

Report of the 41st Scientific Advisory Committee Meeting

March 3–5, 2014, Hiroshima Laboratory

Scientific Advisors

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Special Scientific Advisors

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Introduction

The Scientific Advisory Committee (SAC) met from March 3–5, 2014, in Hiroshima, Japan. Its task, as in previous years, was to review the Radiation Effects Research Foundation (RERF) scientific programs. This year, the SAC conducted an in-depth review of the Departments of Epidemiology, Statistics, and Information Technology. To assist with the detailed review of these three departments, three additional experts joined the Committee this year: Drs. Scott Davis, Toshimitsu Hamasaki, and Divesh Srivastava. Their addition was extremely valuable to the SAC and it was a great pleasure for the Committee to work with these outstanding scholars.

Dr. Michiaki Kai, Member of the Board of Trustees, Professor, Environmental Health Science, Department of Health Sciences, Oita University of Nursing and Health Sciences; Dr. Tomotaka Sobue, Professor, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University; and Dr. Anatoly Dritschilo, Professor and Chairman, Department of Radiation Medicine, Georgetown University School of Medicine, have joined the SAC with the retirement from the Board of Dr. John Mulvihill, the University of Oklahoma; Dr. Kiyoshi Miyagawa, the University of Tokyo; and Dr. Kazuo Tajima, former Director, Aichi Cancer Research Institute in Nagoya.

Dr. Toshiro Okubo, Chairman of the RERF, opened the 41st meeting of the SAC on the morning of March 3, and warmly welcomed all in attendance. He emphasized

how important the SAC's work is to the staff of the RERF. He introduced Dr. Robert Ullrich, who was appointed as Associate Chief of Research at RERF and began his tenure November 1, 2013. He introduced the new member of the SAC, the old members, the special advisors this year, the government officials from the Japanese Ministry of Health, Labour and Welfare and the U.S. Department of Energy, as well as the representatives from the National Academies of Science and the Board of Councilors. He then reported on the RERF administrative activities. A serious issue is the need to restructure RERF in order to maintain high-quality science while decreasing the number of scientists. The rate of attrition mandated by the Japanese government is approximately five per year. At this time, there are less than half the numbers at the time of its inauguration.

Following Dr. Okubo's welcoming remarks, Dr. Roy Shore, Vice Chairman and Chief of Research at RERF, provided an overview of the status of research at RERF. He began with a detailed response to the recommendations made by the report of last year's SAC, and followed with a description of RERF's major accomplishments during 2013. Among the research achievements in 2013 were the convocation of an International Low Dose Workshop at RERF in December 2013, a paper in *Annual Review of Genetics* on the "Radiation Effects on Human Heredity," authored by Dr. Nakamura, and multiple publications evaluating radiation and cancer as well as noncancer diseases and conditions. Dr. Shore further described the crucial ongoing efforts to consolidate, integrate, and support databases, sample

collection, and storage. These efforts were highlighted in the presentation by the Department of Information Technology. Finally, there has been increased transparency of the RERF Research Protocol (RP) review process, such that the reviewers and the RP committee now are able to see all the reviews, responses, and revised RPs.

After Dr. Shore's comments, detailed presentations by the Departments of Epidemiology, Statistics, and Information Technology were given by the department chiefs and selected staff members. Next, brief overviews of activities of the Departments of Clinical Studies, Genetics, and Radiobiology/Molecular Epidemiology were given to the SAC. These presentations gave responses to last year's SAC recommendations and reported on their major accomplishments during 2013, as well as their future plans.

Finally, Mr. Takanobu Teramoto gave the SAC an update of the progress and accomplishments of the Public Relations and Publications Office. New public relations efforts have been developed and are extending the reach of RERF.

Beginning the meeting on March 4, Dr. Okubo gave an update on the new dosimetry estimation, and Dr. Kodama discussed details of the Biosample Center. Regarding future plans, Dr. Okubo outlined some new developments: Improvements in the operating structure, human resource management, and budget. A major point made by Dr. Okubo is that scientists tend to focus on their own work and that there is a critical need to broaden perspectives, particularly as RERF plans for the future.

The formal program concluded with a special presentation on RERF's Future Plans. One of the major functions of the planned re-structuring is to aid the prioritization of projects, which has been continually stressed by the SAC. There is too much diversity in the Department of Clinical Studies portfolio and this issue actually extends to the RERF as a whole. A transition from a departmental structure for prioritization to a working group structure is one solution planned to streamline work at RERF.

Informal meetings were then held between the SAC members and the RERF departments being reviewed. Throughout the meeting the SAC reviewed and discussed the information provided concerning the activities of the RERF, and met with a group of junior investigators over lunch on March 4.

Overview

The SAC believes that the RERF is the world leader in research into the effects of radiation on human populations. The RERF has deep experience, large populations, and outstanding datasets in order to conduct the important investigations that cannot be carried out anywhere else in the world. The long-term support of the Japanese Ministry of Health, Labour and Welfare and the U.S. Department of Energy, as well as the scientific guidance of the National Academy of Sciences, continues to be critical to the mission of the RERF. Such support, coupled with the cooperation of the survivors and their families, make it possible for the substantive research conducted by RERF to have great impact on the world.

Under the sustained senior leadership provided by Drs. Okubo and Shore, and the addition of Dr. Ullrich to the

team, the SAC looks forward to a bright future for science and the development of a Center of Excellence at RERF.

General Recommendations

The Scientific Advisors have three general recommendations, as well as seven additional specific recommendations:

1. Research prioritization: The justification, prioritization, and overall quality of some of the current research programs continue to be of concern. Some progress has been made in streamlining the review of RPs and retiring inactive ones, but this process needs to continue. Within specific program evaluations, more particulars are given. Again, as suggested by the SAC in previous years, RPs should assess clearly articulated testable hypotheses that contribute to the overall goals of RERF. Transparent and interactive discussions on RP evaluation and selection should be used as an opportunity for education and training for young investigators.

The SAC finds the Future Plans to develop working groups an excellent way to help prioritize the multiple demands and needs for the development of integrated science at RERF. These efforts are strongly encouraged.

2. Adoption of new technologies: Developing plans for the use of technology (whole genome sequencing, metabolomics, etc.) is encouraged, but they need careful prioritization in terms of data and biosamples available due to the potential for depleting samples necessary for critical RERF mission-specific studies. Additionally, bioinformatics resources need to be developed simultaneously with high-throughput technologies.
3. Research resource center: The creation of the Research Resource Center is an extremely important centerpiece for RERF. Both the relatively newly created Biosample Center and the data management capacity of the Department of Information Technology are critical for appropriate development of needed studies and for movement on the trajectory to become an international Center of Excellence for radiation research. As the collection and preservation of biosamples is one of the most important and valued scientific assets of RERF, the focus on developing new space for the storage of newly collected samples is clearly of high priority. The SAC was pleased to see that the development of a database for access to sample identification, location, and other information is underway. It is critical that these efforts continue and be supported by all departments. This database must be expanded to include all samples with associated information from every department, with crediting of the current departmental contributions. One example of an important need that can be filled through the Research Resource Center is that of missing data. While some missing data can be imputed and excellent work is ongoing to develop good imputation algorithms, for some types of data, such as missing smoking data, biosamples can be used. So, to fill in missing smoking data for individuals, serum cotinine levels can be measured. Such work requires well-integrated systems.

Specific Recommendations

1. The complete data on every subject ever involved with ABCC-RERF research should be retrievable with ease. This will involve continued effort on the part of the Department of Information Technology in collaboration with each of the other departments.
2. More high-quality publications are essential for the continued success of RERF. The plans outlined in the Future Plans will assist in this effort.
3. Efforts to obtain additional competitive external funds have increased, and the SAC encourages this activity.
4. The “black rain” data analyses are complete and will be submitted for publication. The publication of these data represents an opportunity for public education on the strengths and weaknesses of the ability of science to make conclusions about environmental links to health effects.
5. Multiple genome-wide studies, next generation sequencing studies, and other high-dimensional data analyses are planned. However, it does not appear that these have been prioritized, and due to costs and sample limitations, it is important that these be thoughtfully planned and coordinated between departments.
6. There are many RPs ongoing and new ones being developed, and yet there is concern that there are not enough investigators and insufficient funding to complete these in a timely manner. Therefore, the Future Plans are all the more critical to implement, particularly the development of working groups to integrate hypotheses and studies between and among departments.
7. The SAC commends the ongoing efforts of seminars and interactions within RERF. It is suggested that a formal mentoring system be developed. Ideally, a young scientist would have mentors in other departments as well as his own. These will help young new investigators at RERF in their professional development.

