada, Team Leader, Experimental Radiobiology for Children's Health Research Group, Research Center for Radiation Protection, National Institute of Radiological Sciences

Dr. Ranajit Chakraborty, Professor and Director, Center for Genome Information, Department of Environmental Health, University of Cincinnati College of Medicine

Staff News

As of 30 November 2008, Dr. Yukiko Shimizu resigned from the position of Assistant Department Chief, Epidemiology, and was appointed as Part-time Professional on 1 December 2008. (See her memories of working at RERF for more than 37 years on page 13.)

As of 31 December 2008, Dr. Kei Nakachi reached the mandatory retirement age and retired from Department Chief of Radiobiology/Molecular Epidemiology. He was appointed as RERF Consultant and Project Principal Scientist on 1 January 2009. Dr. Yoichiro Kusunoki was appointed Acting Chief of the Department as of 1 January 2009. Dr. Yasuharu Niwa was recruited and joined the Cell Biology Laboratory of the Department of Radiobiology/Molecular Epidemiology on 1 February 2009.

Drs. Mimako Nakano, Research Advisor, and Dr. Kazuo Ohtaki, Adjunct Specialist (Research Scientist) of Cytogenetics Laboratory, Genetics Department, retired upon expiration of their reappointment terms as of 31 March 2009. Dr. Yoshiaki Kodama, Assistant Department Chief of Genetics, was appointed Acting Chief of the Genetics Department to replace Dr. Jun-ichi Asakawa as of 1 April.

We have asked Dr. Niwa to write a little about himself and his interest in the work of RERF.

Yasuharu Niwa

By way of introduction, my name is Yasuharu Niwa, and I started work at the Department of Radiobiology/Molecular Epidemiology on February 1 of this year. After graduating from the Graduate School of the University of Tokushima, I started work at the same university as a research assistant professor. While I was employed there, I traveled overseas to study at Harvard University, researching mainly mechanisms behind blood platelet secretion and the process of differentiation from stem cells into blood platelets. Following that experience, I studied epigenetic mechanisms of carcinogenesis based on the example of liver cancer as a research scientist at the Cancer Institute of the Japanese Foundation for Cancer Research. After that, I took up the post of laboratory chief at the National Cardiovascular Center, located in Osaka, where I delved into research on environmental factors and causative genes in atherosclerosis and hypertension.

Yasuharu Niwa, Research Scientist

I feel that Hiroshima is a really nice city with an attractive environment, around which I can enjoy wandering by foot or by taking the streetcars. The new baseball stadium is completed and is an interesting addition. Hiroshima's beautiful streets are symbols of the city's recovery following the war, and they symbolize the efforts of the people of Hiroshima and their strong desire for peace.

Our scientists have uncovered associations between the atomic bombings and certain diseases. However, many mechanisms related to the association between radiation exposure and disease development are still unclear, and therefore thorough analysis of such mechanisms must be undertaken in the future. My work at RERF will involve uncovering associations between the bombings and lifestyle diseases through the conduct of basic research. I will be very happy if, based on my prior experience and the leadership of RERF's many researchers, I contribute to the further understanding of such disease processes.

Honors and Awards Received by RERF Scientists

We are pleased to inform you that Dr. Nori Nakamura, RERF Chief Scientist, will be appointed to serve as a member of Committee 1 of the International Commission on Radiological Protection (ICRP) as of 1 July 2009, for a term of four years.

Nori Nakamura, Chief Scientist

Receiving "Excellent Poster Presentation" Award at the 61st General Assembly of the Hiroshima Medical Association

Ikuno Takahashi, Research Scientist
Department of Clinical Studies, Hiroshima

At the 61st general assembly of the Hiroshima Medical Association held on November 29–30, 2008, my report on lifetime risk of stroke, which was based on a stroke study of Adult Health Study (AHS) subjects, received an award for excellence. The relevant stroke study started with the unspectacular work of single-mindedly flipping through the medical charts of a total of 4,500 subjects in order to confirm stroke cases. For several months, when I was engaged in the relevant operations, I had a dream every night about the medical history charts that I had checked during the day; however, I also experienced the emotion that I was coming into contact with globally unique, longitudinal records collected over a half-century, an experience that nurtured my desire to reciprocate the contributions made by the large number of health examination participants and ABCC-RERF staff members to the continuation of AHS.

The analysis of a large number of historically valuable records generated the findings that 20–30% of Japanese people with high blood pressure levels during middle age had risk of stroke onset and that this risk was at least twice as high as that for those with normal blood pressure. This was the first such finding in Japan and could be counted among a limited number of similar results throughout the world. The study elucidating effects of high blood pressure levels on stroke onset emphasized the need for relevant therapies for a large number of asymptomatic patients who have little interest in undergoing lifestyle disease (hypertension) treatment. I sincerely hope that such epidemiological suggestions can contribute to rewarding those involved in the continuation of the AHS.

In addition, recent major advances in medical imaging techniques have increased the opportunity for non-invasive testing. I believe that only RERF can elucidate whether low-level medical radiation exposure is harmful to humans, even though radiation is already widely used in diagnostic imaging. I will do my best to elucidate particularly whether radiation exposure promotes the onset of stroke and other such arterial sclerotic diseases that affect the quality of subsequent life and, if so, mechanisms thereof. Everyone's continued guidance would be greatly appreciated.

Ikuno Takahashi, Research Scientist, with her award

Workshop on Radiation Risk of Breast Cancer

Nori Nakamura, Chief Scientist

The subject workshop was held at the Hiroshima RERF Auditorium on October 10–11. It was the first workshop co-hosted by the National Institute of Radiological Sciences (NIRS) and RERF. Our intent was to organize a workshop that would help the participants readily understand the current status of research on radiation risk of breast cancer (covering fields from biology to epidemiology).

