Report of the 38th Scientific Council Meeting

February 28–March 2, 2011, Hiroshima Laboratory

Scientific Councilors

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Introduction

The Scientific Council (SC) met from February 28–March 2, 2011, in Hiroshima, Japan. Its task, as in previous years, was to review the Radiation Effects Research Foundation (RERF) scientific programs. This year, the SC conducted an in-depth review of the Departments of Epidemiology and Statistics. With its plan for a detailed review of these two departments four additional experts joined the Council. Drs. John D. Boice and Suminori Kono particularly focused on the Department of Epidemiology while Drs. Colin Begg and T. Shun Sato concentrated on the Department of Statistics. Their addition was extremely valuable to the SC and it was a great pleasure for the Council to work with these outstanding scholars. Dr. Kazuo Tajima, Director of the Aichi Cancer Center Research Institute, joined the Board of Scientific Councilors with the retirement from the Board of Dr. Yoshiharu Yonekura.

Dr. Toshiteru Okubo, Chair of the RERF, opened the 38th Meeting of the SC on the morning of February 28, and provided a warm welcome to all in attendance. He explained that this year the SC would provide a focused review of the two departments and how important the SC's work is to the staff of the RERF. He also explained the basics of the change of the Act of Endowment with RERF becoming a Public Interest Incorporated Foundation. The Scientific Councilors will become the Scientific Advisors (Scientific Advisory Committee) who will continue to review the scientific programs of RERF and report their recommendations to the Board of Directors and Board of Councilors.

Following Dr. Okubo's welcoming remarks, Dr. Roy E. Shore, Chief of Research at RERF, provided a review of the status of research at RERF. He began with a detailed response to the recommendations made by last year's SC's report. This was followed by a description of RERF's major accomplishments during 2010. Most importantly the pilot work for the immunological studies of the National Institute of Allergy and Infectious Diseases (NIAID) project was completed and the full-scale studies are beginning. Also progress was being made on both the F_1 cohort of survivor children longitudinal clinical studies and 1,900 new screenees under the age of 10 years at time of exposure were added to the Adult Health Study (AHS). In addition, the tumor registries have been updated through 2005 and significant progress was made in updating the dosimetry databases. Major publications this past year were on radiation-induced heart disease, myelodysplastic syndrome (MDS), and cataracts. Dr. Shore also described the transparency and sharing of data. This involves both the publicly available databases and the sharing of data and biospecimens with outside research collaborators.

Following Dr. Shore's comments, detailed presentations by the Department of Epidemiology and the Department of Statistics were given by the department chiefs and selected staff members. Next, a brief overview of activities of the Departments of Clinical Studies, Radiobiology/Molecular

Epidemiology, and Genetics was given to the SC. Each presentation included responses to last year's SC recommendations and then reported on major accomplishments during 2010 as well as future plans. Dr. Evan B. Douple updated the SC on the work of the Committee on Biological Samples. Major issues confronting the committee include the need of centralized management of all samples including a comprehensive database. Also the urgent need for more storage space was discussed. Finally, Mr. Takanobu Teramoto provided an update of the progress and accomplishments of the public relations office.

Beginning the meeting on Tuesday Dr. Okubo presented the interim findings regarding RERF's information system which is being conducted by the NTT Data Corporation. This report is evaluating both the security and efficiency of RERF's information systems. What was of particular concern was the very large number of requests for changes or creation of new software from all groups at RERF. The SC looks forward to reviewing the final NTT report and RERF's response to the report's recommendations at next year's SC meeting. After Dr. Okubo's special presentation on information systems, informal meetings were held between various SC members and the RERF departments being reviewed. Throughout the meeting the SC reviewed and discussed the information provided concerning the activities of the RERF.

Overview

As stated in previous reviews, the SC continues in its belief that the 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 (MHLW) and the United States Department of Energy (DOE) as well as scientific guidance of the National Academy of Sciences (NAS) continue to be critical to the mission of the RERF. Without such support and the generous assistance of the survivors and their families, the ability of the RERF to conduct substantive research that has great importance 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, c) the threat of nuclear terrorism, and d) the recent tragedy consisting of an earthquake and tsunami that damaged nuclear power reactors in Fukushima and caused releases of radioactivity into the environment and increased worker exposure. These concerns have only intensified since last year's review. The scientific opportunities for improved understanding of radiation effects on humans have also increased. This is the result of new and novel basic laboratory findings in radiobiology that clearly indicate the need for their integration into human risk assessment through systems and computational biology. Secondly, advanced statistical methods using high speed computing have allowed for greater sophistication in model development including the requisite incorporation of measurement and model uncertainties. Thus RERF is well positioned to move forward by rapidly improving our knowledge of quantitative radiation risk assessment. This combination of the increased and continuing needs of society and the scientific opportunities for improved knowledge and understanding of the health effects of radiation hopefully will stimulate the Japanese MHLW and the U.S. DOE to possibly increase or at least maintain their level of basic financial support of RERF even in these difficult times of contraction of available governmental research funds. RERF has an important mission to evaluate the lifetime effects of radiation exposure among atomic-bomb survivors. This is a unique program that cannot be matched anywhere in the world. There is more to be learned and RERF is uniquely situated to provide the much needed answers.

With the outstanding senior leadership of Drs. Okubo and Shore the Scientific Councilors anticipate an even greater future for science at RERF. With the rapid increase in the medical uses of radiation and the worldwide expansion of nuclear power generation, this should be a time for the expansion of the critical radiation health research which RERF is uniquely capable of conducting. The Councilors do, however, understand and appreciate that the continued support from the sponsoring governmental agencies has been well protected during these times of budgetary contractions.

General Recommendations

The Scientific Councilors have two primary general recommendations and five specific recommendations:

- **Research Quality:** A concern that cuts across all programs involves clear articulation of the justification, prioritization, and overall quality of each research project. Research protocols (RPs) need to better articulate the scientific rationale for the proposed research. An RP should be undertaken when the research addresses a topic of compelling relevance to current scientific knowledge. The RPs are all subject to an internal review process where the projects can be prioritized and those that are of low scientific merit can be revised or eliminated. It would be helpful to modify and streamline the process of RP review, to make it both faster but more effective in focusing the research endeavor. This might involve creation of a written document that provides a framework for guiding both the scientific review and the information needed in the RP to justify the research plan. Consideration might be given to adding a priority score as is done with the National Institute of Health (NIH) extramural grant program for evaluation and funding decisions, although we recognize that some research endeavors are necessitated by the special circumstances of studying atomic-bomb survivors.
- **Inter-disciplinary Research:** Contemporary scientific advances increasingly require inter-disciplinary collaborations. Departmental structures as they exist are necessary to nurture disciplinary expertise, but separate programmatic structures can be useful in encouraging inter-disciplinary collaborations. The RERF leadership might consider the option of creating such an administrative structure to help ensure that the research is of high quality and of contemporary relevance. The

program themes should be selected on the basis of the overarching research priorities of RERF, and these could be periodically updated to reflect the contemporary landscape of research emphasis.