Individual Department Reviews

Department of Epidemiology

Overview

The Department of Epidemiology continues to be central to the RERF and its efforts to characterize and quantify the role that radiation exposure from the atomic bombings of Hiroshima and Nagasaki plays in the development of subsequent adverse health effects. Careful follow up of three major cohorts is ongoing: The Life Span Study (LSS) cohort consists of 120,000 individuals, 36% of whom are still alive; the *in utero* cohort consists of 3,600 individuals, 88% of whom are still alive; and the F₁ cohort of children of atomic bomb survivors consists of approximately 77,000 individuals, of whom approximately 90% are still alive. Follow up of over 200,000 individuals is ongoing. Follow up is based on questionnaire, vital statistics based on deaths and cause of death throughout Japan, and cancer incidence in Hiroshima and Nagasaki prefectures. In addition, the Epidemiology Department has developed close relationships with community pathology laboratories

to collect tissue for RERF studies.

The Epidemiology Department plays a crucial role in developing accurate and consistent data to assist with the derivation of dose-response information from radiation exposure, which is critical for both cancer and noncancer outcomes, such as cardiovascular disease. Follow-up data, such as that from the LSS mail survey, are essential to provide information regarding potential confounders and effect modifiers.

The Epidemiology Department continues to produce high-quality publications, although fewer in number than last year (17 published in international journals: 17 published, one in press and two submitted). The proportion published in international journals is higher than in previous years. These papers are generally published in high-quality journals, such as the *American Journal of Epidemiology* and the *International Journal of Cancer*. Another three publications have appeared in Japanese language journals. There have also been 22 presentations at multiple meetings during the past year by members of this department, including presentations in Japan, Brussels, Belgium, the United States, and Ireland.

General Comments

In the last several years, the composition of the Epidemiology Department professional staff has changed considerably. The leadership (Dr. Ozasa as Chief; Dr. Grant as Assistant Chief) is quite young and energetic. Several new staff are quite junior as well. For the first time in a long time, the department is well positioned for a strong transition to the next generation.

1. There are a number of continuing activities that are mostly routine, yet they form the very basis of much of the research conducted at RERF. These large projects (e.g., maintenance of the active cohorts; maintenance and incorporation of the data from the tumor and tissue registries in Hiroshima and Nagasaki; conduct of primary analyses of mortality and incidence from the main cohorts and publication of the findings in as much detail as possible) are defined mostly in Platform Protocols. These should continue, as the cohort is now entering a phase that will be very informative for those exposed at young ages. More attention is also being given to the investigation of how lifestyle affects radiation cancer risk. As studies of individual cancer sites are undertaken, they should take into consideration as much as possible the influence of smoking, alcohol consumption, body mass index (BMI), and other lifestyle factors. Additional detailed analyses are typically undertaken separately from these more routine analyses, often by other investigators working under a separate RP.
2. In the plans for the coming year, it appears that these routine activities are assumed with little or no further discussion. New research activities seem to be focused on issues that are very subtle, or exceedingly difficult to define and carry out in a rigorous way. Examples include all aspects of considering medical doses; identification of “new” risk factors for a number of cancer sites; identifying and controlling for “new” confounders; definition and incorporation of information

regarding “black rain” exposure. In addition, further analysis might be considered for childhood cancer, such as brain tumors and childhood leukemia using the updated dosimetry.

3. A clear statement is needed for the rationale underlying each activity and what the anticipated results might be. The department could be more proactive in describing the uniqueness of the cohorts and the value of the information *still to be obtained* from additional follow up. (i.e., Why should we continue to do this, and can we justify the costs by the value of the information being collected? Is RERF uniquely positioned to address the issues being worked on? Is it the ONLY source of such information?)

It would also be helpful to include in the discussions some idea of the magnitude of any effects being looked for. Not only should the importance be clear, but also whether the numbers are sufficiently large enough to have a reasonable chance of detecting the effects.

4. We are concerned that current projects, and perhaps more importantly future plans for new studies which utilize stored biological samples, are not making the most of the master datasets that are available for the various cohorts. Although this is not an issue that is easy to address, we strongly encourage investigators in the Epidemiology Department to work more closely with colleagues within RERF to design and implement new studies and/or additions to ongoing studies that make maximum use of the stored samples in an efficient manner. Combining expertise and samples could be of substantial value. It will be important, however, that the purpose of such collaborations be explicitly clear. For example, a project involving genomic analysis and follow-up (endpoint) data might be done to investigate genetic susceptibility using germ line samples, or to identify radiation-specific genetic abnormalities using cancer samples. This type of study might be conducted as an internal collaborative working group. This may require in many cases that new collaborations outside RERF be made as well.
5. The question as to whether there are enough staff at all levels to accomplish what is planned and recommended needs to be evaluated. Is there adequate coverage of the main skillsets needed? There is likely need for new recruitment to fill any gaps and to supply adequate manpower.
6. It has long been recognized that radiation exposures from medical procedures, both diagnostic and therapeutic, may significantly impact the radiation dose estimate for an individual, thus potentially making it difficult to interpret the dose-response results. For example, a rapid increase in the number of CT procedures that result in relatively high doses might affect the cancer risk estimates among the survivors. The Epidemiology Department staff are attempting to address this issue using mail survey data from 2008. Exactly how an estimate of the individual dose following medical exposure will be determined and how the incidence data will be analyzed taking the medical dose into account remain to be resolved. Although exceedingly difficult, we encourage them to continue

this work.

7. It is expected that there will be increased interest on the part of the public and the media in the findings reported from RERF, particularly for issues such as change in doses for individuals, exposure to fallout rain, and cancer risk in the children of survivors. RERF should thoroughly prepare for the release of such information, and have a solid plan for communication to the media and the public.

Specific Recommendations

1. Radiation and cancer in the LSS: Significant work on a comprehensive analysis to update through 2007 the radiation risk for cancer incidence has been completed in collaboration with the U.S. National Cancer Institute. New emphases of the analyses will be on radiation risks from early-life exposures and at low doses, and relation to lifestyle factors.

This activity is central to the mission of RERF. It would be helpful to provide a status update of these activities and a timeline for completion. It would also be helpful to define what is meant by “low dose”—how is it defined here? Will you evaluate whether there is an age-at-exposure effect? It is also probably important to reiterate how vital the registries are to RERF follow up, and how they are uniquely suited for the studies conducted here. In this context, it is probably also important to consider whether they are being maximally utilized, e.g., are they being used to collect biological samples?

2. Cancer incidence denominator: Since the cohort members’ residence status is unknown, person-year calculations are adjusted to reflect out-migration, as cancer cases occurring among those residing outside the local prefecture catchment areas will not be detected. An estimate of the confidence in the present estimates would be valuable. There may be things that could be done to improve the methodology, although there could be a point of diminishing return with relationship to any improvements.
3. Site-specific cancer studies with histological reviews in the LSS cohort: Several studies are currently active in collaboration with the U.S. National Cancer Institute. It is of interest as to how cancer sites for study are prioritized.
4. Low-dose symposium: An international symposium on “The evaluation of the effects of low-dose radiation exposure in the atomic bomb survivors” was held December 5–6, 2013, to identify issues and approaches for investigating low-dose radiation risks in the LSS cohort. One difficult issue in looking for effects at low doses is whether other important risk factors are adequately controlled for. Influential risk factors might include smoking, chronic infection (hepatitis B/C virus, *helicobacter pylori*), and should be adjusted for in the analysis.
5. Fallout rain exposure: The Epidemiology Department staff have made a gallant effort to see if exposure to fallout rain may constitute an important factor in the radiation dose-response results. Unfortunately, approximately half or more of the subjects who might

be available to include in an analysis have missing data relevant to this question. Thus, interpretation of the results is exceedingly difficult. There is little evidence of an association with fallout rain exposure, the numbers are small, there is a major missing data problem, and the effect, if any, is quite small. We recommend that RERF consider arranging for professionals in dealing with the media be brought in for some advice before these results are released to the media and the public. We also recommend that the Department of Statistics be consulted when contemplating using a multiple imputation technique when missing data are substantial.

6. Radiation and noncancer diseases in the LSS: These are important evolving areas. The individual studies might benefit from a more structured analytical plan.
7. In utero cohort: An analysis of cancer and noncancer mortality risks for 1950–2008 has been completed and a paper is in preparation. Solid cancer risk was elevated in relation to radiation dose, with a suggestively higher risk among females. An increased risk in relation to low birth weight with *in utero* exposure to high-dose radiation was observed for total noncancer disease mortality; the interpretation of this association is unclear.