At the beginning of the workshop, Dr. Jun-ichi Kurebayashi (Kawasaki Medical University) and Dr. Yang Xiaohong (U.S. National Institutes of Health) delivered lectures on breast cancer subtypes among Japanese and Europeans/Americans. Recently, breast cancer is often classified into about five subtypes, depending on the expression patterns of several key genes, including estrogen receptor gene (prognosis also differs by subtype). In Japan, the background rate of breast cancer overall has been on an upward trend. However, the fraction of basal-type breast cancer (subtype with poor prognosis) among the Japanese people still seems to be lower than that among Americans and Europeans. Whether all or just some of the subtypes increase due to radiation exposure is unknown.

Following the presentations, Dr. Alexander Borowsky (University of California) delivered a lecture on the biology of breast cancer. He explained what is considered to be the source of differences among different pathological types of breast cancer. Dr. Nobuo Nishi (RERF) summarized epidemiologic studies of breast cancer among A-bomb survivors, and Dr. Kiyohiko Mabuchi (U.S. National Cancer Institute) gave an overview of secondary breast-cancer risk for patients who had undergone radiation therapy. Thereafter, Dr. Airo Tsubura (Kansai Medical University) explained biological explanations of factors that are considered in the field of epidemiology to modify breast-cancer risk. He suggested that the low breast-cancer risk among those who experienced their first child-bearing at young ages might be attributable to differentiation of mammary stem cells. Drs. Mike Atkinson and Soile Tapio (Helmholtz Centre Munich) explained to what extent cancer research technologies have advanced with the use of paraffin-embedded tissues.

Lastly, Dr. Tatsuhiko Imaoka (NIRS) reported on results of analysis of gene expression using breast-cancer arrays generated by irradiation of rats. He explained that the gene expression pattern of radiation-induced breast cancer is different from that of spontaneous breast cancer. The presentations were followed by a general discussion session.

Dr. Mabuchi, Dr. Otsura Niwa (NIRS), and I have discussed possibilities for organizing this workshop for the past two years or so. Immediately prior to the workshop, two important international conferences were held in Japan. It was a great pleasure for us that some of the foreign scientists who attended those conferences also participated in our workshop. Through the workshop sessions, we keenly realized how much more diverse than imagined cancer mechanisms are and how rapidly cancer research has advanced. The general discussion session suggested that subtyping of breast cancer among A-bomb survivors would be a worthwhile project. A number of participants stated that future workshops of this kind would be indispensable for promotion of comprehensive research on radiation and breast cancer.

Workshop on radiation risk of breast cancer held at the auditorium, Hiroshima Laboratory

On a final note, I would like to express my sincere appreciation to the staffs of the Secretariat and the Department of Genetics, who contributed to the convening of this workshop.

Radiation Cataractogenesis Workshop

Kazuo Neriishi, Assistant Chief
Department of Clinical Studies, Hiroshima

The Radiation Cataractogenesis Workshop was held at the RERF auditorium on March 9 and 10, 2009. The following speakers were invited to the workshop: Drs. Gabriel Chodick (Maccabi Healthcare Services, Israel), Norman J. Kleiman (Columbia University, USA), Eleanor A. Blakely (Lawrence Berkeley National Laboratory, USA), Polly Chang (SRI International, USA), Leo T. Chylack (Harvard Medical School, USA—web-conference participation), Francis A. Cucinotta (NASA Johnson Space Center, USA—Dr. Leo T. Chylack made a presentation on behalf of Dr. Cucinotta), Atsushi Minamoto (Minamoto Eye Clinic), Takashi Kitaoka (Nagasaki University), Takashi Kumagami (Nagasaki University), Yoshiaki Kiuchi (Hiroshima University), Takashi Kanamoto (Hiroshima University), and Noriko Fujii (Research Reactor Institute, Kyoto University). Drs. Ohtsura Niwa, Shin Saigusa, and Shinji Yoshinaga from the National Institute of Radiological Sciences attended the workshop as observers.

The objective of the workshop is to elucidate epidemiological characteristics of radiation cataract through comparative review of several epidemiological studies, and mechanisms of radiation cataract development through discussion of molecular biological studies. Invited participants, who are researchers engaged in epidemiological studies of the radiation-exposed (radiologic technologists, interventional cardiologists, astronauts, Chernobyl clean-up workers, and A-bomb survivors), engaged in comparative discussions of their studies of cataract development attributable to low-dose radiation exposure. Other invited participants, who are researchers studying molecular biological changes to the lens (apoptosis protein, crystallin, and ATM protein) due to radiation, conducted in-depth discussions of their studies of molecular biological changes due to radiation. By sharing such epidemiological and molecular biological information on radiation cataract, in-depth discussion was carried out to get to the bottom of the matter concerning mechanisms of radiation cataract development.

The following conclusions were obtained:

1. Dose thresholds are probably lower than those assumed in the past.
2. In substance, radiation damage to the lens comprises apoptosis, changes in matrix structure, and crystallin racemization (optical structure change of protein).
3. Expression of specific molecular biological proteins is involved.
4. Collaborative research should be conducted in the future.

It was proposed to publish the proceedings of this workshop in a scientific journal, and the proposal was approved unanimously. We look forward to presenting scientific highlights from this workshop in future editions of *Update*.

Participants of the radiation cataractogenesis workshop

What and How Large Are the Risks from Prenatal (*In Utero*) Radiation Exposure?