Specific Recommendations

1) The Council continues to strongly recommend that the many and varied databases of participant information and biological samples be integrated into a central database for the use of researchers in all departments. There is also the need for the incorporation of sophisticated, user-friendly relational database software into RERF's library of computing tools. The complete data on every subject ever involved with ABCC-RERF research should be retrievable with ease.
2) One of the most important and valued scientific assets of the Foundation is the collection of biological samples. Storage space for the newly collected samples will soon be filled. RERF must give the highest priority to either the building or the reassignment of space for the storage of these unique biological samples.
3) With the limited availability of governmental research funds it is important that the senior research staff be given the opportunity to apply for extramural funding and that the administrative process to do so be made streamlined and time-efficient. It is also important that travel funds for international scientific meetings be protected without compromising the funding of the basic high priority research activities. RERF scientists need to present their seminal findings to the world as well as stay current on the latest research relevant to radiation health effects.
4) Collaborations with universities and other Japanese colleagues should be strengthened, and more graduate students and postdoctoral fellows should be encouraged to carry out research based on RERF's unique resources and databases.
5) High quality publications by senior scientists are essential for informing the world of new findings and for the continued success of RERF. More such publications are needed.

Individual Department Reviews

Department of Epidemiology

Overview

The Epidemiology Department provides a critical underpinning for the entire efforts of the RERF and forms a platform for the three major exposed cohorts (the Life Span Study [LSS], AHS, and *in utero* cohorts) and the F_1 cohort of the children of atomic-bomb survivors, with follow-up of over 200,000 individuals. The research conducted has provided critically important and much sought after dose-response information for both incidence and mortality of hematopoietic and solid tumors. Nonetheless, approximately 40% of LSS subjects, including 85% of those exposed before age 10, were alive at the end of 2006, so there is a great deal to learn from continued follow-up of these populations. Long-term radiation effects on diseases other than cancer are emerging, such as thyroid, myelodysplastic, liver, and cardiovascular diseases or conditions.

The department has been active during the past year. The LSS mortality study now covers the period 1950–2003. Analyses have been completed and publications are being prepared to summarize these data. A mail survey to participants is one-third complete and should add to the database and our understanding of the effects of radiation. A feasibility study to collect saliva as part of the mail survey indicated a lack of response. The *in utero* cohort and the F_1 cohort of survivor children have been followed through 2003 and mortality and cancer incidence evaluated. The F_1 cohort is large, 77,000, but the numbers of outcomes are relatively small (418 incident cases of solid cancer, 57 hematopoietic malignancies, and 1,270 non-cancer deaths). While radiation-related risk has not been identified in the F_1 offspring study, the majority are still young, and this is the only such study in the world evaluating possible inherited radiation risks in the adult children of exposed parents. Approximately 12 papers are in process.

Studies of site specific cancers with histological review are underway. These include basal cell skin cancer, cancers of the thyroid, breast, ovary, uterus, lung, soft tissue and bone, and malignant lymphoma. Many of these are in collaboration with the U.S. National Cancer Institute (NCI). Hematological studies have been forthcoming and include a new and important publication on myelodysplastic syndrome in the *Journal of Clinical Oncology* this year, and another on leukemia and related diseases is in process in collaboration with the Statistics Department. Updating cancer incidence and mortality is almost complete through 2005. Pathologic studies are intensively being carried out. Analyses of smoking in relationship to lung cancer and total disease mortality have been ongoing in collaboration with Oxford University. Such collaborations are critical to the continued productivity of the Epidemiology Department. Other collaborations include those with the University of Washington, the Asia Cohort Consortium, the U.S. NCI, Kurume University, Kyushu University, the Japanese National Institute of Radiological Sciences, Hiroshima University, Nagasaki University, and local hospitals.

Evaluation and Critique

The department has been responsive to most of the suggestions from the previous review. They have further developed collaborations with research groups in Japan and other countries in order to optimize their productivity. The time frame for project conduct has been recorded, although it could be more specific. The database of pathological specimens is being re-structured which is a huge undertaking. It is unclear as to how much longer this will take. All collaboration adds to the burden of the investigators; however, to make scientific progress such collaborations are essential and have so far been quite profitable.

Recommendations

Several critical recommendations, if followed, would make this department even more successful.

1. Projects should be prioritized. There remains a great deal of work to be accomplished and few "investigators" are available. The department has a small number of

scientists and this fact makes it all the more critical to carefully plan the goals for the program, and to focus work on the highest priority studies. Increased collaboration with the Department of Statistics would also help in providing additional research time for the scientists in Epidemiology.

2. At present, the denominator for LSS cancer incidence studies is estimated. Due to the restrictions now placed on obtaining addresses from the *koseki* attachment, the available addresses are out of date. Current addresses of LSS residents are needed to correctly relate the cancer cases reported to the Hiroshima and Nagasaki cancer registries to the population at risk. Out migration, for example, is a potential concern which could bias the estimation of incidence rates, i.e., the denominator may be inaccurate based on old residential histories. The need to have an accurate denominator for cancer incidence studies is very important, so efforts should continue to obtain current residential addresses of atomic-bomb survivors. Current addresses will also improve the response rate for the mail survey for which many questionnaires are returned as not deliverable.
3. The Scientific Councilors would find it informative to have dose distributions presented and compared for each of the cohorts being studied, i.e., the LSS, AHS, *in utero*, F_1 cohorts, as well as for the residents of Hiroshima and Nagasaki assumed to be in the catchment areas covered by the cancer registration. Such information already exists but not, it seems, in a single table using the same dose categories.
4. Publications in international journals this year number 13 with 2 of those in press. The department should be pleased as this is an increase in numbers and substance from the previous year. However, a nagging lack of first author papers is still noted and more efforts should be made to improve the publication rate.
5. Important methodologic considerations for this program include the following:
   a. Continued research in the area of genetic risk. Because of the importance of genetic factors in disease etiology and interactions with environmental exposures (notably radiation), continued research in this area should be encouraged.
   b. Evaluate or clarify the reasons for the low rate of saliva collection. To facilitate future research in the area of genetic research, it would be helpful to learn the reasons behind the high refusal rate. Focus group discussions, for example, might be considered with individuals who did not respond to the feasibility saliva collection. If the reasons that some did not participate can be addressed, future RERF studies of genetic factors in relationship to risk may be enhanced. It is recognized, however, that many of the high-dose survivors have provided blood samples and other biological specimens in the course of the AHS.
   c. Compare the cohorts' rates with general population rates using SMRs (standardized mortality ratios) and SIRs (standardized incidence ratios). Such population comparisons add an additional perspective as well as usefulness when evaluating rare outcomes such as mesothelioma.
   d. Evaluate exposures to medical imaging in cohorts. Medical imaging such as CT and PET scans has increased dramatically in Japan but it is unclear what impact such improvements in diagnostic accuracy might have on age-specific risk coefficients in addition to the effect of the increased exposures received.
6. The SC feels that there is insufficient collaboration between the Departments of Epidemiology and Statistics. The two departments have similar interests and it is important that the Department of Epidemiology make extensive use of the expertise in the Department of Statistics.