Department of Statistics

Overview

The Department of Statistics provides statistical consultation and collaboration with investigators in other departments at RERF and conducts original independent research on statistical methods to provide insight and enhancement of design and analysis of studies conducted at RERF. The department is ably led by Dr. Cullings and consists of seven statisticians, and hopefully an eighth statistician will be recruited. The department also has the support of two research assistants. There is one full-scale research protocol on shielding and dosimetry, as well as seven Type-A (smaller) research protocols one of which has been terminated. Of these eight protocols, an outside investigator is the principal investigator on five. Twenty-one papers were published in English language journals, six of which were first author publications. Finally, of the 21 published papers, two were in the critical area of A-bomb dosimetry, and of the eight protocols, five have not resulted in any publications for the last three years.

The Statistics Department has been responsive to the recommendations from last year's review. Most importantly, they have continued to develop collaborations with other research groups both in internal RERF departments and external institutions in Japan and other countries in order to optimize their productivity.

Finally, it should be said that the "template" used by the Statistics Department in their write-up sent to the SAC should be adopted by all. It is very clear and easy to follow.

Evaluation

Organizationally, the department is running smoothly under the able direction of Dr. Cullings. Importantly, the department has successfully recruited two new statisticians

who are expected to make important contributions to the department, and hopefully an additional statistician will soon be recruited. The department should continue on its current path with emphasis on:

- 1) Continued priority of its primary role as statistical collaborators with RERF researchers especially with those in the Epidemiology Department.
- 2) Continue its research productivity in statistical methodology and also the important area of the development of skills in bioinformatics.
- 3) Continue the support for academic collaborations with researchers at other institutions, as well as making presentations at international scientific meetings.

The SAC was impressed with the progress of the dosimetry research that has reached the point of incorporation into the basic LSS databases. This is highly important for RERF to immediately incorporate this improved dosimetry into its research studies.

The department continues to explore the "big data world," meaning methodologies for the gathering of large-scale scientific data from internal sources and the public domain, the manipulation, integration, and statistical or empirical analysis of these data, including modeling and simulation. However, in addition to advanced statistical analysis knowledge and skill, this will require a suite of technical skills such as the knowledge of databases and search engines, algorithm development, machine learning, visualization tools, and the ability to quickly create research-grade programs and scripts.

Overall, the Statistics Department has been very productive in both their collaborative work and their basic research as it applies to RERF's research agenda. Dr. Cullings has been an effective leader of the department, and the SAC believes that it will continue to be a productive and critical component of RERF.

Recommendations

1. For the upcoming cancer incidence studies, the estimation of the structure of the LSS population adjusted for outmigration needs to be completed and reported as a technical report with precise explanation regarding what data sources were used. Secondly, the uncertainty in these estimates should be incorporated into the overall uncertainty in risk estimates for cancer incidence. Finally, and most importantly, the new dosimetry needs to be incorporated in the upcoming cancer incidence analysis.
2. The department should continue working on measurement errors and averaging errors of the exposures in order to reduce possible bias in the risk estimates and to improve the precision of the estimates. The degree of the impact of these errors in the risk analyses needs to be evaluated in order to understand the relative importance of this effort.
3. The new work on non-parametric smoothing in dose-response estimation especially as it applies to low-dose risk estimation is new, interesting, and is encouraged.
4. The training and development of genomic data analysis skills is applauded and its continuation is strongly encouraged. It is expected that these data analysis skills will be required in the near future.

5. The work on statistical imputation for missing data in analyses should continue and its impact in individual studies should be carefully evaluated, especially for the adjustment of confounding effects due to influential risk factors, such as smoking and chronic infection.
6. The Statistics Department is encouraged to continue its work on machine learning methods such as the support vector machine to evaluate gene-environment interactions and to also establish a relationship with external experts/organizations to accelerate the work.

Department of Information Technology

Overview

The Department of Information Technology (ITD), led by Dr. Katayama, plays an essential support role in RERF's research, based on the activities of its two sections: (i) Systems Technology and (ii) Library and Archives. ITD supports the needs of all other departments in RERF, and also participates in collaborative projects with outside research organizations in Japan and the rest of the world.

The Systems Technology Section supports two tasks: (i) maintenance of hardware and networking environments, with three staff members, and (ii) maintenance of databases and development of relevant application software, with eight staff members. The first task includes the prevention of illegal attacks on the RERF network, inspection of email for viruses and SPAM, and protection against leakage of personal information. The second task includes the construction of databases for analysis, creation of a data dictionary and a document-management database, and ensuring of reliable backup of RERF's data.

The Library and Archives Section supports two tasks: (i) acquisition of and providing access to scientific journals, books and papers, with one temporary staff member, and (ii) management, digitization, and distribution of historical archival material, with one staff member.

ITD has not been reviewed since 2008, and it was done in response to suggestions made to RERF at the 40th SAC meeting in 2013.

Evaluation

Organizationally, ITD is functioning smoothly under the able leadership of Dr. Katayama. The department has had many achievements during 2013, including:

1. Strengthening of RERF security and access control: Specifically, computers that have access to the resource database (which contains sensitive information about subjects) are no longer permitted to access any outside network. Further, most RERF computers are now only allowed to access the research database that contains only de-identified data, with additional access control permissions to particular data.
2. Migration of physical servers to a virtual server: Specifically, the database servers running on the Solaris operating system were completely migrated to a virtual server, which provides a lower cost solution than the previous approach.
3. Initiated linkage of biosamples to other databases: Specifically, ITD has worked with the Biosample Center to support linkage of biosamples to other databases,

so that researchers can more easily obtain integrated data.

4. Library and archives enhancements: Specifically, the Library Unit has enabled researchers to rapidly obtain hard copies when a reference is not available locally or online. Also, the Archives Unit has the ABCC-RERF history forum, so early employees can provide historical information that is not available in written form.

Overall, ITD has been productive in 2013 despite being resource constrained in terms of the number of staff members, and it is expected that ITD will play a critical support role in the future of RERF.

Recommendations

Our recommendations touch upon each of the main activities of the ITD.

1. Complete searchable meta-data: RERF has outstanding datasets. However, some of these data are not always known to many RERF researchers, e.g., (i) old datasets that exist on CDs, tapes, etc., (ii) datasets used in published RERF research results, and (iii) datasets generated in ongoing research efforts. To support collaborative data-driven research in working groups, meta-data about ABCC-RERF's datasets, including documentation on proper usage, should be improved and made searchable. Early development of user-friendly interfaces may help reduce search requests from departments, easing some of the pressure on ITD.
2. Easy access to integrated subject data: Multiple research efforts have collected data about a large number of subjects, but these data are hard to integrate. To address the needs of the research resource center, complete data on every subject ever involved with ABCC-RERF research should be retrievable with ease, subject to access control policies. This would involve continued effort on the part of ITD along with other departments. The ability to efficiently retrieve data and identify available biosamples, with crediting the current departmental contributions, will help to foster collaboration and reduce duplication of effort as plans to implement approaches such as whole genome sequencing go forward.
3. Investigation and evaluation of new technologies: ITD has invested considerable effort into virtualization of servers, which can provide a lower cost solution than previous approaches. To evaluate the tradeoffs, ITD should evaluate the speed and responsiveness of this technology for RERF applications. Also, ITD should investigate technologies that can further reduce the overall infrastructure cost, including Hadoop/Hadoop Distributed File System (HDFS) for analytics and Condor for cooperative computing.
4. Enhancements to archives: The archives at RERF are a treasure that should be used effectively and nurtured. Resources should be provided to complete the digitization of historical RERF material, including documents, photos, and newspapers. Fire extinguishers should be installed in the archives to protect these materials from risk of fire damage.

5. Recruitment and training of staff members: To enable ITD to play a critical support role in the future of RERF, ITD needs to recruit or train professionally competent staff members.

Department of Clinical Studies

Overview

As Chairman of RERF, Dr. Okubo introduced the RERF administrative activities, including a reply to last year's criticism on the relationship between radiation exposure and cataract development. The Acting Department Chief of the Department of Clinical Studies, Dr. Ohishi, prepared a point-by-point response for the 2013 SAC recommendations, carefully addressing each concern of the SAC. The main reports included staffing, collaborations, achievements in 2013, milestones, and future plans. Special attention was given to hot topics, including cataract and cardiovascular disease (CVD) studies (in-depth responses), respectively.

Evaluation

Although it is very important to investigate the noncancer risks in the Adult Health Study (AHS) and F₁ offspring cohort studies, the biological significance together with deep consideration of aging effects and changing of the observation period should be integrated in each research project. The diversity of these research projects such as targeting the different organ functional abnormalities should be re-evaluated and prioritized to achieve a background hypothesis on radiation-induced noncancer effects in cooperation with other departments such as the Department of Radiobiology/Molecular Epidemiology.

To avoid misunderstandings and misleading results of RERF research progress on noncancer risk analysis, it is important to consider not only statistically positive findings, but to interpret the biological significance of negative data, also.