Roy Shore,[1] Misa Imaizumi,[2] Yoshimi Tatsukawa,[3] Nori Nakamura[4]

[1]Vice Chairman and Chief of Research, Departments of [2]Clinical Studies (Nagasaki) and [3]Clinical Studies (Hiroshima), and [4]Chief Scientist, RERF

Introduction

Since the early publications of the Oxford Study of Childhood Cancer (OSCC) by Alice Stewart and colleagues in the 1950s and 1960s,[1] it has been widely believed that the embryo and fetus are especially sensitive to the carcinogenic effects of ionizing radiation. The results of their very large case-control study (~14,000 childhood cancer deaths, of whom ~2,200 received prenatal X ray)[2] of *in utero* medical diagnostic irradiation and childhood cancers were largely supported by a number of other case-control studies (see Ref. 3). Based on the OSCC study, an excess absolute risk (EAR) estimate of about 6% per Gray (Gy) was derived for childhood cancer mortality.[4,5] However, the support for a prenatal irradiation effect upon types of childhood cancer other than leukemia was mixed in various other studies (e.g., Ref. 6). Furthermore, the several cohort studies of prenatal radiation exposure lent weak or no support to a risk of childhood cancer, although that generalization needs to be qualified by noting that the cohort studies had limited statistical power.[3]

Childhood Cancer after Prenatal A-bomb Exposure

The atomic-bomb study was rather uninformative regarding prenatal exposure and childhood cancer, and could be interpreted in different ways. Jablon and Kato[7] reported that only one childhood cancer was observed before age 10 in the atomic-bomb study of 1292 children exposed prenatally, whereas 0.75 would have been expected from Japanese population baseline rates alone, and from the lower bound of the radiation risk estimate based on the Stewart study at least 5 excess cancers would have been expected. The estimated maternal uterine dose was 1.43 Gy for the only cancer case diagnosed in the prenatal cohort before age 16: a liver cancer at age 6. Delongchamp *et al*.[8] analyzed cancer occurring at ages 16 or under in the cohort and indicated a positive association based on the high dose received by that cancer case. They indicated that, while this case was consistent with the large excess risk during childhood suggested by the OSCC study, it was also compatible with a broad range of risk estimates, and provided only weak support for the OSCC results.

Adult Cancer after Prenatal A-bomb Exposure

Given the high estimates of risk of childhood cancer after prenatal exposure, one might hypothesize that the adult-cancer risk would be as great or greater for prenatal exposure than for childhood exposure. Long-term follow-up of the prenatally exposed cohort of A-bomb survivors has continued. We are unaware of any other published study of adult cancer in relation to purely prenatal radiation exposure, although there is a Techa River study report on adult cancer among those exposed both pre- and postnatally.[9] Perhaps due to the relatively low dose distribution in that cohort, the dose response was not significant for either pre- or postnatal exposure.

The RERF Epidemiology and Statistics Departments recently reported on the dose-related incidence of solid cancers over the age range of 12–55 years among the prenatally exposed A-bomb cohort (n = 2,452), compared to the dose-related incidence among the 15,388 exposed in early childhood (ages 0–5).[10] A total of 94 solid cancers was found in the prenatal group and 649 in the larger childhood irradiated group. The doses reported for the prenatal cohort in the present summary are maternal uterine doses. Estimates of fetal doses *per se* are currently not available, but uterine doses are probably a reasonable first approximation, since preliminary calculations suggested that fetal doses vary only around 5% from the estimated uterine doses and also vary relatively little by gestational age for a given tissue kerma in air.[11] In future work, we hope to derive direct estimates of fetal doses.

There was a dose-dependent excess of cancer among the prenatal cohort (excess relative rate [ERR] = 1.0 per Gy, 95% confidence interval [CI]: 0.2–2.3), which was fairly comparable to that seen in the childhood-exposed cohort (ERR = 1.7 per Gy, 95% CI: 1.1–2.3). However, when this was examined on the excess absolute risk (EAR) scale and plotted by attained age, there is a strong suggestion that the temporal trajectories of risk are different, in that the EAR per 10,000 person-year Gy is rising sharply with age for the childhood-exposure cohort but remains flat for the prenatal cohort (Figure 1).

The study of solid cancer in adulthood after pre-

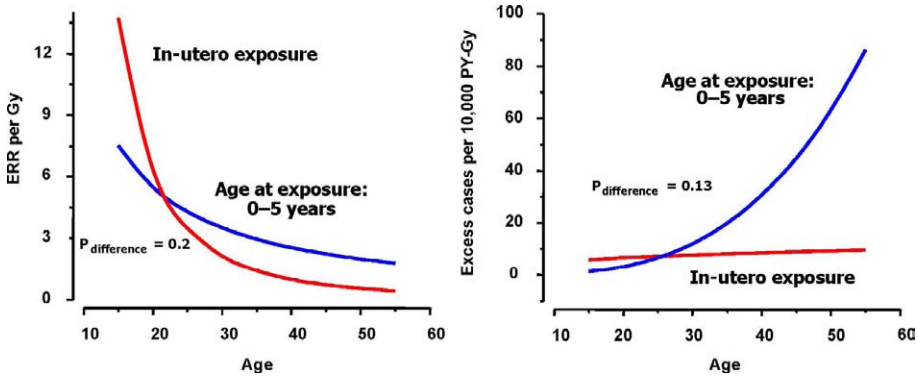

Figure 1. Excess relative risk (ERR) and excess absolute risk (EAR) for solid cancers, ages 12–55, among those exposed to the A-bomb *in utero* or at ages 0–5. Adapted from Ref. 10.

natal or early-childhood exposure[10] had some other interesting sidelights. The risk estimates for those exposed during the first, second, and third trimesters of fetal development were virtually identical; there was no evidence for a window of susceptibility by gestational age at exposure. Based on the combined prenatal and early-childhood exposure cohorts, the radiation EAR was about twice as large for women as for men (female:male ratio of 2.1, p = 0.02). For the prenatally exposed, the EAR per 10,000 person-year Gy was 9.2 for females and 4.3 for males.