In sum, we applaud the current efforts of the Epidemiology Department and recognize the critical role that this department plays in all the work of the Radiation Effects Research Foundation.

Department of Statistics

Overview

The Department of Statistics has two primary roles. The first is to provide statistical consultation to investigators in other departments at RERF. The second role is to conduct original independent research on statistical methods that could provide new insights or otherwise enhance the design or analyses of studies conducted at RERF. The department is led by Dr. Harry Cullings and consists of eight statisticians, seven of whom have doctoral degrees. There are two research assistants. The written report provided a bulleted list of achievements in the past year, a similar list of future projects, and a "5-year plan" that described the specific projects in methodology research that are considered to have high priority. These were each later described in somewhat more detail, including progress made to date, and future plans.

Evaluation and Critique

The published output of the department indicates that the major activity is in fact collaborative work, a perception that was confirmed in our meetings with the professional staff. There are 26 articles listed in the bibliography (either published in 2010 or "in press"), of which 7 are first author publications by members of the department. This indicates substantial involvement in the broader program of research at RERF. One particular area of current importance is new epidemiologic study designs that have been developed, such as two-stage case-control studies, case-specular designs, and case-crossover studies. The RERF statisticians should have deep familiarity with these study designs. It is also important to understand the inverse probability sampling methods used in case-control studies conducted within a cohort. Application of these methods to the RERF studies requires collaboration with the Epidemiology Department and with expert biostatisticians outside the RERF.

In future reports it will be important to dwell on the organizational aspects of the group for provision of statistical collaboration, the extent to which the department is involved in the research of each of the other departments, the manner in which the quality of the statistical work is

assessed internally (within the department), in addition to the tangible products of this work (such as published articles, involvement in new research protocols, etc.). In the face to face meetings Dr. Cullings described the weekly meetings of the staff which are used to foster discussions of analyses in progress. He pointed out that all of the statisticians were engaged with various investigative groups, and described his own role in triaging orphan projects to appropriate statisticians. In last year's critique there was a specific recommendation to build expertise in the analysis of data from "omics" technologies. However, in discussion it was pointed out that the group does have expertise in such analyses, but unfortunately there are no "omics" investigations completed yet by investigators in other departments at RERF.

The primary focus of the written report was on a series of studies to develop new statistical methods. The first project concerns efforts to use recent advances in geographical information system (GIS) technology to better map the positions of the survivors at the time of the bomb in order to refine their radiation dosages. This work involves Dr. Cullings, Dr. Okubo (RERF Chairman), experts at the Japan Geographical Survey, and various experts in the U.S. Three articles submitted or published are reported. Clearly this project is important and productive. We note that dosimetry estimation is a pivotal role of the statistics group at RERF. The group needs to carefully consider whether fine-tuning of doses is truly making a difference to the conclusions of the various studies of radiation effects. A second project involves Bayesian modeling of individual data from the studies linking radiation dose to all the major cancers in preference to the traditional Poisson modeling of grouped data. The idea is that this approach will provide a better modeling strategy that may alter dose estimates and could produce more realistic estimates of uncertainty (i.e., wider confidence intervals). The project seems to be somewhat stalled due to the computational burden of the Markov Chain Monte Carlo (MCMC) method. A third project which appears to be an active project by an outside collaborator involves waist circumference (WC), needed for the diagnosis of metabolic syndrome (MS). Unfortunately WC was not collected on early questionnaires. The basic goal here is to use later WC data to estimate WC at earlier time periods in studies of MS. The results seem to contradict the expected relationships, and plans are afoot to try to understand the reasons for this discrepancy. The group needs to consider the relevance of this project to the RERF mission. There are four papers in the recent past on this topic (two in conference proceedings and one book chapter), so again this appears to be an active project. A fourth project involves determining whether results from the LSS cohort are consistent with predictions from theoretical models of carcinogenesis (Moolgavkar's two-mutation model). The project is in progress but there are no results yet. The goal of a "causal modeling" project is to examine the relevance of inflammation (as a mediating effect) on the relationship between radiation and cataract incidence. Early results show that all three factors are related and that the "mediating proportion via inflammation is roughly 7% of the total radiation effect," but as yet there are no publications. Another project involves the development of novel survival analysis methodology to project long-term survival in groups who have only been followed after disease incidence for a relatively short period. The method involves parametric modeling, augmented with baseline survival estimates from age and gender matched data from vital records of a reference population. There are no results or publications yet. A project was described that seeks to derive the impact of uncertainty in radiation dose estimates. There is insufficient detail presented to figure out exactly how the investigators plan to accomplish this, other than a brief reference to "instrumental variable" analysis. A final project seeks to map out an analytic strategy to deal with the issue of "mediating" intermediate outcomes: outcomes caused by radiation exposure that also indicate risk of subsequent cancer, such as HBV infection and hepatocellular cancer, chronic inflammation, etc. It looks like the research will proceed along the lines of comparing different analytic strategies, such as path analysis, a regression imputation method, and a full likelihood approach, and these will be compared using structural equation modeling. This project is in progress but there are no publications or reports yet.

These projects are mixed in terms of their levels of development, general scientific merit, and productivity. Overall the projects are potentially valuable, but some prioritization is in order. However, the three projects presented at the meeting were discussed in greater depth, and constitute valuable contributions. The use of external experts to facilitate completion of projects is a strategy that has been used to good effect in the past, and may be beneficial for some of the higher priority projects on this list.

Recommendations

- **Statistical Collaborations:** Collaborative work should enjoy high priority in the overall mission of the department. The reviewers are pleased that the department takes a proactive approach to consulting, beginning with early involvement in study design. In discussions the group was seen to have a broad array of expertise, and provided convincing evidence that most types of analyses could be addressed with relevant expertise by one or other of the current group. However, the SC feels that there is insufficient collaboration with the Department of Epidemiology. The two departments have similar interests and it is important that the Department of Epidemiology make extensive use of the expertise in the Department of Statistics. New statistical methods are continually being developed, and it is important that the staff strives to keep up to date with important recent developments in the field in order to enhance the effectiveness of the collaborations.
- **Methodological Research:** Original research on statistical methodology should continue to be an important goal. This is necessary to encourage the professional staff of the department to maintain an interest in developments in the field, to generally enliven the intellectual environment, and ideally to bring recognition to the department. Efforts in this area should be focused on projects that have both high merit and are likely to be successful, and should be motivated by RERF studies. There are eleven first author papers during 2010 (or in

press) and three of these are in the statistical literature. This is a good response to last year's SC recommendations.