Furthermore, the eight short presentations in the breakout, informal session showed a radiation-related rationale and hypotheses that have been better articulated and have been advanced with new crucial collaborations (ophthalmologists and cardiologists). Attention has been paid not only to a specific cancer risk analysis such as thyroid, breast, and liver in each, but also to common diseases, like diabetes mellitus type 2, cardiovascular diseases, chronic kidney disease, and non-alcoholic fatty liver disease.

Overall, we commend Dr. Ohishi, the Acting Department Chief, together with Chief Scientist Dr. Kodama, in responding to the prior year's SAC comments and recommendations.

Recommendations

1. The ophthalmologic study needs to be completed and a definitive statement regarding the dose-response relationship for cataractogenesis should be formulated for publication and public distribution. The availability and application of the more precise technology (slit lamp and retro-illumination) and the proposed quality controls will improve the precision of the study and reliability of the data. In the comparisons to previous

studies, careful interpretation of data is required to diminish any possible confusion in the setting of standards by international radiation protection institutions.

2. Cardiovascular studies are proposed to investigate possible roles of atomic bomb radiation in these non-mutagenic and noncancer causing health effects. The common hypothesis that has been proposed to explain the observed impact on health focuses on vascular endothelial damage. Alternative hypotheses, such as effects of aging, stress and/or psychosocial stress should not be excluded. The initial rationale for performing these health effect studies should be based on a radiation dose-response relationship, although the final result may prove otherwise. The observation that some of the late health effects that may be observed in the atomic bomb-irradiated population but may not show a clear radiation dose relationship will also provide important data for research and clinical application.

Four new research protocols based on AHS were presented. We view these to have merit in addressing the "other health issues" observed in atomic bomb survivors. The new studies include cardiovascular diseases, kidney diseases, diabetes mellitus, and cardiac arrhythmia. The study designs have been improved, the priorities have been changed appropriately, and the relationships of these health effects to radiation exposure should be definitively established. Whether the findings show direct relationships to radiation or a lack thereof, the results will be important in clinical care and in decisions for population radiation protection.

3. Late-life neurocognitive function studies of AHS subjects are well under way and are expected to provide information relating to aging in the atomic bomb survivors as compared to the control population.
4. The leadership of the Clinical Studies Department is encouraged to mentor the enthusiastic junior investigators in intra-department collaborations, international cooperation, and publications/presentations in high-quality journals. This will provide visibility for the RERF and opportunities for professional development of junior faculty.

Department of Radiobiology/Molecular Epidemiology

Overview

The Department of Radiobiology/Molecular Epidemiology (RME) has two major laboratories performing independent but complementary research: the Cell Biology Laboratory and the Immunology Laboratory. The primary focus of the department is to clarify the molecular basis of radiation-induced malignant and non-malignant diseases with a focus on immunosenescence. There are 11 professional staff in the department.

The Department Chief, Dr. Kusunoki, will reach retirement age within two years. Dr. Nakachi, the PI on the U.S. National Institute of Allergy and Infectious Diseases (NIAID) project and the former Department Chief, has retired, but maintains a presence in the department as a Consultant. His experience and continued interactions

continue to be important to the ongoing success of this department and the NIAID work in particular. Dr. Hamatani resigned as the Chief of the Laboratory of Cell Biology at the end of December 2013, and Dr. Kusunoki is now concurrently serving as the Laboratory Chief. It is not clear what the plans are for this position going forward. The need for planning the future departmental structure and leadership is critical, and action must be taken immediately.

In 2013, the department reported 24 RPs, seven of which reported publications, with two more having submitted manuscripts for review. Fifteen papers originating in the department were published or in press in 2013, plus another four papers as co-authors. Only five of the first author papers were in international English language journals, representing a loss of ground from previous years. Of these articles, all but three were associated with an RERF RP. An additional three articles, all with RME first authors, and all with associated RPs, were submitted for review in 2013. Although this bibliography remains solid, the importance of primary authorship on papers in international journals still needs to be emphasized. The department lists 26 external collaborations continuing for the next year, all but seven of which are associated with RPs. Members of this department have also given 13 presentations at domestic meetings in the past year, plus four presentations at international meetings, an increase in international presence over last year. This activity is important for both the exchange of ideas, and for maintaining domestic and international recognition for RERF and its mission.

Evaluation and Critique

Concerns raised by the SAC over the past several years concerning the future structure and leadership of the department have still not been addressed. This issue has been critical for some time, and plans for the future of the department cannot be deferred indefinitely. There is a need for strong leadership to take RME into the future.

This department is comprised of diverse groups containing a relatively small number of investigators. The projects under study are very ambitious and complex. While all are potentially interesting, the SAC again recommends that clear priorities should be set, along with criteria for the continuation of projects. Projects that show a lack of radiation effect should be published, but serious consideration should be given to shifting focus to new areas rather than continuing to support further negative studies in the same area.

Specific Recommendations

1. As always, emphasis should be placed on maintaining and improving the publication record of the department, especially with respect to principal authorships in international journals. Citation metrics (such as from ISI or Google Scholar) would be useful for tracking impact.
2. The issue of future leadership and potential departmental restructuring needs to be resolved.
3. The NIAID contract has shown productivity this year, with several publications and more in preparation. There seems to be optimism that the contract will be renewed, but the exact stage of progress in this

direction remains unclear, and few details pertaining to the renewal of this contract were presented. Some contingency planning would be appropriate given the current state of the National Institutes of Health (NIH) funding.

4. RME reported that seven grant applications had been submitted in the past year, which is highly commendable, but no details of these applications were presented to the SAC. The presentation of the hypotheses and specific aims of these proposals, and the agencies to which they were submitted, would be helpful.
5. There are signs of closer collaboration within the department, such as the focused attention on colon cancer that addresses several potential mechanisms through linked but independent studies. This approach is greatly encouraged. The department could still benefit from more collaboration with other departments within RERF, however. The concept of focus groups and a program project-like model should be explored and encouraged.
6. The department should support efforts to integrate the RERF databases, which would make information and sample availability easier to search and cross reference, encouraging collaborations and greatly benefiting all future RERF work.
7. An introductory slide describing the aims, background, and history of the project should be presented at the beginning of each presentation: in other words, the scientific rationale and motivation of the proposal. SAC members have not necessarily heard the story in previous years. For instance, in one study, recently diagnosed tumor tissues were collected to compare with the early-diagnosed tumors in terms of the tumorigenesis pathway. The aim of this study was not clearly presented, making it difficult to assess.
8. Printed handouts are also helpful for the informal session.
9. Dependence of reactive oxygen species (ROS) level on the genotype of *IL6R* has been analyzed and a phenomenological correlation has been demonstrated. The mechanism underlying the difference and its potential impact on carcinogenic risk should be investigated.
10. In spontaneous hypertensive-stroke prone (SHRSP) rats, irradiation with 1–4 Gy gamma rays accelerated the appearance of stroke-related symptoms. Confirmation with lower doses is recommended. Also, extrapolation of the finding to the human situation should be considered.

Department of Genetics

Overview

The Department of Genetics has, for two years now, been headed by Dr. Y. Kodama, who took over that role previously held for a number of years by Dr. Nakamura. It remains comprised of two laboratories. Historically, the Cytogenetics Laboratory has studied somatic mutations and issues related to biodosimetry, while the Biochemical Genetics Laboratory has concentrated on mutations in

the F₁ generation. The department contains ten members including Dr. Nakamura, who is formally retired and now listed as a Consultant. Both the department chief and the Biochemical Genetics Laboratory chief are on fixed-term appointments, which means that they are technically of retirement age.

Including papers submitted and in press, the department lists 13 publications appearing for calendar year 2013. At least two more publications from 2012 should be considered in this total, since they were submitted and published in 2012 after last year's review. These include four publications in peer-reviewed scientific journals of international repute. Actually, over the past two years there has been marked improvement in this area. Ten meetings were attended, two of which were at international venues. The SAC continues to believe that such outside activities serve to promote the exchange of scientific ideas and to maintain the international presence of RERF. The Genetics Department lists 13 RPs, two of which are platform/data collection and processing protocols. Although not necessarily a negative development, this appears to represent a declining trend, as there were 14 and 18 proposals in years 2012 and 2011, respectively.