Leukemia in adulthood is also being examined in the prenatally-exposed group. In the last completed analysis through 1992[8] there were few leukemias to analyze: 2 in the exposed group and 4 among the unexposed (<0.01 Gy). That analysis indicated that the excess leukemia rate in the irradiated group was marginally significant (p = 0.054), with an excess rate that was about half as large as, but statistically compatible with (p = 0.10), those seen after childhood exposure. However, there was no dose response, as the two leukemia cases had estimated doses of only 23 and 40 mGy. An updated analysis is now underway but is not yet completed.

Experimental studies at RERF have also been conducted to seek to explain the generally weak or null findings with regard to cancer risk after prenatal exposure in the A-bomb studies. The Genetics Department examined chromosome aberrations (translocations) in blood lymphocytes by the G-banding technique from a group with *in utero* A-bomb exposure and by bi-color FISH (fluorescent *in situ* hybridization) of painting three sets of chromosomes from their mothers, and found a dose response for mothers but not for those exposed prenatally when examined at age 40 years old. This result was confirmed experimentally by irradiating pregnant mice and observing the rates of chromosome translocations with bi-color FISH at 20 weeks of age in both the mothers and the offspring. Those studies are described more fully in an earlier *Update* article (Nakamura *et al*., *Update* 16:7–12, 2005). More recently, to exclude the possibility that the bone marrow cell pool was derived from a small number of fetal stem cells, and hence translocation data from four chromosomes might not have been representative of the other chromosomes, a whole-genome multicolor FISH (m-FISH) analysis was applied to the same samples of mice; this confirmed the lack of dose response for the prenatally exposed mice (Nakano *et al*., manuscript in preparation). However, new preliminary data suggest for epithelial cells there may be a dose response after prenatal exposure, unlike for lymphocytes, so the story is still evolving.

Thyroid Disease after Prenatal A-bomb Exposure

Since so little is known about the effects in adulthood of prenatal radiation exposure, it seemed important to examine other health outcomes besides cancer. The prevalence of thyroid nodular disease was examined, since the thyroid gland is one of the most radiosensitive sites, especially among those who are young at exposure.[12] It was possible in the Hiroshima and Nagasaki Adult Health Study (AHS) to screen 319 prenatally-exposed persons with known doses about 55–58 years after exposure. The mean uterine dose in the exposed group (≥5 mGy) was about 0.26 Gy (range of 0.02 to 1.79 Gy). For comparison to the prenatally exposed cohort, thyroid nodule prevalence also was examined among the 437 examined individuals who were ages 0–5 years at exposure; the mean dose in that exposed group was much higher, 0.92 Gy, because for postnatal AHS study subjects it was possible to enrich the sampling of higher-dose persons.

As shown in Figure 2, Dr. Imaizumi and colleagues[13] found an apparent increase in the risk of solid thyroid nodules (odds ratio [OR] at 1 Gy = 2.78, 95% CI: 0.5, 12) although the radiation risk was not

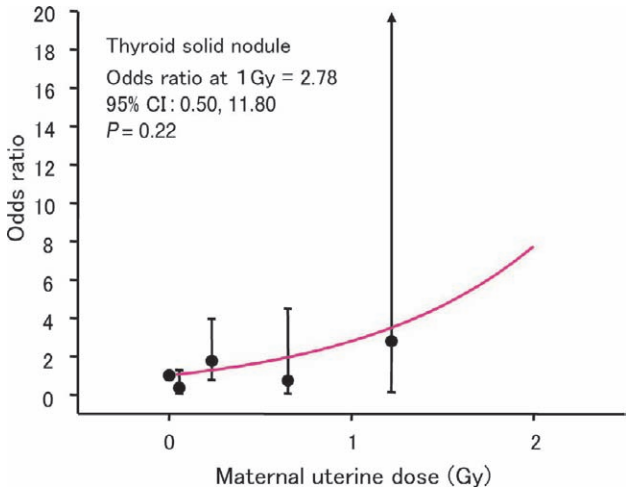

Figure 2. Risk of solid thyroid nodules by radiation dose for the *in utero*-exposed clinical cohort. Adapted from Ref. 13.

statistically significant, probably owing to the limited statistical power due to the relatively small sample size and low dose distribution. However, this risk estimate was similar to the study's estimate for childhood exposures (OR at 1 Gy = 2.65, 95% CI: 2.0–3.7). An examination of thyroid nodule risk in the prenatal cohort did not show any differences by gestational week of exposure.

They also evaluated the prevalence of autoimmune thyroid disease in the prenatally exposed cohort. No dose-related associations were found for tests of antithyroid antibodies, antithyroid-antibody negative or positive hypothyroidism, or Graves' disease. Nor did they show any differences in dose response by gestational week at exposure. The findings regarding autoimmune thyroid disease were not surprising, since the results have been null in the AHS study, too.[12]

Circulatory Disease after Prenatal A-bomb Exposure

The other set of health outcomes examined in the AHS prenatal cohort are circulatory diseases and conditions, because mortality from circulatory diseases shows an association with radiation exposure in the epidemiologic Life Span Study (LSS). The incidence rates of primary hypertension, hypercholesterolemia, stroke, and myocardial infarction were examined in relation to radiation dose among the AHS participants between 1978 and 2003 by Dr. Tatsukawa and colleagues.[14] Because the numbers of strokes and myocardial infarctions were so small, they were combined for analysis. These conditions were considered positive when AHS clinic measurements or assessments met standard defined criteria, or when there was a relevant confirmed diagnosis or prescription by another physician. For comparison, the dose-related incidence of these conditions was examined in parallel fashion for those in the AHS who were ages 0–9 years at exposure. There were 506 prenatally exposed AHS subjects and 1,053 exposed at ages 0–9.