- **Academic Outreach:** The intellectual environment could be enhanced by greater outreach to biostatistical experts in other institutions. Some of these collaborations are in progress, but in general these are to be encouraged, with the goal of enhancing the research productivity, and possibly attracting funding to the department. The department enthusiastically entertains extramural collaboration with outside experts at the University of Washington, the Fred Hutchinson Cancer Research Center, the University of Buffalo, Pennsylvania State University, the University of Southern California, and colleagues in numerous Japanese universities. The SC also emphasizes the importance of contributions to academic societies, the academic community in general, and the Japanese government. Presentation of findings at statistical meetings should be a priority, since this will encourage recruitment of junior professional staff. The encouragement of student internships could be beneficial to increase the research output, to bring recognition to the department, and to provide valuable experience to the trainees.
- **Leadership/Mission:** A mission statement to clarify the overall goals of the department would be valuable. This should include capacity to meet the on-going and future consulting requirements, mentoring of junior investigators, and the career development of the staff. There should be a clear policy regarding the value to the department of independent research, and the extent to which independent work is mandatory for promotion of individual professional staff members. While independent methodological research may not be crucial for a career at RERF, it should be recognized that it is essential for the career development of professional staff who wish ultimately to re-enter academic life.

Department of Clinical Studies

Overview

From a very well prepared annual report, the Department of Clinical Studies reports nine professional staff members, five in Hiroshima and four in Nagasaki. In response to last year's SC recommendations, Dr. Fujiwara mentioned a one-day strategic planning session between the two units to address priorities. We are pleased that the cardiac ultrasonography equipment is being procured. Now, a consulting clinical cardiologist must be engaged to interpret the tracings, especially for advanced interpretation of, e.g., ventricular strain. Hopefully, abdominal aortic measurements can be added to certain protocols, with the availability of this machine. Publications in 2010 and in press number 34, of which 13 have department members as first authors, 16 as last author. Three were book chapters, seven articles were in Japanese journals, and 13 had no underlying RP. Total effort, according to the list of RPs, is 12.4 professional and 57 technical/clerical help, of which four platform protocols consume 5.2 professional and 54.5 technical staff. Eight protocols bear dates of 2009 and 2010, reflecting good initiatives. Seventeen protocols, with a total of just 2.27 profession, and 0.75 staff FTEs, have just 11 publications and seven have none. Those RPs older than five to seven years might deserve consideration for termination. Of 15 presentations of results at meetings in Japan, and only seven were overseas. One hopes that international travel opportunities are given priority.

AHS has provided valuable information on morbidity and biochemical measurements in relation to radiation exposure. Notable are studies on hepatocellular carcinoma (HCC) and cataract. Risk increments of HCC with or without infection by hepatitis viruses (HBV and HCV) are analyzed by a nested case-control study for the AHS. The risk of HCC increased with radiation dose, after accounting for HBV and HCV infection, smoking and alcohol use. Protective factors on HCC, e.g., coffee drinking and exercise, should be evaluated by using the same materials for future prevention of HCC.

A series of cross-sectional studies are examining the relation of radiation dose to diverse inflammatory biomarkers and risk for atherosclerosis and arteriosclerosis. It may be that too many biomarkers and indices are being studied. Perhaps a conceptual framework for causal inference on the possible association needs to be re-evaluated.

Recommendations

- Gain a clinical cardiology consultant.
- Put priority on first-authored publication of work on RPs, in international English-language journals.
- Address a full range of confounding factors in interpreting results
- Provide a full rationale for all association studies

1. AHS

The LSS gives information on cancer incidence and cause-specific mortality. Studies on cancer incidence in the LSS are limited because of uncertainties in estimating the denominators and consideration of confounding factors. Thus the AHS should be continued to clarify radiation effects on diverse morbid and pre-morbid conditions with consideration to confounding and effect modification. A total of about 15,000 subjects have participated in the AHS, and currently about 4,900 subjects are taking biennial health examinations. The cohort recently added 1,960 younger subjects who had been exposed to the A-bomb at ages less than 10 years.

Recommendation

- Full support is required for the routine work of invitation, examination, and data compilation. Informed consent for important genetic analyses is only possible in the AHS and F_1 Clinical Study.

2. F_1 Clinical Study (FOCS)

Approximately 12,000 offspring of A-bomb survivors participated in the study health examination during the period 2002 to 2006. The study showed no radiation effect on the so-called adult-onset multifactorial diseases. More specifically, cross sectional analyses of risk for multifactorial chronic diseases by paternal, maternal, and both exposure levels among 11,951 offspring of A-bomb survivors in 2002–2006 are started and there is no evidence of any increased

risk of parental exposure on any individual disease endpoint. There are several issues to be solved in this study, e.g., accuracy of diagnosis of individual multifactorial diseases should be clarified, a limited number of cases due to relatively younger average age (<60 years), so follow-up should be continued.

Recommendation

- The offspring are still young and further follow-up is highly recommended. It should be noted that this type of study has not been undertaken anywhere else in the world.

3. Cataract

It was previously found in the AHS that radiation was related to increased prevalence odds of cataract. A prospective study on cataract just started in August, 2010. The prospective study itself is important, and tissue storage could be a valuable first step in clarifying the mechanisms of radiogenic cataracts (as well as other cataracts). We understand collection is in phase one, to show feasibility, so we hope criteria for continuing and using the collection will soon be spelled out. It is not clearly stated what sort of studies are planned on the basis of tissue samples.

Recommendation

- Clarify and implement criteria for success in the phase one collection of lens tissues.

Overall

As we review the report and eight break-out presentations (without reading all the reprints), we sense some limitation in considering confounders or alternative explanations: why estrogen and testosterone levels increase with radiation in postmenopausal women; whether family history or hemachromatosis might explain radiation effects in hepatocellular carcinoma; whether mutations in *BRCA1/2* or *TP53* explain the cases of breast cancer in the *in utero* cohort; whether intervening diagnostic irradiation, single gene (mendelian) conditions, or familial aggregation contribute to any of the radiation effects.

We hope that the units are considering their responsibility for assuring the emergence of bright radiation-oriented physician-scientists, such as themselves, for the future workforce, e.g., by offering experiences to medical students and clinical residents in training. One such young physician hoped that more formal training in epidemiology could become available.

One wonders if the findings of one organ of special sense, the eye, could be extended to another special sense, the ear. Given that this department is the interface with the survivors and their children, we hope that the concept of community-based participatory research is explored, where the affected population is a true partner in research, even in identifying the issues or priorities of subsequent formal investigation. An example might emerge from clarifying the reasons for a poor response to the request for saliva samples. The local liaison committees, perhaps augmented with additional survivors, their children, and their spouses, might begin or help define such a process.