Evaluation and Recommendations

1. The Committee was heartened to see that last year's productivity, in terms of publications in peer-reviewed journals, had been more-or-less maintained. This speaks well to the competence of the new department head. The department should strive for more such papers in English-language journals. Review articles are, of course, helpful here, but original work should be a priority.
2. The Committee raised two overarching issues during last year's review that remain. As alluded to last year, departmental leadership is aging. Once again, the Committee would feel more comfortable to see this issue addressed straightforwardly. Departmental response to this matter in this year's report was notably absent. It is somewhat reassuring that Dr. Nakamura remains in the department—if only formally in the capacity as a Consultant. Nevertheless, the department needs to start thinking *seriously and promptly* about grooming younger replacements in leadership roles to secure the long-term vitality of the department.
3. The second major issue involved the extent to which next-generation sequencing (NGS) approaches should be embraced. Last year the SAC recommended that a measured approach to sequencing be adopted for the time being, perhaps taking the form of a smaller focused pilot project, whose results could be used to reassess the workability of whole genome sequencing (WGS) at RERF. The Committee was encouraged to see that a smaller ongoing RP (RERF RP 2-13) using WGS is being applied to inbred mouse strains. This seems very much in keeping with the Committee's recommendation. It is evident from the current five-year plan that the Genetics Department has plans to incorporate WGS or whole exome sequencing (WES). Last year's report raised two points in this regard. The first involved the absolute need for bioinformatics expertise in this area, and whether RERF possessed—

or could reasonably be expected to develop within a suitable time frame—the necessary bioinformatics expertise.

4. The other point revolved around RERF's level of commitment to the department toward that end. Shortly after last year's review, RERF sponsored a workshop devoted to the post-genomic era, which included discussion of germ cell mutation detection by WGS. While this—together with WGS being a stated objective of RERF's future plans—demonstrates a welcome level of commitment, questions on both the aforementioned points remain in the eyes of some SAC members. There is little doubt that both the department and RERF upper management have been seriously weighing the relative benefits of WGS in the context of budgetary constraints. Nevertheless, the Committee would feel more at ease about the situation if RERF management would encapsulate its position regarding NGS in more concrete terms. The “measured approach” to NGS recommended by the SAC last year was based on the logic that it would encourage relatively smaller scale proposals that would serve the purpose of allowing investigators the opportunity to familiarize themselves with the technology and the problems they were almost certain to run into along the way. At the same time, it was reasoned that RERF upper management would have time to assess any reappropriation of resources that would be required in the event that these smaller scale NGS projects were fruitful. Since now the Genetics Department has undertaken such smaller-scale NGS projects, it is incumbent on RERF leadership to consider what they will do for the long term should these smaller scale project produce the desired results, and therefore require more resources.

As has become customary, after the first day formal overview, brief presentations were given to members of the SAC in the informal session to apprise us of recent progress on current projects. The Committee finds this to be a useful exercise for the evaluation process, and considers these presentations, in some sense, to highlight the department's key achievements and planned future direction. A few comments germane to these presentations follow.
5. The large majority of presentation time (and associated discussion) involved work presented by Dr. Asakawa. These RPs centered on comparative genomic hybridization (CGH) (RP 1-10, RP 4-11, and RP-S1-11) and NGS approaches (RP-S3-11, RP 2-13), including WGS and a new WES plan. The following is a brief summary of SAC's opinion of this interesting presentation and the lively discussion that followed. Whereas the absolute yields of mutations detected in irradiated samples was not any larger than that for controls, subsequent validation was used to argue that radiation-induced mutations were indeed identified by high-density microarrays. The yield per unit dose, however, casts some doubt on whether the approach as currently implemented would ever be useful for the purpose of constructing a proper dose response for deletion mutations.
6. The remainder of this presentation involved arguments

aimed at convincing the Committee that the next logical step in implementing NGS was WES applied to F₁ trios. The argument essentially was that smaller deletions could be detected, and that sequencing the exome would be more straightforward and economical. Whereas the Committee was not altogether encouraged about the prospect of studying single nucleotide variations (SNVs) or single nucleotide polymorphisms (SNPs) per se, WES data could address the issue, once and for all, of whether a significant fraction of mutations are due to small base pair changes instead of larger scale changes such as deletions and rearrangements. While Dr. Asakawa mounted a forceful argument as regards the need to move forward with this line of work, the Committee felt the proposal was a bit premature, in part due to the seemingly tenuous connection the PI had to collaborators with all-important bioinformatics expertise. The Committee thought that better use of resources would be made by directing WES to the mouse model for which CGH had already been established for mutations. In fact, the Committee was enthusiastic about this prospect. This CGH sample set is comparable to the material in which the radiation was given to females reciprocally (RP 2-13) presented in further detail during this informal session. The F₁ samples from the reciprocal irradiation scheme to mature oocytes were already subjected to WGS, so WGS/WES analyses and comparisons should give the department a basis for determining the future direction and scale of the NGS studies. At the same time, they should make a more standardized plan for the NGS sequencing system. They should either outsource the sequencing to companies, as has been done in RP 2-13, or collaborate with Hiroshima University as proposed in a new WES plan. Similarly, the bioinformatics part of the NGS analysis must be integrated more effectively. They must decide with whom they will continue to collaborate and/or train themselves to handle such huge datasets. Meanwhile, we recommend deferring the large-scale NGS analyses of human trios as well as the further analysis of WGS data from the irradiated tissue culture cell lines. Depending on the outcome of an aforementioned smaller, more focused study, the Committee looks forward, with a tempered degree of enthusiasm, to seeing in the future an RP involving WES on F₁ material.

7. The Committee continues to see potential in the RP presented by Dr. Noda, which involved the development of a clever fluorescent reporter system based on knock-in constructs in the mouse, which affords the opportunity to visualize mutated cell foci within tissue *in situ*. The system, as originally designed requires precise reassembly of targeted DNA sequences in order to produce a measurable signal. Consequently, it is responsive to DNA repair processes largely dependent on illegitimate consequences of homologous recombination (HR). Probably for this reason, the response of this hypoxanthine-guanine phosphoribosyltransferase (HPRT)-dup-green fluorescent protein (GFP) system to ionizing radiation (IR) is not robust. The investigator has since been

working to develop a similar system able to detect forward mutations. Because, in theory, this new system would be able to detect mutations resulting from non-homologous end-joining (NHEJ), it stands a better chance of being more responsive to radiation damage. Some progress has been made and some alternative strategies have been considered, but results from such efforts have been slow in coming. It is past time that results from this study are published in the peer-reviewed literature. At the very least, a methods paper for HPRT-dup-GFP would be in order. Another idea might be to test this system using a genotoxic agent whose damage is more amenable to processing by illegitimate homologous recombination, and publish a fuller paper comparing the effects of that agent(s) to IR. The Biochemical Genetics and Cytogenetics Laboratories are currently focusing on germline and somatic mutations, which reveal the radiation effect in each individual and offspring, respectively. Thus, both analyses of the irradiation effect of genotoxicity are equally important and the SAC again strongly recommends a further integration between the two labs.

8. For two years now SAC has been impressed with work presented by Dr. Kodaira, which involves molecular characterization of DNA breakpoints detected by array CGH. The radiation community would be most interested to see how various HR and NHEJ DNA repair pathways are apportioned in the processing of damage leading to deletion-type mutations. This is another project whose efforts and results are sufficient to justify submission to peer-reviewed journal without delay. While the study does not yet contain a large number of mutations, it is the view of SAC that this dataset is adequate for publication.
9. The presentation by Dr. Hamasaki represents work that was also reviewed favorably last year by the SAC. The transmissibility of chromosome aberrations to offspring following fetal irradiation is a topic that RERF should encourage. It was established previously by these investigators that the aberration transmissibility was tissue specific. Results have led to a peer-reviewed publication, with the prospect of more papers coming later. It was satisfying to see that Dr. Hamasaki has developed a testable hypothesis to explain his results, and the Committee anticipates this may open new avenues of investigation.
10. The SAC feels compelled to comment on studies coming to an end that involve electron spin resonance (ESR) measurements on tooth enamel and chromosome aberrations measured by fluorescent *in situ* hybridization (FISH), for which summary reports are being prepared. The SAC looks forward to a comprehensive comparison among these endpoints and updated physical dosimetry measurements of DS02. The Committee appreciates this to be a potentially contentious and scientifically complicated matter. Nevertheless, it is hard to imagine that these studies do not belong somewhere in the context of dose estimations, and mention of this topic was conspicuously absent in the context of the "Dosimetry Update."

RERF International Symposium: The Evaluation of the Effects of Low-dose Radiation Exposure in the Atomic-bomb Survivors

December 5–6, 2013, Hiroshima Laboratory

Eric J. Grant, Assistant Chief, Department of Epidemiology, Hiroshima

On December 5–6, 2013, RERF hosted an international symposium titled “The Evaluation of the Effects of Low-dose Radiation Exposure in the Atomic Bomb Survivors.” As radiation’s effects at low-dose levels remain uncertain, this symposium was organized to refine the epidemiological and statistical methodologies for studies of low-dose radiation effects and to obtain important insights into the biological basis for such effects.

The aims and outline of the symposium were introduced by Dr. Kotaro Ozasa, Chief of the Department of Epidemiology, RERF, who described the Life Span Study (LSS) of atomic bomb survivors as being a rich source of data for elucidating the health effects of ionizing radiation, while at the same time reminding the group that low-dose radiation effects remain uncertain. The symposium was organized against the backdrop of public concern regarding low-dose exposures, particularly after environmental exposures as seen in the case of the Fukushima nuclear power plant disaster.

