Report of the 42nd Scientific Advisory Committee Meeting

March 2–4, 2015, Hiroshima Laboratory

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Introduction

The Scientific Advisory Committee (SAC) of the Radiation Effects Research Foundation (RERF) met March 2–4, 2015, at Hijiyama Park, Hiroshima, Japan to review RERF's scientific programs. This year the SAC conducted an in-depth review of the Departments of Genetics and Radiobiology/Molecular Epidemiology. Dr. Sally A. Amundson (Columbia University) rotated off the committee in 2014, and we welcomed Dr. Francesca Dominici (Harvard School of Public Health) as Dr. Amundson's successor and a new regular member. Two additional special SAC members were added this year to provide needed expertise in matters relating to the review of the Departments of Genetics and Radiobiology/Molecular Epidemiology: Dr. Ryo Kominami (Niigata University) and Dr. Ralf Kittler (The University of Texas Southwestern Medical Center).

Dr. Toshiteru Okubo, RERF Chairman, opened the meeting, warmly greeting all in attendance, and emphasizing the importance of the SAC's work to RERF. Following Dr. Okubo's introductory remarks, Dr. Roy E. Shore, RERF Vice Chairman and Executive Director, provided an overview of the status of research at RERF. He addressed specific recommendations made by the SAC last year, and described some of RERF's major accomplishments during 2014.

Dr. Robert L. Ullrich, RERF Associate Chief of Research, next gave a detailed presentation concerning proposed major restructuring in the way traditional departments interact with one another, as a means to foster collaboration, encourage development of novel ideas, and generally streamline the scientific process at RERF. He explained how research would be prioritized and the role of Scientific Clusters (i.e., Working Groups), an idea he first made public during last year's review. As part of this proposed restructuring, the Departments of Genetics and Radiobiology/Molecular Epidemiology would be merged to form the Department of Molecular Biosciences (tentative name).

Next, a series of short presentations from the Departments of Genetics and Radiobiology/Molecular Epidemiology were given by researchers describing individual projects. The remainder of the day was spent listening to overviews given by representatives of the Departments of Clinical Studies, Epidemiology, and Statistics, concluding with a report by Mr. Takanobu Teramoto on the newly added topic of public relations.

Overviews continued the next morning, starting with a presentation given by Dr. Kazunori Kodama, Chief Scientist, concerning the status of the Biosample Center. Chairman Okubo then talked about plans for a longitudinal cohort study related to the Fukushima incident. He finished the last of the formal presentations by giving his vision for future plans at RERF. As customary, for the rest of the day committee members were free to interact with individual members of various departments on a less formal basis, typically listening to short presentations of individual projects, a setting at which detailed questions of the presenter were more appropriate. Throughout the meeting the SAC reviewed and discussed the information provided concerning RERF activities, and was given the opportunity

to interact with junior investigators over lunch.

SAC spent the bulk of the last day of the meeting in discussion and writing of reports, in preparation for a formal read-back of committee recommendations later that afternoon.

Recommendations

The SAC makes five general recommendations to RERF and six specific recommendations.

General Recommendations

1. Restructuring: The new restructuring described in the "Five Year Future Plans of the Merged Department of Molecular Biosciences (tentative name)" holds the opportunity to address many of the difficulties RERF now faces. The merger is part of a larger restructuring effort that also involves the creation of Working Groups (Research Clusters), an idea first introduced by Dr. Ullrich during last year's review, and described more fully by him during the first-day session. The SAC views this change with substantial, but tempered, enthusiasm. On the one hand, it aims to bring researchers in related but otherwise disjoint research disciplines together towards larger goals common to RERF. A good example might be a comprehensive study of organ-specific carcinogenesis. Another benefit is the focus such a structure brings as it relates to funding opportunities. On the other hand, most members of the SAC have been through major restructuring efforts at their own institutions, with mixed results. A stated aim of the Research Cluster is to minimize bureaucracy, and it appears to have the potential to do this. It also has the potential of becoming yet another benign organizational layer with little or no benefit to the researcher. It will be up to upper management to implement these changes with the conviction necessary to insure their success. In either case, the SAC most certainly and unanimously appreciates the large amount of work involved in making these changes, and looks optimistically forward to seeing the long-term results of these efforts.
2. Emerging Technologies: The "omics" issue was discussed at some length during last year's review as it relates to prioritization. RERF seems acutely aware of the difficulties being faced. The SAC appreciates the situation, and can imagine the problems it brings regarding, for example, reallocation of limited resources. Everyone agrees that moving forward with tempered caution is appropriate, and whereas the committee is heartened to see that RERF is taking this issue seriously, they have yet to deal with it in terms that are concretely understandable to the SAC. An immediate source of pressure requiring clearer prioritization comes from the RPs generated by the Genetics Department, although it almost certainly will come from other departments as well. Still unsettled are decisions about what equipment will be purchased in-house, and what equipment is better utilized through outside collaboration. There is evidence that the Statistics Department is working hard to improve computational and statistical informatics capability. Nevertheless, most omics-related problems point to an overall deficiency in bioinformatics at RERF. Hiring a computational biologist should be a priority. Establishing relationships with outside bioinformatics experts in the areas of Next-Generation Sequencing (NGS) and metabolomics seems like a viable solution, at least for the short term. As an ultimate objective, RERF has been discussing, for some time now, the prospect of developing in-house bioinformatics expertise, and the Statistics Department is already providing welcome relief in this area. Various staff members have attended small seminars; Dr. Eric J. Grant, Assistant Chief of the Epidemiology Department, is taking a course at Cambridge University; Dr. John B. Cologne, Senior Scientist, Statistics Department, is spending several months at the University of Hawaii to collaborate with and learn more about high-dimensional data treatment. Until rather recently, the work within RERF has not demanded strong bioinformatics; however, the time is near when it will be needed. As an example of where things stand now, it seems that investigators proposing new RPs are left not knowing the extent to which they can expect institutional bioinformatics support, or whether instead it is their responsibility to forge relationships with outside entities for that purpose.
3. Sample and Data Sharing: In response to last year's review, a stated goal of RERF is to make outside investigators aware of the unique opportunities available to them through collaborative relationships. The database and samples managed by RERF are uniquely valuable, and there are many researchers who would enjoy access to them. Whereas the committee can appreciate the necessity to protect this resource at all costs, and is cognizant also of problems that arise with the public over this issue, the general consensus is that RERF has been too guarded in this endeavor. Irrespective of any plans to improve infrastructure, RERF needs to learn how to leverage its unique data and sample base for the purpose of forging research alliances that can help with its mission. Dr. Okubo indicated as much in his presentation on the second day.