It is gratifying to learn that cases with some infrequent single gene traits are being identified. As they might explain occurrences of some common diseases, like liver or colon cancer or cardiac arrhythmias, awareness and thorough recognition of such conditions, not so rare in the aggregate, must be assured by the clinician. Again, merging of all observations on individual subjects might improve the completeness of such recognition. We are thrilled to witness the beginning of collecting family history, a major confounder in many endpoints of interest. We recognize and treasure (and encourage more) the serendipitous recognition of unexpected clinical results, such as the improvement of Brugada-type electrocardiogram (ECG) abnormalities after castration in three of four males with prostate cancer.

Recommendations

- Address a full range of confounding factors in interpreting results
- Emphasize training of the current young staff
- Put a high priority on a thorough reconsideration of the congenital defects in the F_1, including the possibility of looking at clinical subjects being seen in the FOCS studies.
- Consider new topics, such as hearing impairment, total look at mendelian genetic disorders, and whatever the survivors groups might nominate for study.

Department of Radiobiology/Molecular Epidemiology

Overview

The Department of Radiobiology/Molecular Epidemiology (RME) is headed by Chief Dr. Kusunoki, with Dr. Hayashi as Assistant Chief. The department has two major laboratories. The Laboratory of Immunology has six scientists with Dr. Hayashi as the Laboratory Chief. The Laboratory of Cell Biology has four scientists with Dr. Hamatani as the Laboratory Chief. Dr. Nakachi, the former department chief, retired three years ago and is serving as Project Principal Scientist for the NIAID project. Fifteen full-scale RPs and seven type-A RPs/Pilot Studies are in place. Of the 15 full RPs, only two produced publications in 2010. Some of the RPs have been continued since the "last Century," and some reevaluation and reorganization of RPs based on scientific rationale and RERF overall priorities should be considered. Furthermore, some of the RPs are not research-based but support sample collection/storage. This kind of activity should be carried out not by a research department but by a specialized supporting section. A consolidated section for sample/specimen collection and storage is needed and could be a benefit to RERF as a whole.

Several of the projects that were reported on last year were not updated this year, perhaps reflecting a change in priorities of the department. These include the study of epigenetic changes in squamous cell lung carcinoma and the genome-wide association study (GWAS) pilot study of single nucleotide polymorphisms (SNPs) associated with cancers in the AHS. The study showing an association between an elevated rate of glycophorin A (*GPA*) mutation in response to radiation exposure and specific *53BP1*

haplotypes, but not *ATM* or *NBS1* haplotypes, was presented again, but did not include information on polymorphisms in associated genes such as *p16*, *LIG4*, *XRCC4* or *MRE11*, which the response to last year's Science Council recommendations indicated was being undertaken.

The primary focus of the department is to ascertain the molecular basis of radiation-induced malignant and non-malignant diseases with a current strong focus on immuno-senescence and potential epigenetic mechanisms of disease causation. The two-laboratory structure was implemented at the founding of the department, and since that time, the department has worked in two complementary areas. Analysis of molecular events associated with radiation-related cancer among A-bomb survivors is the major subject for the Laboratory of Cell Biology. The Laboratory of Immunology investigates the involvement of immunological mechanisms in the development of cancer and non-cancer diseases. Both groups have functioned in a complementary and synergistic fashion. Relevant biospecimens from exposed and unexposed individuals serve as a basis for most of their work. Overall, the department efforts are consistent with RERF's mission. New questions are being addressed, especially in terms of the NIAID-funded projects and new techniques have been developed and applied.

In the past 60 years, the central dogma of radiation carcinogenesis has been the straight-forward hypothesis that radiation-induced DNA damage causes mutations responsible for the development and progression of cancer. However, the working hypothesis of the immunology group challenges this dogma by offering an alternate, but not necessarily mutually exclusive, hypothesis that radiation-induced immunosenescence plays a major role in the late development of both cancer and non-cancer diseases, and generally contributes to accelerated aging. The Laboratory of Immunology's current focus is on potentially accelerated immunosenescence in A-bomb survivors. A pilot study on effects of radiation and aging on the response to influenza vaccination has successfully detected differences in the response of young and elderly volunteers to flu vaccine, and the study will be expanded to investigate the potential impact of radiation exposure. To develop an integrated scoring system for evaluating the immunological and inflammatory status of individuals, large numbers of immune markers have also been measured. Investigations have also been begun examining both gene-specific and global methylation patterns as a function of age and radiation exposure. It is not entirely clear if these studies are intended to lead into global epigenetic studies, however, nor how such studies would be focused.

The Laboratory of Cell Biology is mainly focusing on the relationship between radiation exposure and carcinogenesis by analyzing epigenetic changes and genomic alterations in several types of cancers. The laboratory has found that the incidence of *ALK* rearrangements in thyroid cancers is high in exposed cases not showing *BRAF* point mutation or *RET* rearrangements, and most *ALK* rearrangements characterized to date result in ALK-EML4 fusion proteins. These observations clearly indicate that chromosomal rearrangements play a crucial role in radiation-induced thyroid carcinogenesis, and the biological effects of the specific ALK-EML4 fusion protein should be further investigated. Another novel finding is the involvement of microsatellite instability in colorectal cancers among A-bomb survivors, which was revealed by a pilot study.

Evaluation and Critique

In 2010, members of the department were authors on eight publications in English language journals, a decrease from thirteen publications in the previous year. Of these articles, five were associated with an RERF research protocol (RP). Four of the eight publications had RME staff as first or last author, and all these were associated with an RP. Four additional articles, two with RME first authors and two co-authorships, and all with associated RPs, were submitted for review in 2010. The decrease in publications in the last year is a trend that should be reversed, and the importance of primary authorship on papers in international journals should be emphasized. Members of this department have also given a large number of presentations at domestic and international meetings in the past year. This activity is important for both the exchange of ideas, and for maintaining a high profile for RERF and its mission.

Recommendations

1. Emphasis should be placed on maintaining and improving the publication record of the department, especially with respect to primary authorships in English language journals.
2. Pilot studies should incorporate clear milestones for making decisions on when the results of a pilot study indicate a high probability of success for larger scale studies versus when a study should not be pursued further. If large-scale studies will be undertaken no matter the outcome of pilot studies, the role of the pilot in refining the experimental approach should be clarified prior to the start of research. Furthermore, statistical power calculations should be incorporated into the design of any new studies.
3. Investigation of the biological significance of *ALK* rearrangements found in papillary thyroid carcinoma (PTC) is needed to clearly support their role in carcinogenesis. Establishment of mammalian cells or transgenic mice harboring the rearranged *ALK* gene should be a high priority.
4. The pilot influenza vaccination study should incorporate a careful evaluation of previous infections and the previous vaccination history of each subject.
5. More comprehensive approaches, such as multiplex SNP typing for multiple candidate genes, genome-wide SNP typing, genome-wide array-based methylation assays, and collaborations with other universities or institutes, should be considered and encouraged where appropriate. Any such multiple-comparison study must be approached with appropriate statistical power, however, and the SC understands that while attractive, such approaches are not always feasible.
6. Sample collection and storage activities should be consolidated in a specialized support section, rather than being the responsibility of individual research sections.