Because a series of lifestyle-related factors besides radiation impact the risk of circulatory diseases, smoking, alcohol consumption, and obesity (body mass index) were included in the analyses. The risk estimates for the cohorts with prenatal and childhood exposure are shown in the Table. For hypertension and hypercholesterolemia the radiation risk estimates for the prenatal and childhood cohorts

Table. Dose-related (RR at 1 Gy) risk of incident circulatory diseases or conditions for the prenatally- and childhood-exposed cohorts in the AHS

	Prenatally-exposed cohort		Childhood-exposed cohort	
Outcome	RR (95% CI)	*P*-value; No. cases	RR (95% CI)	*P*-value; No. cases
Hypertension	1.20 (0.6–2.4)	0.60; n = 155	1.15 (1.0–1.3)	0.06; n = 318
Hypercholesterolemia	1.33 (0.7–2.4)	0.35; n = 223	1.05 (0.9–1.2)	0.45; n = 508
Nonfatal CVD*	0.09 (<0.01–80)	0.49; n = 6	1.72 (1.2–2.4)	<0.001; n = 37
Fatal+nonfatal CVD*	3.94 (0.8–20)	0.10; n = 9	1.76 (1.3–2.4)	<0.001; n = 48

* CVD (cardiovascular disease) here combines stroke and myocardial infarction. Adapted from Ref. 14

are similar. For nonfatal stroke and myocardial infarction combined (labeled cardiovascular disease [CVD]), there was no apparent association for the prenatal cohort for nonfatal disease, although a dose-dependent risk was seen in the childhood-exposed cohort. However, when both fatal and nonfatal CVD were examined together, there appeared to be a radiation-related risk, though it did not quite attain statistical significance. The instability of the purely nonfatal vs. the nonfatal plus fatal CVD risk estimates clearly indicates that longer follow-up with a larger number of CVD diagnoses is needed to provide a more precise assessment. Again, statistical power was the principal limitation in examining the prenatally exposed cohort, but we conclude that the radiation-associated risks appear reasonably similar for the prenatal and childhood cohorts.

To summarize, the ABCC-RERF data provide weak or no support for a large childhood cancer risk from prenatal radiation exposure as has been reported by the OSCC and other smaller case-control studies of medical diagnostic irradiation during pregnancy. However, the statistical power to assess childhood cancer risk in the LSS was limited. A major concern by the radiation risk assessment community has been that the large radiation risks for childhood cancer reported by the OSCC would continue on into adulthood, such that the lifetime cancer risk would be appreciably larger than that for childhood radiation exposure. This does not appear to be the case—the risk from prenatal exposure may even be smaller than that for early childhood exposure for solid cancers, though it is too early to reach a firm conclusion. For thyroid nodules the radiation risks from prenatal and childhood exposure are similar. For hypertension and circulatory diseases (stroke and myocardial infarction), again the radiation dose-dependent risks are comparable for prenatal and childhood exposures.

In conclusion, the prenatally exposed cohort of atomic-bomb survivors appear to represent a sensitive population. It is unclear whether their degree of risk is as great as that for the early-childhood exposed cohort, although the two sets of risk estimates are broadly compatible. Since the prenatal cohort is entering the age period for the maximum expression of adult-onset diseases, the next one to three decades of follow-up will provide unique and valuable data.

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Taking Early Retirement

Yukiko Shimizu, Part-time Professional
Department of Epidemiology, Hiroshima

I decided to take early retirement last November, but have continued to stay at RERF for some time as a part-time professional in the Department of Epidemiology. Your continued support and guidance would be appreciated.

At the end of 1972 when I was a student at the Department of Mathematics, Faculty of Science, Hiroshima University, my seminar professor, Dr. Sumiyasu Yamamoto, recommended that I interview with the Atomic Bomb Casualty Commission (ABCC, RERF's predecessor). After an interview with Dr. Iwao Moriyama, Chief of the Department of Statistics at that time who also happens to be the uncle of the famous singer Ryoko Moriyama, I joined the Department of Statistics at ABCC in April 1973. Then, in July of the same year, Dr. Gilbert Beebe assumed the position of Statistics Department Chief. The attached photograph shows the research scientists of the department at that time.

The Department of Statistics in those days included the present-day departments of Epidemiology, Statistics, Information Technology, and part of the Clinical Studies Department (Clinical Administration Section, etc.), comprising two-thirds of all ABCC employees. With no personal computers installed in individual offices at that time, two researchers had to share one office. My officemate was Dr. Charles Land, who collaborates with RERF scientists and still visits RERF occasionally, and we apparently were able to get our messages across to each other, speaking a mixture of English and Japanese.

Staff of the ABCC Statistics Department in 1973

I am amazed at how fast the 36 years have passed since then.