   Pressure being exerted on RERF by emerging technologies is manifold, indirectly affecting researchers who want to use this technology on existing samples. Consequently, RERF should anticipate overtures made on behalf of outside research entities for access to biological data and physical samples. The emergence of newer technologies that encompass various aspects of the "omics revolution" will place additional demands on RERF in key areas. The SAC urges them to consider how they will deal with requests from potential collaborators beforehand, and to prioritize accordingly. This includes not only biological specimens but data associated with high-throughput technologies that may require additional bioinformatics development. The SAC would feel more sanguine regarding the issue of sample sharing with outside entities if it was convinced that definitive steps are being taken in this direction. The committee appreciates that this is made all the more

difficult in the face of implementing new technologies, but that is precisely why the issue has become acute. The proposed expansion of the Biosample Resource Center is seen as a positive step that helps to mitigate the lingering perception that RERF remains tentative about moving decisively forward in this area.

4. Research Resource Center: The collection and preservation of biosamples is among the most important responsibilities of RERF. If it is to become an international Center of Excellence for radiation research, the data-management capacities of the Information Technology Department and the recently created Biosample Center are critical. The SAC was pleased to see that the development of a database for access to sample identification, location, and other information is underway, and expects that these efforts will continue. Ideally, this database should be expanded to include all samples with associated information from every department. Where possible, this should include the ability to input "missing data." As RERF explains in its response to last year's critique, this goal is neither easy nor straightforward, a task made even more difficult by messy issues of intellectual rights and cross-platform databases. The committee empathizes with RERF's plight as regards the onerous (and perhaps even overly optimistic) prospect of computerizing all such information, especially for legacy samples. But, it needs to know exactly what RERF's ultimate goal is, and the institution's level of commitment to it. A tentative schedule for this task seems a reasonable step.
5. Recruitment: Unless conscious steps are taken to revitalize itself through the recruitment of new personnel, every institution will begin to suffer decline. It is somewhat disconcerting that a number of researchers in key departments are approaching retirement age, some of them in leadership positions. In conjunction with pressures imposed by emerging technologies, this makes it all the more important for RERF to place a high priority on recruiting young researchers, a sentiment echoed in the Five-Year Plan presented to the committee. Attracting top-notch talent in this environment will be challenging. As an important first step, it requires a firm commitment on the part of RERF. Beyond that, RERF needs to somehow project an image to prospective recruits that showcases its unique research opportunities and that reassures them they can make a career at RERF. These are issues fully recognized by RERF leadership, but they bear repeating.