Department of Genetics

Overview

Following the recently adopted format, the Department of Genetics was not scheduled to receive extensive emphasis by the SC. Briefly, the Department of Genetics is comprised of two laboratories, Cytogenetics and Biochemical Genetics. Altogether the department lists eight members, including five research scientists and three fixed-term research scientists. Dr. Y. Kodama has become the Department Chief, with Dr. Noda as Chief of the Laboratory Cytogenetics and Dr. Kodaira as Chief of the Laboratory of Biochemical Genetics. Although formally retired in 2006, Dr. Nakamura still remains involved in providing overall consultation in the scientific design of the studies of this department.

In addition to the formal overview given on the first day, several brief presentations were given to members of the SC in the informal session to apprise us of recent progress on current projects.

Dr. Satoh gave a wide-ranging talk that involved the future sequencing of offspring involving maternally and paternally exposed F_1 cohorts. The idea was to isolate flow-sorted chromosome 19 for eventual sequencing, at first by long range haplotype determination.

One of the most interesting talks involved data shown by Dr. Hirai who showed data that strongly indicated no correlation between electron spin resonance (ESR) tooth enamel signals and distance from the Hiroshima hypocenter at distances beyond the prompt radiation dose zone. This serves to dispel the notion that fallout contributed substantially to absorbed dose.

Dr. Hamasaki addressed the previously discovered phenomenon that, while maternal exposures lead to dose-dependent increases in chromosome translocation frequencies in rats for lymphocytes, no such dose dependence was observed in the fetus. Apparently this lack of fetal response is tissue-dependent, and specific to T cells, at least in rodents.

Dr. Noda reported on continuing progress made toward a knock-in mouse model which used a clever GFP-HPRT reporter mutation system that would appear to have potential for both somatic and germ-line radiation-induced *in vivo* mutagenesis studies. He also investigated the possibility of using repair-related foci for determining persistent radiation damage.

Two separate, interesting talks, using high-density comparative genomic hybridization (CGH) arrays were given, one by Dr. Takahashi using an Illumina Bead-Chip array system, and another by Dr. Asakawa, using a 2 M feature array from NimbleGen. The second talk was especially impressive as regards overcoming various sources of artifact from such systems for copy number variation (CNV) analysis.

Evaluation and Critique

For 2010–2011, the department lists several meeting abstracts and some ten publications either published or in press, several of which were published in the open peer-reviewed literature, and all related to specific RP objectives. Productivity is judged as being good. A more extensive evaluation will be provided during next year's meeting of council, but in general the department seems pointed in the right direction.

Specific Recommendations

1. This department continues to be a strength of RERF, and by implementing new technologies and novel approaches, illustrates how basic science research can flourish in a mission-oriented environment. This department appears still to be somewhat in a state of flux since the retirement of Dr. Nakamura. While his positive influence is clearly still felt, leadership positions need to be solidified in order to ensure long-term stability of the group.
2. Even in its transition years, the Genetics Department should act as THE genetic counselor to the entire enterprise, bringing awareness and access to all the astonishing advances in genetics and genomics and considering their applications to the mission of RERF. For example, it might address the development of any concept for an RP even as its embryonic form, considering the merit of focused genetic markers studies *versus* the notion of genome-wide studies at little extra cost; considering total genomic sequencing, rather than a smaller target; considering total epigenetic assays *versus* a small panel. The 5-year vision of the U.S. National Human Genome Research Institute (*Nature* 2011 [February 10]; 470:204–13) should be studied in view of RERF's mission, resources, and opportunities. To further that leadership role, presence and abstracts at international human genetics meetings is essential (e.g., this year is the International Congress of Human Genetics).
3. In the formal presentation, it was stated that improving dosimetry was a major priority, but two questions arise—how do they assess if their changes have actually made the dose estimates more accurate, and will any such changes have any impact on the conclusions of other studies or on risk assessment? If not, it is unclear how and why this is a departmental priority and should perhaps be reassessed.
4. Usage of next-generation DNA sequencing: As the first test of the methodology, the sequencing of chromosome 19 separated by a cell sorter as well as whole exome sequencing is planned. A long-term strategy for massive sequencing for a large number of family samples in the future should also be considered.
5. CGH study with high-density microarrays (Asakawa and Kodaira): Model CNV analysis using high-density microarray in mouse strains has established this technology firmly in the department. The technology is now ready for extending to the study of the effect of atomic-bomb radiation.
6. Identification of a significant difference in the frequency of MDM2 SCP309(G/T) in Hiroshima indicates the possible involvement of altered DNA damage response mediated by the p53-dependent pathway in early-onset breast cancer among A-bomb survivors. However, the study using samples from Nagasaki does not support this finding. Pathological sub-typing of breast cancers should be conducted to address this issue.

Public Relations

Making RERF visible and accessible, Mr. Teramoto's goal for Public Relations, has achieved an impressive leap forward this year. We appreciate his responsiveness to the suggestions of the SCs over several years. Such a noble enterprise as RERF's deserves no less than the splendid advances he has led, doubtless with the endorsement of senior leadership and the working scientists, of note this year, Drs. K. Kodama, Nakamura, and Douple, the latter featured in a (U.S.) National Geographic one-hour television special on RERF in the anniversary month of August 2010. Other huge steps have been an RERF exhibit at the Peace Memorial Museum, the tour of three research centers in the U.S., the novel RERF Public Seminar, and the on-going open houses and school tours which should be sustained. Senior scientists could help further by preparing summary scientific articles every four years in prestigious international journals in science and medicine, such as *Lancet*, *Science*, *Nature*, and the *New England Journal of Medicine*. We especially appreciate the meticulous tracking of the number of website hits and attendance at events. The SC does recommend that an emphasis be given to producing well-written press releases at the time of major RERF publications.

Future directions to explore include working with the public and media relations offices of MHLW, DOE, and NAS to amplify the RERF message; engaging major print outlets, such as *The New York Times*, *The Washington Post* (to sustain U.S. interest and awareness), and other major newspapers around the world; and even developing (under grant funding and with educational experts) curriculum in radiation epidemiology and protection for physician residents in radiology and radiation oncology, graduate students in biomedicine programs, and even medical students. The museum exhibit might also be offered for touring (at the expense of hosting museums).