Yukiko Shimizu in her present office

They say that it is fortunate to be blessed with good teachers and superiors when you are young, and that is exactly the case with me. I owe my many years of devotion to epidemiological research to Dr. Hiroo Kato, who taught me the field of epidemiology from my entry level. In those hectic days, whenever I asked him the deadline of the work he had requested, he would reply, "by yesterday." Dr. Shoichiro Fujita, who always used to shout at me, with warm-heartedness behind his sharp words, taught me statistical techniques. Mr. Tetsuo Imada and Ms. Kyoko Katagami, from the Computer Section (today's Department of Information Technology), taught me about actual data. They grew tired of how I always bombarded them with questions, and finally bestowed upon me the nickname "Yuki, the soft-shelled turtle" (based on the idea that such turtles refuse to let go once they sink their teeth into something, imagery that connotes persistence), but I remember they always taught me kindly. I consider myself very lucky to have had such strict but warm-hearted superiors. I also was blessed by talented subordinates, who provided me with the latest information and helped with my research. In addition, I was able to learn state-of-the-art statistical methods still unknown in Japan from non-Japanese research scientists.

On the occasion of my retirement, I would like to express my deepest appreciation to such kind superiors and capable subordinates, those mentioned here, and all other RERF members, for their support. Retiring two years earlier than mandatory retirement, I would like to make good use of that time taking care of my elderly parents.

Recontacting Work

Toshiko Tsukamoto
Former Recontactor, Hiroshima

About five US military Quonset-hut buildings were located in Hijiyama Park at the top of a small hill in Minami Ward, Hiroshima City. In Japan, I had never seen such structures, which looked like elementary or junior high-school buildings. Although there were no job listings in newspapers, my mother-in-law heard from somebody that they were looking for workers and told me to go there. If memory serves me correctly, that was in July 1957. I was told to be there by 8:30. I walked up the hill, entered the building from the front entrance and, following the signs on the walls, went upstairs to the auditorium. Surprisingly, half of the seats were already occupied. After we waited for about 15 minutes, a tall woman, who looked to be older than I was, came in and said, "I am the supervisor of the reception unit. I will now explain the work we do here. Today 165 people have gathered together. Thank you for coming. Six men and six women among you will be hired by the foundation after taking written exams for four days and undergoing a chest X-ray exam on the fifth day."

About one-and-a-half months after managing to pass the written test, I finally received notice that I had been accepted. Starting in September of that year, my busy days began, as my job started at 8:30. I got up at 5:00 in the morning, prepared breakfast, left home at 7:30, took a bus and a streetcar, and walked up Hijiyama Hill. Though I was busy, I was full of youth and energy, and was intensely involved in the work like a tireless child. I worked thusly for 23 years until my mandatory retirement age.

Let me tell you about some of the impressive contacting work I did during that time. Out of 30 contactors, about five were men. There were as many jeeps and drivers as contacters. Drivers got on the left side of the jeeps because the steering wheels were on that side, and we contacters rode on the right side, which had no door. Without holding onto the leather ring hanging from the ceiling, we would have been thrown from the vehicle. Although the work was hard on rainy or snowy days, we contactors did our best to overcome such difficulties. Finding houses was not as easy as it is now. Address numbers were not sequential, and sometimes we had to run around to find the right houses. Once I had a card with the address of a professor, but I later found that his residence was in an old wooden apartment building. I first was looking for a nice big house because his occupation indicated "university professor."

Jeeps used for contacting work around 1949

Sometimes, a card indicated that the person I was looking for was a mobster (*yakuza*) boss. I once went to the house of a *yakuza* boss in a certain town that had a gorgeous gate. After I rang the doorbell, five or six young men in black suits appeared and grunted "Hey!" My unit supervisor had told me a cautionary tale of the time he visited a *yakuza* boss near a certain train station and was chased away by someone with a kitchen knife, who shouted, 'I hate ABCC. Go away.' My heart fluttered, but I spoke to them with a calm expression. Two dogs also appeared. The big dogs were Great Danes. They approached me, growling. I had a Spitz breed at home, but these dogs were three times as big. Telling myself that if I ran, I would be the loser, and recognizing that such a situation was part of my job, I approached the dogs, saying "Good boys, good boys…" One of them suddenly stood on his back legs, and put one paw on my shoulder, peering into my eyes. I looked back at him and smiled. When one of the young men in a black suit called the dog's name, pulled on his collar and put him down on the ground, the *yakuza* boss appeared and said, "What's the matter?" He was a small man of ordinary appearance. I gave him my name card and desperately explained the purpose of my visit. "Aren't you afraid of dogs?" he asked. I said, "No. I love dogs and cats. I have a small dog at home." Then he said, "My dog probably smelled your dog on you. If you'd have run, he would have chased you."

He then turned and called to his wife, who was inside the house, and told her to take me to the living room and listen to my explanation. I was taken to a beautifully decorated room, and was served black tea. After we talked, I was able to make an appoint-

ment for a health examination. It was also agreed that the boss would undergo health examinations every two years. Our driver, who was waiting in the jeep, said, "I was worried about you. You made an appointment with a *yakuza—wow!*" Even yakuza are human beings and Japanese. I learned that if you are polite to them, they will be polite to you.

After about 10 years of such service, during which the unit supervisor, the section chief, and the department chief positions were each replaced twice, my bosses said, "Mrs. Tsukamoto, you are good at making appointments, so please take charge of recontacting work." And that is how I started recontacting work. I reviewed cards indicating that the first contact had been refused. I never started out by asking these people to come for an examination. Instead, I asked them, "Why do you dislike ABCC (or RERF) so much?" As I asked these people questions one by one, they talked about their various experiences. I used to listen to them, imagining how I would have felt if I had been them. Some people, with tears in their eyes, talked about the death of their parents, children, brothers, sisters, or grandparents due to the atomic bombing.