On the opening day of the symposium, Dr. Richard Wakeford (University of Manchester) gave a presentation on low-level radiation epidemiology, in which he discussed the current status of the field and explained the difficulties in assessing low-dose radiation risks, and related study designs that are currently yielding helpful results. Dr. Wakeford’s talk was followed by an introduction to the current status of low-dose effects research in RERF’s LSS by Dr. Ozasa.

The following speakers then made presentations and led discussions aimed at refining methodologies for low-dose effects studies:

- Dr. Tomotaka Sobue (Osaka University) spoke about factors affecting cancer rates in Japan;
- Dr. John B. Cologne (RERF, Department of Statistics) touched on the potential for bias in risk estimates when non-confounding risk factors are ignored in nonlinear models;
- Dr. Eric J. Grant (RERF, Department of Epidemiology) talked about the data that have been collected by ABCC/RERF via questionnaires and interviews since the inception of the LSS that could be used to help model variations in background risks;
- Dr. Harry M. Cullings (RERF, Department of Statistics) spoke twice—the first talk described how the doses calculated by the current RERF dosimetry system depend on the level of detail available regarding shielding conditions at the time of exposure, and the second discussed exposure to residual radioactivity;
- Dr. Ritsu Sakata (RERF, Department of Epidemiology) discussed her recent findings on the effects of fallout rain on mortality and cancer incidence risks;
- Dr. Atsuko Sadakane (RERF, Department of Epidemiology) discussed work that had been done to estimate

doses from diagnostic and therapeutic X rays in the Adult Health Study (AHS) subjects, as another source of radiation exposure among the LSS cohort is medical procedures, both diagnostic and therapeutic;

- Dr. Amy Berrington de González (U.S. National Cancer Institute) spoke about the online radiation-risk assessment tool RadRAT, which estimates the lifetime risk of radiation-related cancer with uncertainty intervals following a user-specified exposure history;
- Dr. Dale L. Preston (Hirosoft International Corporation) discussed the need to consider the choice of comparison group when investigating low-dose risks and the dose-response shape in the LSS data;
- Dr. Kyoji Furukawa (RERF, Department of Statistics) touched on improving dose-response estimation in radiation risk analysis using a Bayesian semi-parametric model; and
- Dr. Nobuhiko Ban (Tokyo Healthcare University) discussed how mathematical models and reality often diverge.

On the second day of the symposium, the topic of estimates of external doses in Fukushima was introduced by Dr. Seiji Yasumura (Fukushima Medical University), who spoke on the methods and results from the Basic Fukushima Health Management Survey, which is an attempt to estimate external radiation exposures for all of the 2.05 million Fukushima residents as of 11 March 2011. Various issues related to the biological basis of effects were then discussed by Dr. Ohtsura Niwa (Kyoto University), including the models used for radiation epidemiology and how they relate to mechanistic models. Dr. Nori Nakamura (RERF, Consultant), picking up on the same theme, made the presentation “Breast cancer risk and age at the time of the bombing: A bridge between epidemiology and biology.” And Dr. Preetha Rajaraman (U.S. National Cancer Institute), with the last presentation, spoke on the topic of individual differences in radiation sensitivity.

The symposium concluded with a final roundtable discussion in which an overall summary of the gathering was delivered and suggestions about the future direction of RERF research by the participants were made.

In conclusion, many complex questions regarding the effects of low-dose radiation remain unanswered. We must recognize that not all of these questions can be solved by the LSS study alone and that RERF needs to continue publishing its methods and results to facilitate progress for all radiation researchers.

— Program —

December 5, 2013

Opening remarks

Toshiteru Okubo (RERF)

Introduction of participants

Kotaro Ozasa (RERF)

Aims and outline of the symposium

Kotaro Ozasa (RERF)

Session I. Current status of detecting low-dose risks*Moderator: Roy E. Shore (RERF)*

“Low-level radiation epidemiology—where we are now and where we might be going”

Richard Wakeford (University of Manchester)

“Current status of RERF LSS study at low-dose level”

Kotaro Ozasa (RERF)

Session II. Epidemiological limits—recognition and strategies for expansion**Part 1. Background heterogeneities***Moderator: Hiromi Sugiyama (RERF)*

“Potential effects of confounders in the cancer risk assessment of low-dose radiation”

Tomotaka Sobue (Osaka University Graduate School)

“Evidence for/effects of differing background rates”

John B. Cologne (RERF)

“RERF data for background rates”

Eric J. Grant (RERF)

Discussion

Session II. Epidemiological limits—recognition and strategies for expansion**Part 2. Quantifying radiation exposures***Moderator: Kotaro Ozasa (RERF)*

“Dosimetry methods for distal vs. proximal survivors”

Harry M. Cullings (RERF)

“Exposure due to residual (induced and fallout) radioactivity”

Harry M. Cullings (RERF)

“Effects of fallout rain on mortality and cancer incidence among LSS”

Ritsu Sakata (RERF)

“Evaluation of medical radiation exposure in the LSS subjects: Mail Survey 2008”

Atsuko Sadakane (RERF)

“Low-dose radiation risk projection using NCI RadRAT”

Amy Berrington de González (U.S. National Cancer Institute)

Session II. Epidemiological limits—recognition and strategies for expansion**Part 3. Analytical methods***Moderator: Harry M. Cullings (RERF)*

“How the choice of comparison group affects inference about the dose-response shape and low-dose risk estimates in the LSS solid cancer data”

Dale Preston (Hirosoft International Corporation)

“Improving dose-response estimation in radiation risk analysis—Why is the “LNT” model inconvenient?”

Kyoji Furukawa (RERF)

“Risk of low-dose radiation: Model and reality”

Nobuhiko Ban (Tokyo Healthcare University)

Discussion

*Moderator: Kotaro Ozasa (RERF)***December 6, 2013****Session III. Fukushima Health Management Survey***Moderator: Eric J. Grant (RERF)*

“Estimated external radiation exposure in Fukushima”

Seiji Yasumura (Fukushima Medical University)

Session IV. Radiobiological methods and tools*Moderator: Robert L. Ullrich (RERF)*

“How much of the epidemiological data be explainable by current mechanistic model?”

Ohtsura Niwa (Kyoto University)

“Breast cancer risk and age ATB: A bridge between epidemiology and biology”

Nori Nakamura (RERF)

“Individual variation in radiation sensitivity”

Preetha Rajaraman (U.S. National Cancer Institute)

Session V. Round-table discussions and future directions*Moderator: Kazunori Kodama (RERF)*

Closing remarks

Roy E. Shore (RERF)

Participants**Nobuhiko Ban**, Professor, Faculty of Nursing at Higashigaoka, Tokyo Healthcare University**Amy Berrington de González**, Senior Investigator, Radiation Epidemiology Branch, U.S. National Cancer Institute**Kazutaka Doi**, Researcher, Project for Human Health, Fukushima Project Headquarters, National Institute of Radiological Sciences**Tatsuhiko Imaoka**, Team Leader, Radiobiology Research Team, Radiobiology for Children’s Health Program, Research Center for Radiation Protection, National Institute of Radiological Sciences**Ohtsura Niwa**, Professor Emeritus, Kyoto University**Dale Preston**, Principal Scientist, Hirosoft International Corporation, USA**Preetha Rajaraman**, South Asia Program Director, Center for Global Health, U.S. National Cancer Institute**Shin Saigusa**, Senior Researcher, Regulatory Science Research Program, Research Center for Radiation Protection, National Institute of Radiological Sciences**Tomotaka Sobue**, Professor, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University**Richard Wakeford**, Professor of Epidemiology, Institute of Population Health, University of Manchester, UK**Seiji Yasumura**, Professor, Department of Public Health, Fukushima Medical University School of Medicine**<Observer>****Isaf Al-Nabulsi**, Senior Technical Advisor, Office of Health and Safety, U.S. Department of Energy**<RERF>****Toshiteru Okubo**, Chairman**Roy E. Shore**, Vice Chairman and Executive Director**Takanobu Teramoto**, Executive Director**Robert L. Ullrich**, Associate Chief of Research**Kazunori Kodama**, Chief Scientist**Nori Nakamura**, Consultant, Department of Genetics

Kotaro Ozasa, Chief, Department of Epidemiology, Hiroshima and Nagasaki

Harry M. Cullings, Chief, Department of Statistics

Eric J. Grant, Assistant Chief, Department of Epidemiology, Hiroshima

John B. Cologne, Senior Scientist, Department of Statistics

Kyoji Furukawa, Associate Senior Scientist, Department of Statistics

Ritsu Sakata, Associate Senior Scientist, Department of Epidemiology, Hiroshima

Hiromi Sugiyama, Acting Chief, Tumor and Tissue Registry Office, Department of Epidemiology, Hiroshima