Mini-workshop: Roles of Smoking on Radiation Risk of Lung Cancer

February 4, 2011, Hiroshima Laboratory

Nori Nakamura, Chief Scientist

A mini-workshop titled "Roles of smoking on radiation-risk of lung cancer" was held in the RERF Auditorium on the afternoon of February 4, 2011. The workshop was organized in response to the proposals by Dr. Michiaki Kai (Oita University of Nursing and Health Sciences) and Dr. Ohtsura Niwa (formerly with National Institute of Radiological Sciences). It was motivated by a controversy over possible interpretation of higher risk of lung cancer among smokers with the same radon concentration, which had resulted from reassessment of radon effects by the International Commission on Radiological Protection (ICRP) in 2009, and by a finding last year (paper by Furukawa *et al.*) suggesting higher risk of lung cancer attributable to radiation among A-bomb survivors who smoke (excluding heavy smokers) than among the survivors who do not. We also hoped to understand interactions between radiation and smoking at the cellular (stem cell) level.

Dr. Okubo's welcome address was followed by the presentations "Trends of lung cancer in Japan" by Dr. Kotaro Ozasa (Chief, Department of Epidemiology), "Joint effects of radiation and smoking on lung cancer among atomic-bomb survivors" by Dr. Kyoji Furukawa (Department of Statistics), and "Pilot study: Genetic and epigenetic alterations in lung cancer among atomic bomb survivors" by Dr. Masataka Taga (Department of Radiobiology/Molecular Epidemiology). After a short break, the session resumed and Dr. Yuichi Ishikawa (Cancer Institute of Japanese Foundation for Cancer Research) spoke on "Present status of lung cancer in Japan: Characteristics of Japanese lung cancer and genotype-phenotype correlations," Dr. Michiaki Kai on "Multistage carcinogenesis and lung cancer risk," Dr. Suminori Akiba (Kagoshima University) on "Indoor radon and lung cancer risk," and Dr. Charles Land (formerly with U.S. National Cancer Institute) on "Comments on radiation cancer risk in smokers and nonsmokers compared with previous risk." The presentations were followed by a general discussion that concluded the event.

The findings already elucidated are as follows:

1) Non-smokers develop lung cancer, although at a lower rate. The majority of such lung cancer is said to be adenocarcinoma occurring in the lung periphery.
2) Earlier, it was mentioned that risks for squamous cell carcinoma (SCC) and small cell carcinoma (SmCC) developing in the central region of the lungs increase among smokers. However, adenocarcinoma is recently on the increase (which is hypothesized as attributable to improved filters).
3) Not all smoke particles from cigarettes infiltrate deeply into the lungs.
4) The risk increase from radiation exposure in SmCC is observed both in A-bomb survivors and in radon miners (Land's 1993 paper).
5) Smoking and radiation enhance each other's effects (synergistic effects).
6) Radon is absorbed into the lungs not only in the form of a gas, but also in the form of solids attached to atmospheric dust particles. The range of its α particles is short. Therefore, it would be difficult to assess which parts of the lung are affected by radon. (If stem cells are located several layers of cells deep below the surface of the respiratory tract, they might not be exposed to radiation.)

Taking the above points into consideration, I gave some thought to possible interactions between smoking and radiation.

A-bomb radiation effects: A-bomb radiation affected the entire lung uniformly. The lung cancer subtype that increases with radiation exposure is said to be SmCC. Therefore, it seems likely that SmCC is as sensitive to radiation as it is to smoking, and conversely that SCC and adenocarcinoma are less sensitive to radiation.

Effects of radon α particles: The lung cancer subtype that is increased by radon exposure is said to be SmCC, which means that α particles from radon and its daughter nuclides reach stem cells, the originating point of SmCC. The lower risks for SCC and adenocarcinoma can be explained by lower radiosensitivity even if radon α particles reach stem cells.

Interactions between radiation and smoking: Whether exposure to A-bomb radiation or to radon, effects are greater when radiation and smoking are combined than when each exerts effects independently ($1 + 1 > 2$; i.e., joint effects are greater than their simple additive effects). However, risk from smoking is far greater than that from radiation, meaning that radiation is not smoking's equal. Looking at this from the viewpoint of radiation effects, although SmCC is not the most prevalent subtype of lung cancer attributable to smoking, it is still affected by smoking as its effects are that much stronger. Because radiation and chemical compounds in tobacco smoke exert different kinds of damage on DNA and have different cell stimulatory effects, radiation and tobacco smoke probably complement each other's weaknesses during the multistage process of carcinogenesis.

At the mini-workshop, I learned that percentages of various lung cancer subtypes differ between the Japanese and Caucasians and that smoking effects are smaller among Japanese than among Westerners. I felt as if I was learning the history of smoking in the 20th century in various countries. I had a great time, seeing Dr. Land after a long time, and engaging in lively discussions. Above all, I became interested in knowing whether or not the latest Life Span Study data will support the conclusion made by Dr. Land in his above-mentioned paper published in 1993, which is now almost 20 years ago (i.e., the lung cancer subtype increased by radiation exposure is SmCC).

Lastly, I would like to take this opportunity to express my appreciation to all those who helped me organize this workshop.

— Program —

Greetings
Toshiteru Okubo

Chairperson: Michiaki Kai
"Trends of lung cancer in Japan"
Kotaro Ozasa
"Joint effects of radiation and smoking on lung cancer among atomic-bomb survivors"
Kyoji Furukawa
"Pilot study: Genetic and epigenetic alterations in lung cancer among atomic-bomb survivors"
Masataka Taga

Chairperson: Ohtsura Niwa
"Present status of lung cancer in Japan: Characteristics of Japanese lung cancer and genotype-phenotype correlations"
Yuichi Ishikawa
"Multistage carcinogenesis and lung cancer risk"
Michiaki Kai
"Indoor radon and lung cancer risk"
Suminori Akiba
"Comments on radiation cancer risk in smokers and nonsmokers compared with previous risk"
Charles E. Land

Chairperson: Nori Nakamura
General Discussion

Speakers

Suminori Akiba, Professor, Division of Epidemiology and Preventive Medicine, Department of Human and Environmental Sciences, Health Research Course, Graduate School of Medical and Dental Sciences, Kagoshima University
Charles E. Land, Former Senior Investigator, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute
Yuichi Ishikawa, Chief, Department of Pathology, Cancer Institute, Japanese Foundation for Cancer Research
Michiaki Kai, Professor, Laboratory of Environmental Health Science, Department of Health Sciences, Oita University of Nursing and Health Sciences
Ohtsura Niwa, Emeritus Professor, Kyoto University

【RERF】
Toshiteru Okubo, Chairman
Nori Nakamura, Chief Scientist
Kotaro Ozasa, Chief, Department of Epidemiology
Kyoji Furukawa, Associate Senior Scientist, Department of Statistics
Masataka Taga, Research Scientist, Laboratory of Cell Biology, Department of Radiobiology/Molecular Epidemiology