When the bomb was dropped, I was living with my mother and my younger sister, both of whom were outside the house. My mother died that day, August 6. My sister (21 years old then) suffered burns on 90% of her body, vomited blood, and excreted bodily waste without any control. In spite of my desperate attempts at nursing, she died on August 16. I was left alone, and spent a long time crying everyday. I thought of hanging myself from a tree in the garden of my house, but decided to live, telling myself that I was the only one who could protect my family grave. I told about my experiences to some candidate health examinees, and sometimes we cried together hand in hand. Once I was talking to a woman who was about 30 years older than I and had refused to undergo any examinations. While talking, I had tears in my eyes because she looked like my mother. Then she hugged me, and we cried together. With that, she agreed to come to the foundation for health examinations.

Some people refused to come for examinations because they believed that 1) ABCC was collecting a large amount of blood from each examinee to mix it together and sell it, or 2) ABCC diagnosed even healthy people with this and that illness, did not provide any medicine, and referred them to university hospitals, which paid gratuity to ABCC in return. I gave detailed explanations on both of these issues, and such misunderstandings were thereby resolved. Because I listened intently to their stories, they eventually opened their minds, and about seven of ten people who had initially refused agreed to make appointments. I cannot explain why exactly this happened. One of those people, a woman about five years older than I was, once said to me, "I was waiting for you because I knew that it was time for you to come soon." On such occasions, I felt happy about my work. One of the contactors asked me, "Mrs. Tsukamoto, don't you ever feel frustrated with this work? Aren't you fed up with it?" I responded that I actually enjoyed the work, but she replied, "I can't understand why." Once one of the contactors asked me, "Do you use hypnosis or something?" and I answered, "No, I don't, because I know nothing about it."

Fifty years have passed since I joined ABCC. Around then, one of the foreign doctors said that though he had heard Japan was an advanced country, he thought the Japanese were 30 years behind in terms of taking care of their own health. Nowadays, many people willingly apply for complete medical checkups or undergo health examinations in mobile screening buses that visit cities, towns, or villages. Preventive medicine has certainly made great strides. However, no matter the era in which we live, it is important for human beings to have strong determination to follow good examples and refuse to engage in harmful behaviors. Animals, such as dogs and cats, have to be told repeatedly what is right and what is wrong. It might be my prejudice, but I have heard that only humans have "shame" and "conscience" and use these two emotions as standards for making judgments. Along these lines, I believe it is important for human beings to think carefully and question ourselves.

In Memoriam

Thelma and Judith Jablon

Twice we were saddened to learn that family members of one of ABCC's most distinguished scientific leaders died. Thelma Jablon died January 16, 2009, at the age of 89 at her home in Bethesda, Maryland. She was the wife for 67 years of the scientist who had a major role in designing and implementing the early important ABCC study cohorts, Seymour Jablon. Mrs. Jablon was a teacher for most of her life and lived with her husband in Japan from 1960–1963 and from 1968–1971 where she taught at an international school and became a connoisseur of Japanese art. One of the daughters of Thelma and Seymour Jablon, Judith Jablon, died in Bethesda, May 10, 2009.

Seymour (right) and Thelma (left) Jablon with the Health and Welfare Minister Juro Saito in his office in 1987

Takashi Takemoto

We received word that Dr. Takashi Takemoto died on January 2, 2009, at the age of 83. He worked for the Department of Genetics in the early period of the ABCC, 1950–1954. Dr. Takemoto entered Hiroshima the morning after the bombing after arriving from Okayama Medical University in Okayama City where he had been staying. In an interview about the ABCC in the *Chugoku Shimbun* (7 June, 2007), Dr. Takemoto discussed his first work at ABCC which was to study newborn infants. He and others made door-to-door visits to homes in which a baby was born, based on cards on which addresses had been typed. In order to eliminate prejudice and bias, the examiners did not know whether the parents were A-bomb survivors or not. They examined the babies to note if they had congenital anomalies, and upon leaving the homes, gave soap to the mothers that was made in the U.S.

Takashi Takemoto around 1950

Over the years, some people have been critical of the fact that ABCC conducted examinations but did not provide medical treatments. Dr. Takemoto was very upset with the article with his interview that was printed in the newspaper because "nothing was written about ABCC's great contribution to medical care in Hiroshima, and its cooperation with medical organizations in the city." He explained to the reporter and to RERF in a letter that it was quite natural that ABCC did not provide medical treatment because "the nature of ABCC was not to compete with other medical organizations in the city of Hiroshima."

After resigning from ABCC, Dr. Takemoto was employed as a hospital doctor by the Department of Otorhinolaryngology at Hiroshima City Hospital. He pointed out that all of the histopathological tests at the city hospital depended on ABCC. In addition, personnel exchanges between the Departments of Pathology at ABCC and Hiroshima University resulted in fruitful results. Because of the good relationship between the two organizations, private practitioners were able to receive reliable test reports. Also, there was very little non-Japanese literature in medical libraries in Japan during the war, but there was a large volume of U.S. and a small amount of U.K. literature stored at ABCC's library which was made available to Japanese physicians. ABCC apparently provided photocopies of articles and lent various books to physicians free of charge.

RERF Research: Themes, Prioritization, 5-year Program Goals, Interdepartmental Programs, and a New Contract with the U.S. National Cancer Institute

Roy Shore, Vice Chairman and Chief of Research

The 36th Scientific Council Report indicated that Scientific Councilors were pleased with the 5-year program goals that were developed by RERF to provide a road map for establishing research priorities, allocating resources, and setting research project timelines. RERF leadership has worked interactively with the departments to accomplish this and to develop a working set of priorities for existing research projects. We have identified major research themes and have begun working on mechanisms to allocate resources, and to set and review project milestones and timelines.

The Scientific Councilors were also pleased that interdepartmental committees or working groups have been established for programs related to **cardiovascular disease (chair: Dr. Roy Shore)**, **children of A-bomb survivors (F_1 studies) (chair: Dr. Kazunori Kodama),** and **dosimetry (chair: Dr. Toshiteru Okubo)**. We expect additional interdisciplinary working groups will be developed for cataract studies, the genetics of various types of cancer, and immunological studies.