Atsuko Sadakane, Acting Chief, Pathology Laboratory, Department of Epidemiology, Hiroshima

Ikuno Takahashi, Research Scientist (concurrent assignment), Department of Epidemiology, Hiroshima

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

RERF Workshop: The Storage and Utilization of Biological Samples for Studies on the Health Effects of Atomic Bomb Radiation

February 10, 2014, Hiroshima Laboratory

Misa Imaizumi, Chief, Division of Clinical Laboratories, Department of Clinical Studies, Nagasaki (Research Scientist, Biosample Center, Nagasaki)

On February 10, 2014, RERF hosted an international workshop, “The Storage and Utilization of Biological Samples for Studies on the Health Effects of Atomic Bomb Radiation,” at the Hiroshima Laboratory’s Auditorium. Increased incidence of solid cancers among A-bomb survivors as a function of their estimated radiation dose is still observed even today, more than 60 years after initial exposure to A-bomb radiation, but most of the molecular mechanisms and biological characteristics underlying this increase remain uncertain. To gain insight into these matters, molecular studies using blood, pathological, and other biological samples are essential. Experts from Japan and overseas participated in the workshop, which was organized to consider RERF’s future direction regarding storage and utilization of the unique and valuable biological samples obtained from A-bomb survivors.

We invited Dr. Geraldine A. Thomas, professor of Molecular Pathology, Imperial College London, who launched and now coordinates the Chernobyl Tissue Bank, to participate in the workshop, as well as four professors from Hiroshima and Nagasaki Universities and two pathologists from local hospitals in Japan.

The event opened with remarks from Dr. Toshiteru Okubo, RERF Chairman. Dr. Kazunori Kodama, RERF Chief Scientist, then defined the aims and outline of the workshop, followed by a special lecture by Dr. Thomas, who delivered an extensive presentation on an overview of the Chernobyl Tissue Bank and approaches to radiation-associated thyroid cancer studies, covering ethical aspects and study findings. The lecture also included reference to methods used at the Chernobyl Tissue Bank for collection and utilization of thyroid tissues and blood.

The next session included the following presentations: “Establishment of the RERF Biosample Center and its role” by Dr. Kazunori Kodama, RERF Chief Scientist; “Current preservation status of pathology samples at RERF and development of an archival system for surgical cancer samples from members of the Life Span Study in collaboration with hospitals in Hiroshima and Nagasaki” by Dr. Kotaro Ozasa, Chief, Department of Epidemiology, RERF; “Preservation of fresh thyroid samples obtained from participants of the Adult Health Study” by Dr. Imaizumi, Chief, Division of Clinical Laboratories, Department of Clinical Studies, Nagasaki; and “Storage of biosamples from atomic bomb survivors at Nagasaki University” by Dr. Shunichi Yamashita, Director and Vice President, Nagasaki University. The presentations reported on the current situation regarding the storage and utilization of biological samples at RERF and Nagasaki University, and the discussion that ensued focused on future directions for storing and using biological samples.

At the session that followed, Dr. Norio Takahashi, RERF

Consultant, presented “Ethical guidelines for human genome/gene analysis research,” which explained ethical issues related to the storage and utilization of biological samples, based on the Japanese ethics guidelines that were revised in February 2013. The findings of studies using tissue and blood samples from A-bomb survivors were then reported by Dr. Yoichiro Kusunoki, Chief, and Dr. Tomonori Hayashi, Assistant Chief, both of the Department of Radiobiology/Molecular Epidemiology, RERF. Their presentations were titled “A molecular oncology study of radiation-associated thyroid cancer among atomic bomb survivors” and “Immunobiology and immunogenome studies among Adult Health Study participants,” respectively. The discussion that followed focused on the current status and future prospects of studies using biological samples.

In a general discussion scheduled for the end of the event, participants actively considered, from both scientific and societal perspectives, the future direction for storage and utilization of biological samples from A-bomb survivors for use in radiation effects studies. This discussion included reference to actual examples from the operation of the Chernobyl Tissue Bank. The workshop concluded with remarks by Dr. Roy E. Shore, RERF Vice Chairman, who expressed his gratitude to the participants.

— Program —

Opening remarks

Toshiteru Okubo (RERF)

Introduction of participants

Kazunori Kodama (RERF)

Aims and outline of the workshop

Kazunori Kodama (RERF)

Session I. Special lecture

Moderator: Shunichi Yamashita (Nagasaki University)

“The Chernobyl Tissue Bank: Integrating research on radiation-induced thyroid cancer”

Geraldine Anne Thomas (Imperial College, London)

Session II. Current storage status of biological samples and future plans

Part 1. RERF

Moderator: Waka Ohishi (RERF)

“Establishment of the RERF Biosample Center and its role”

Kazunori Kodama (RERF)

“Current preservation status of pathology samples at RERF and development of an archival system for surgical cancer samples from members of the Life Span Study in collaboration with hospitals in Hiroshima and Nagasaki”

Kotaro Ozasa (RERF)

“Preservation of fresh thyroid samples obtained from participants of the Adult Health Study”

Misa Imaizumi (RERF)

Session II. Current storage status of biological samples and future plans

Part 2. Research institutions in Hiroshima and Nagasaki

Moderator: Kenji Kamiya (Hiroshima University)

“Storage of biosamples from atomic bomb survivors at Nagasaki University”

Masahiro Nakashima (Nagasaki University)/Shunichi Yamashita (Nagasaki University)

Session III. Ethical issues related to storage and usage of biological samples

Moderator: Wataru Yasui (Hiroshima University)

“Ethical Guidelines for Human Genome/Gene Analysis Research”

Norio Takahashi (RERF)

Session IV. Current status and future prospects of studies utilizing biological samples

Moderator: Eric J. Grant (RERF)

“A molecular oncology study of radiation-associated thyroid cancer among atomic bomb survivors”

Yoichiro Kusunoki (RERF)

“Immunobiology and immunogenome studies among Adult Health Study participants”

Tomonori Hayashi (RERF)

Session V. General discussion

Moderator: Kazunori Kodama (RERF)

Closing remarks

Roy E. Shore (RERF)

Participants

Geraldine Anne Thomas, Professor of Molecular Pathology, Imperial College, London, UK

Toshiya Inaba, Professor and Director, Research Institute for Radiation Biology and Medicine, Hiroshima University

Kenji Kamiya, Vice President of Hiroshima University, Professor, Research Institute for Radiation Biology and Medicine, Hiroshima University

Masahiro Nakashima, Professor, Department of Tumor and Diagnostic Pathology, Atomic Bomb Disease Institute, Nagasaki University

Shunichi Yamashita, Director and Vice President, Nagasaki University

Wataru Yasui, Professor, Department of Molecular Pathology, Vice Director, Institute of Biomedical and Health Sciences, Hiroshima University

<Observers>

Megumu Fujihara, Chief, Department of Pathology, Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital

Hiroo Matsuura, Senior Department Chief, Department of Pathology, Hiroshima Citizens' Hospital

<RERF>

Toshiteru Okubo, Chairman

Roy E. Shore, Vice Chairman and Executive Director

Takanobu Teramoto, Executive Director

Kazunori Kodama, Chief Scientist, Director of Biosample Center

Waka Ohishi, Acting Chief, Department of Clinical Studies, Hiroshima

Kotaro Ozasa, Chief, Department of Epidemiology, Hiroshima and Nagasaki

Misa Imaizumi, Chief, Division of Clinical Laboratories, Department of Clinical Studies, Nagasaki

Norio Takahashi, Consultant, Office of Associate Chief of Research

Eric J. Grant, Assistant Chief, Department of Epidemiology, Hiroshima

Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology

Tomonori Hayashi, Assistant Chief, Department of Radiobiology/Molecular Epidemiology

Hiroaki Katayama, Chief, Department of Information Technology

Yoshiaki Kodama, Chief, Department of Genetics

Ayumi Hida, Assistant Chief, Department of Clinical Studies, Nagasaki

RERF Workshop: Remaining Issues for Shielding Calculations

February 19–20, 2014, Hiroshima Laboratory and Nagasaki Laboratory

Harry M. Cullings, Chief, Department of Statistics

On February 19 and 20, 2014, an international workshop was held on remaining issues in shielding calculations for the atomic bomb survivors. The plan for the workshop was to begin by summarizing the progress that has been made in a project that was recently completed at RERF to provide improved input data on individual survivors' locations and terrain shielding. This work represents several years of dedicated effort and will be described in detail in a manuscript and an RERF report that are now in preparation. Then the program moved to a discussion of remaining issues in the calculation of shielding, particularly for survivors whose doses are currently classified as "unknown" because their shielding cannot be calculated with dosimetry system 2002 (DS02). In addition to a series of presentations at the Hiroshima Laboratory, the workshop included a field trip to sites of interest in Nagasaki that are related to special shielding problems.