International Workshop on Potential Improvements to Organ Dose Calculation for the Atomic Bomb Survivors Using DS02

February 23, March 7–8, 2011

Harry M. Cullings, Chief, Department of Statistics

One of the notable strengths of RERF's studies is their dosimetry—estimation of the radiation doses received by survivors, without which study results cannot be stated in terms of risk or effect per unit dose for use in radiation protection. A series of dosimetry systems for calculating survivors' doses based on their detailed location and shielding information have been developed over the last sixty years by international scientific working groups, culminating in Dosimetry System DS02. One of the hallmarks of DS02, and its predecessor DS86, is that they calculate detailed dose estimates for particular organs and tissues of the human body, which can differ substantially with an organ's effective depth in the body, especially for the dose from neutrons. DS02, however, uses the same organs and organ dose computational methods as DS86, which reflect the state of knowledge and computing power that were available in the early 1980s. DS86 and DS02 calculate dose only to certain organs, which were chosen in light of the understanding of radiation biology in that time period, and were limited to fifteen organs for practical reasons. For other organs and tissues it has therefore been necessary to choose surrogates from among the 15 organs to provide rough estimates of dose. Moreover, it has been recognized in recent years that there has been an explosion of detailed three-dimensional anatomical data on the human body from medical imaging technologies, and that computing power is much greater than it was some thirty years ago.

The above considerations suggested that it would be useful to explore ways to take advantage of the great effort expended on DS02, by using the detailed radiation fields that it calculates at individual survivors' locations, with new organ dose modules to calculate dose to a wider variety of organs with improved accuracy. Many of the aspects of such improved calculations could utilize resources that are already available in the radiation protection community, including Monte Carlo computational packages and methods for developing detailed models of the human body. On February 23 and March 7–8, 2011, the "International Workshop on Potential Improvements to Organ Dose Calculation for the Atomic Bomb Survivors Using DS02" was held at the Hiroshima Laboratory. In addition to two RERF speakers, the workshop included six speakers from four Japanese research institutes and universities (National Institute of Radiological Sciences, Japan Atomic Energy Agency, Kyoto University Reactor Research Institute, and Hiroshima University) and five speakers from international agencies and universities (Helmholtz Centre Munich, Health Canada, Science Applications International Corporation, Oak Ridge National Laboratories, and Vanderbilt University).

The purpose of the workshop was to discuss some key needs for improved organ dosimetry and the practical means by which the organ dose calculations of the DS02 dosimetry system could be improved. There are a number of organs for which specific dose estimates are desirable but not currently available. Special meetings were held in connection with the workshop to discuss the technical issues involved in biodosimetry measurement of radiation dose using electron spin resonance (ESR) on donated teeth and the need to obtain accurate DS02 calculations of dose to tooth enamel for comparison to measurements. As DS86 and DS02 include only three models of the human body for different age categories, there is a need for better modeling of the body at various ages during childhood and adolescence. Another need is for gestational age-specific doses for survivors who were exposed *in utero*. The workshop ended with focused discussions of what methodologies, software, and models of the human body should be used and adapted to the Japanese population of the 1940s, and the participants agreed to collaborate on developing a new series of models for improved calculations. Short papers based on the proceedings of the workshop will be published in a special issue of the journal *Radiation Protection Dosimetry*.

Tooth Dosimetry Pre-meeting
February 23, 2011

— Program —

Greetings and introduction
Harry M. Cullings

"Tooth ESR measurements and measurements of ^{41}Ca activation by thermal neutrons at RERF"
Nori Nakamura

"DS02 computational methods and available fluences of neutrons and gamma rays at survivors' locations"
Harry M. Cullings

"Computational methods using Japanese phantoms for tooth enamel dosimetry"
Fumiaki Takahashi

"Tooth ESR measurement at HMGU and computational methods for photon dose to tooth enamel"
Albrecht Wieser

General discussion

Summary and concluding remarks
Nori Nakamura and Harry M. Cullings

List of Participants

Albrecht Wieser, Physicist, Helmholtz Centre Munich, Institute for Development Genetics, Germany (HMGU)
Fumiaki Takahashi, Researcher, Research Group for Radiation Protection, Nuclear Science and Engineering Directorate, Japan Atomic Energy Agency (JAEA)
Shin Toyoda, Professor, Department of Applied Physics, Graduate School of Science, Okayama University of Science

【RERF】
Nori Nakamura, Chief Scientist
Harry M. Cullings, Chief, Department of Statistics

Main Workshop
March 7–8, 2011

— Program —

March 7, 2011
Greetings and introduction
Toshiteru Okubo
Opening remarks
Roy E. Shore

"Desired improvements for DS02's organ dose calculations"
Harry M. Cullings
"The available shielded fluences of DS02 and how they are calculated"
Stephen D. Egbert
"How DS86 (and DS02) calculate organ dose"
George D. Kerr
"Fetal dose calculation"
Jing Chen
"The Vanderbilt University series of phantoms and related computational considerations"
Michael G. Stabin
"The contemporary JAEA Japanese phantoms"
Kaoru Sato
"Summary of Tooth Dosimetry Pre-meeting"
Harry M. Cullings

March 8, 2011
"Development of the first Japanese reference man model"
Hisao Kawamura
"Japanese anthropometry for DS86 (1945 Japanese population)"
Takashi Maruyama
"External gamma dose from soil activation and radiation survey data just after the bombings"
Tetsuji Imanaka
"Estimation of beta-ray skin dose from fission fallout"
Satoru Endo

Discussion I
Chair: Masaharu Hoshi
Discussion II
Chair: Harry M. Cullings
Summary
Harry M. Cullings
Concluding remarks
Harry M. Cullings

List of Participants

George D. Kerr, Researcher, Kerr Consulting Corporation
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Jing Chen, Researcher, Head of Radiological Impact Section, Radiation Protection Bureau, Health Canada
Takashi Maruyama, Former Researcher, National Institute of Radiological Sciences
Masaharu Hoshi, Professor, Department of Radiation Biophysics, Research Institute for Radiation Biology and Medicine, Hiroshima University
Tetsuji Imanaka, Associate Professor, Research Reactor Institute, Kyoto University
Kaoru Sato, Researcher, Research Group for Radiation Protection, Division of Environment and Radiation Sciences, Nuclear Science and Engineering Directorate, Japan Atomic Energy Agency (JAEA)
Satoru Endo, Associate Professor, Institute for Radiation Biology and Medicine, Hiroshima University
Hisao Kawamura, Former Researcher, National Institute of Radiological Sciences
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Munechika Misumi, Research Scientist, Department of Statistics
Ravindra Khattree, Senior Scientist, Department of Statistics
Robert D. Abbott, Senior Scientist, Department of Statistics