To further communication, monthly colloquia are held for all RERF research scientists, and departments have "work in progress" presentations every one or two weeks that usually include members of other departments and research leaders. Other approaches to enhance productivity and collaborative interactions among RERF scientists are being considered, including the establishment of shared core facilities, centralization and integration of the management of databases and biosamples, and facilitation of international collaborations. Stay tuned and we will keep you informed as those plans develop.

In September 2008, RERF scientists prepared a research proposal in response to a Request for Proposal (RFP) titled "Support for Epidemiological Studies of Cancer Among Atomic-bomb Survivors" that was issued by the U.S. National Cancer Institute (NCI). RERF was notified that the proposal was evaluated and was found to be acceptable and a contract was awarded with funding in December 2008. The contract is approximately $300,000 per year for a period of five years and is a continuation of a long-term collaboration between RERF and the Radiation Epidemiology Branch of the NCI that goes back to 1979. The original project was supported by means of a prime contract between the NCI and the National Academy of Sciences (NAS) with a subcontract between NAS and RERF. The new contract will provide funding directly to RERF and the project co-directors are Kazunori Kodama (RERF Chief Scientist) and Roy Shore (RERF Vice Chairman and Chief of Research).

Roy Shore, Vice Chairman and Chief of Research

The contract will focus on enabling NCI scientists to work with RERF research scientists to analyze data and prepare reports on cancer incidence risks that are associated with the Life Span Study (LSS) cohort. Some of the projects include: completion of a series of reports on cancer incidence in the *in utero* cohort and the subset of the LSS that includes people exposed in early childhood (see review of these studies on page 9 of this issue of *Update*); updated analyses of radiation effects on lympho-hematopoietic malignancies (leukemia, lymphoma, and multiple myeloma); lung cancer incidence; and other mutually agreed upon projects that might be developed during the term of the contract.

The past support from the NCI has enabled the tumor registries in Hiroshima and Nagasaki to be strengthened and the solid tumor data has been recently updated an additional 11 years through 1998 (Preston et al., *Radiation Research* 168:1-64, 2007). The updated report evaluated risks for total solid cancers and for 18 specific tumor sites plus a residual category. More detailed analysis of the residual category identified, for the first time, urothelial cell cancer as a radiation-related cancer type. Multidisciplinary studies will involve the acquisition and use of biological materials and mail surveys will be used to provide valuable information on risk factors that is not available from routine mortality and cancer incidence follow-up of the LSS cohort. Finally, case-control studies will continue to explore whether changes in blood nutrient, hormone, or antibody levels pre-diagnosis correlate with the risk of cancer for selected sites.

Research Protocol Approved in October 2008–March 2009

RP 6-08 Liver Stiffness Study Using Elastometer in Hiroshima Atomic-bomb Survivors
Ohishi W, Tatsukawa Y, Fujiwara S, Hsu WL, Kohata M, Yamada M, Nishi N, Tsuge M, Chayama K

During two examination cycles (four years), we will measure liver stiffness as a marker of liver fibrosis severity with an elastometer for about 3,800 participants of the Adult Health Study (AHS) (including the expanded group of younger survivors) in Hiroshima to examine the relationship between liver stiffness and radiation exposure. In analyzing liver stiffness, we will evaluate possible confounding factors, such as biomarkers related to chronic inflammation, insulin resistance and others, body mass index (BMI), alcohol intake, diet, and hepatitis virus infection. We will also examine the involvement of liver stiffness in the prevalence of atherosclerotic disease.

Recent Publications

(Japanese): the original article is in Japanese.

Aragane NS, Imai K, Komiya K, Sato A, Tomimasu R, Hisatomi T, Sakuragi T, Mitsuoka M, Hayashi S, Nakachi K, Sueoka E. Exon 19 of *EGFR* mutation in relation to the CA-repeat polymorphism in intron 1. Cancer Science 2008 (June); 99(6):1180-7.

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Fukuzawa M, Yamaguchi R, Hide I, Chen Z, Hirai Y, Sugimoto A, Yasuhara T, Nakata Y. Possible involvement of long chain fatty acids in the spores of *Ganoderma lucidum* (Reishi Houshi) to its anti-tumor activity. Biological and Pharmaceutical Bulletin 2008 (October); 31(10):1933-7.

Hagino H, Furukawa K, Fujiwara S, Okano T, Katagiri H, Yamamoto K, Teshima R. Recent trends in the incidence and lifetime risk of hip fracture in Tottori, Japan. Osteoporosis International 2009 (April); 20(4):543-8.

Hamatani K, Eguchi H, Cologne JB, Soda M, Abe K, Hayashi T, Nakashima M, Sekine I, Hayashi Y, Nakachi K. Gene alterations preferentially occurred in papillary thyroid cancer among atomic bomb survivors. Nagasaki Igakkai Zasshi [Nagasaki Medical Journal] 2008 (September 25); 83(Special issue):264-7. (Proceedings of the 49th Late A-bomb Effects Research Meeting, 2008) (Japanese)

Haruta D, Matsuo K, Ichimaru S, Soda M, Hida A, Sera N, Imaizumi M, Nakashima E, Seto S, Akahoshi M. Men with Brugada-like electrocardiogram have higher risk of prostate cancer. Circulation Journal 2009 (January); 73(1):63-8. (RERF Report 3-08)

Katayama H. How the personal information is protected in the cancer registry. JACR Monograph 2008 (March); No.13:35-9. (Japanese)

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