Following greetings and an introduction by Dr. Toshiteru Okubo, RERF Chairman, Dr. Harry M. Cullings, RERF Department of Statistics, gave an overview of the work on improved survivor locations and terrain shielding. That project encompassed several methods of using original source documents with new technology to provide improved estimates of location and related terrain data. The first method compared various original source documents such as the Master File, Migration, and Radiation Questionnaires and the 1949 Radiation Census to determine the most reliable estimate of each survivor's location at the time of the bombing, in terms of the coordinates of the 1945 U.S. Army maps that were used at ABCC and RERF from early times up until the present work. Mr. Takashi Oda, Master File Section, RERF Department of Epidemiology, gave the results of a detailed study of the reasons for noted discrepancies among source documents and the related changes in estimated location for certain survivors, a small fraction of which involved large changes in distance from the hypocenter. He also described the restoration of digits representing tens of yards in the U.S. Army map coordinates of many survivors that had been truncated for unknown reasons sometime in the past.

Dr. Cullings then described the creation and use of a key tool in the map work of this project: orthophotographic mosaics of the cities made from pre-bombing aerial photographs. The pre-bombing photographs were geometrically corrected with special software to remove the effect of aircraft altitude, terrain relief, camera angle, and so on, to make them of uniform scale, and were then assembled into a mosaic. Each mosaic was accurately located in the coordinates of the new Japan Geodetic Datum 2000 (JGD2000) using landmarks visible in both the mosaic and accurate new maps, in a Geographical Information System (GIS). The first use of the orthophotographic mosaics was to align the U.S. Army maps with the mosaics using a "rubber sheeting" method based on a large

number of landmarks such as street intersections. This provided mathematical transformations that correct for local distortions in the placement of features on the U.S. Army maps. These transformations were then applied to the U.S. Army map coordinates of the survivors for whom a set of U.S. Army map coordinates represents the only estimate of their location at time of bombing. Dr. Eric J. Grant, RERF Department of Epidemiology, then described an even more accurate method of obtaining improved survivor location estimates for survivors with shielding histories: the neighborhood drawings were aligned with the orthophotographic mosaics using features such as street corners. For more information, see the *Facts and Figures* section by Dr. Toshiteru Okubo, Chairman of RERF, in the Winter 2013 *RERF Update*, Volume 24, Issue 2.

The focus then shifted to remaining issues, with Dr. Cullings and Mr. Tadaaki Watanabe, Master File Section, RERF Department of Epidemiology, describing several cases in which factory shielding was incorrectly classified as wooden house shielding in some early records, and several cases involving special types of terrain shielding such as retaining walls that are depicted in some shielding histories but are not suitable for calculation by the DS02 terrain shielding module.

Dr. Cullings then discussed a possible statistical approach to the "survival bias problem" in calculating doses for survivors in heavy shielding such as concrete buildings and air-raid shelters, by using information about both likelihood of occupancy and likelihood of surviving potential combined injury, as a function of location within a structure. This elaborated on a talk given at the workshop on Heavy Shielding one year earlier (please refer to "RERF International Workshop: Heavy Structural Shielding," in the *RERF Update*, Summer Edition, Volume 24, Issue 1, 2013). Next, Dr. Stephen D. Egbert of LEIDOS (formerly Scientific Applications International Corporation, SAIC) gave a presentation titled "Ideas for Generic Shielding Models That Could Be Used for Monte Carlo Calculations to Support a Sensitivity Analysis of Shielding among Survivors with Currently-Unknown Doses." He discussed requirements for such generic models and how they might be used for various kinds of odd shielding, such as vehicles, large trees, boats, and containers, among others. He also discussed several schema for enhanced calculation of terrain and urban shielding, improved organ doses, and calculation of heavy shielding. Finally, Dr. Grant discussed the available information resources at RERF available for construction of three-dimensional models of Hiroshima and Nagasaki that could be used in the future to validate the localized terrain shielding calculations of DS02 by a large, full-city calculation of the transport of radiations from the bomb in the air-over-buildings-and-terrain environment.

The second day of the workshop was spent outside in Nagasaki. After an orientation at the RERF Nagasaki

Laboratory provided by Mr. Hiroshi Fuchi, Master File Section, Department of Epidemiology, RERF Nagasaki, participants visited a number of locations of air-raid shelters and special terrain shielding situations that have been preserved sufficiently for their locations to be reliably and accurately identified in the present-day city and to allow visualization of the spatial relationship between the shielding and the epicenter of the Nagasaki bombing.

— Program —

February 19, 2014 (Hiroshima Laboratory)

Greetings and introduction of participants

Toshiteru Okubo (RERF)

“Overview and scope of recent efforts”

Harry M. Cullings (RERF)

“Understanding the reasons for needed distance changes”

Takashi Oda (RERF)/Tadaaki Watanabe (RERF)

“Creation of orthophotographic mosaics and their use for ‘rubber sheeting’ alignment of the U.S. Army maps”

Harry M. Cullings (RERF)

“Use of shielding histories and geographical information systems (GIS) to determine the position of proximal survivors”

Eric J. Grant (RERF)

“Survivors with misclassified shielding—workers in slate buildings misclassified as being in wooden houses”

Harry M. Cullings (RERF)/Tadaaki Watanabe (RERF)

“Calculation of terrain shielding for survivors close behind retaining walls or other nearby, massive barriers with vertical or near-vertical faces”

Harry M. Cullings (RERF)

“Possible statistical approaches to survivors with unknown doses in the current implementation of DS02”

Harry M. Cullings (RERF)

“Ideas for generic shielding models that could be used for Monte Carlo calculations to support a sensitivity analysis of shielding among survivors with currently-unknown doses”

Stephen Egbert (LEIDOS)

“Extent and limitations of RERF materials to construct 3-D models of Hiroshima and Nagasaki at the times of the bombings”

Eric J. Grant (RERF)

“Summary of survivor’s locations in air-raid shelters (Nagasaki fieldwork)”

Tadaaki Watanabe (RERF)/Hiroshi Fuchi (Nagasaki RERF)/Tomoaki Yamashita (Nagasaki RERF)

Summary of first day’s discussion

Harry M. Cullings (RERF)

(Travel to Nagasaki)

February 20, 2014 (Nagasaki Laboratory)

“Summary of survivor locations in air-raid shelters and questionable shielding-history drawings”

Hiroshi Fuchi (Nagasaki RERF)/Tomoaki Yamashita (Nagasaki RERF)/Tadaaki Watanabe (RERF)

(Move to Peace Park)

Field investigation of air-raid shelters (newly discovered air-raid shelter nearby the Peace Park)

Field investigation of air-raid shelters (Yamazato Elementary School)

Field investigation of the place of questionable shielding-history drawings (Ishigami and Ebira area)

Field investigation of the place of questionable shielding-history drawings (Zenza area)

Participants

Stephen Egbert, LEIDOS, Inc. (Former Senior Scientist, Science Applications International Corporation), USA

Tetsuji Imanaka, Assistant Professor, Research Reactor Institute, Kyoto University

<RERF>

Toshiteru Okubo, Chairman

Roy E. Shore, Vice Chairman and Executive Director

Takanobu Teramoto, Executive Director

Kazunori Kodama, Chief Scientist

Harry M. Cullings, Chief, Department of Statistics

Kotaro Ozasa, Chief, Department of Epidemiology, Hiroshima and Nagasaki

Yoshiaki Kodama, Chief, Department of Genetics

Hiroaki Katayama, Chief, Department of Information Technology

Eric J. Grant, Assistant Chief, Department of Epidemiology, Hiroshima

Ritsu Sakata, Associate Senior Scientist, Department of Epidemiology, Hiroshima

Atsuko Sadakane, Acting Chief, Tumor and Tissue Registry Office, Department of Epidemiology, Hiroshima

Fumiko Nakamura, Chief, Master File Section, Department of Epidemiology, Hiroshima

Takashi Oda, Group Leader, Master File Section, Department of Epidemiology, Hiroshima

Tadaaki Watanabe, Adjunct Specialist, Master File Section, Department of Epidemiology, Hiroshima

Sachiyo Funamoto, Unit Supervisor, Statistical Analysis Laboratory, Department of Statistics

Keiko Marumo, Unit Supervisor, Systems Technology Section, Department of Information Technology

Tomoaki Yamashita, Chief, Master File Section, Department of Epidemiology, Nagasaki

Hiroshi Fuchi, Assistant Chief, Master File Section, Department of Epidemiology, Nagasaki