Specific Recommendations

1. Considerable discussion during last year's review centered on the need for prioritization, at various levels. Among these was the way that research protocols (RPs) were assessed as to overall quality and testable hypotheses in connection with RERF's mission. There was an overall feeling among the SAC members that the entire RP selection-retention policy was in need of streamlining. Once fully implemented, the SAC is hopeful that the overall restructuring discussed in the General Recommendations above will alleviate these problems.
2. Projects studying electron spin resonance (ESR) signals from tooth enamel and their relationship to both chromosome aberrations and physical dose calculations have been conducted for some time, producing interesting results that seem applicable to dose-reconstruction efforts. Ostensibly such data would find use in helping to refine the latest DS02 estimates, but the committee is not clear as to exactly how this would be done or what to expect from this effort when it is completed.
3. New plans for the biosample repository are impressive. The committee notes that researchers will need information about the quality of samples, and in particular about the samples' intended use for studies involving the newer technologies of metabolomics, proteomics, and transcriptomics.
4. During the 40th meeting of the SAC a major issue arose concerning cataract studies that had been based on older slit-lamp imaging, and the extent to which the newer imaging based on retro-illumination would impact results. This conceivably puts RERF in the precarious position of needing to alter its conclusions about radiation cataractogenesis. The SAC was told that such a reassessment of cataract cases using the newer camera system would be completed in four years, and the SAC would like to be kept apprised of progress on this important issue.
5. There was near-universal agreement that RERF's recent commitment to the Fukushima incident was a positive development, especially in terms of public relations. We understand that additional funding was made available to RERF for this purpose, but in terms of personnel assigned to this project (FTEs), there was some concern that it could divert resources away from RERF's primary mission.
6. Public lecture fora have been conducted in Hiroshima and Nagasaki, and these events are appreciated by the SAC. To further contribute to public understanding, a few SAC members even suggested that building a small museum, more-or-less dedicated to RERF, would be helpful in informing the public, especially younger generations, as to RERF's role in the area of radiation protection.

DEPARTMENTAL REVIEWS

DEPARTMENT OF GENETICS

Overview

As part of the major restructuring started last year, the organizational scheme of the Department of Genetics has changed. The Laboratories of Cytogenetics and Biochemical Genetics have become the Laboratories of Cytogenetics and Molecular Genetics. These now represent two of the four laboratories comprising the Department of Molecular Biosciences (tentative name), which was formed from a merger of the Departments of Genetics and Radiobiology/Molecular Epidemiology. Dr. Yoshiaki Kodama retired last

year as Chief of the Genetics Department at the time of the merger. Dr. Yoichiro Kusunoki is interim Chief of the new department. Drs. Asao Noda and Tomonori Hayashi were appointed as Associate Chiefs, representing the remnant structure of the Departments of Genetics and Radiobiology/Molecular Epidemiology, respectively. In large part, the internal reorganization addresses concerns expressed last year by the SAC that the Genetics Department had not dealt with aging leadership. These changes notwithstanding, in order to simplify its review during this time of transition, the SAC presents a critique in the context of the conventional departmental structure.

The department lists 15 active RPs, several of which were terminated or are scheduled to cease at the end of 2015. Last year, the SAC encouraged more peer-reviewed publications in non-Japanese journals. There were seven publications originating from this department in 2014, all of which are associated with RPs. Four of these were in non-Japanese journals, and another has been submitted. Several others are listed as being in preparation. This compares favorably with the overall rate of three such publications from this department in 2013. The Genetics Department was well represented by presentations given at a number of scientific meetings and workshops. Understandably, most of these meetings were held in Japan; RERF should encourage presentations at international venues as well.

Evaluation and Recommendations

1. Looking at its five-year plan, it seems clear that the Genetics Department is invested in state-of-the-art genomic approaches, and the committee commends in particular the efforts to utilize next generation sequencing (NGS) approaches such as whole genome and whole exome sequencing for the identification of radiation-induced mutations in response to the SAC recommendations made last year. The department has generated compelling preliminary data using both array comparative genomic hybridization and next generation sequencing, which suggests that the global mutation rate induced by radiation is much lower than expected from estimates obtained from the seven locus test. Whereas these results have been known to RERF for some time, we note that the outside scientific community will view them as an extraordinary claim for the effects of radiation on the genome, which requires extraordinarily strong data that must be beyond reproach to protect the reputation of RERF.
2. Considering the increasing role of genomic approaches in RPs of the department, both the robust analysis of genomic data and the use of appropriate genomic techniques are of utmost importance. The SAC considers the use of appropriate and rigorous computational analyses essential for gleaning any useful information from genomic data generated by the Genetics Department; in particular the analysis of NGS data requires extensive bioinformatics expertise and computational infrastructure. We acknowledge the efforts of the department to establish external collaborations and the development of in-house capabilities to satisfy these needs. We think that the latter is desirable in the long term, but we caution that it is critical to have the proper expertise, and we are somewhat concerned that training of RERF scientists through attending courses would be insufficient to obtain this critical expertise. Therefore the SAC recommends the recruitment of an investigator with a research and publication record in computational biology to establish a bioinformatics group at RERF.
3. We would also like the department to reconsider the use of whole exome sequencing (WES) to identify radiation-induced mutations. We find this approach problematic because this technique interrogates only a small portion of the genome and is limited to the detection of single nucleotide variation, making it doubtful that WES will provide a reliable tool for the detection of mutations induced by radiation. We think that the use of whole genome sequencing (WGS) would enable a nearly complete characterization of the genetic changes caused by radiation. We are aware that this approach is more expensive, and fully harnessing the wealth of information whole genome sequencing data can provide requires very sophisticated computational analyses. That said, we feel that WGS would be the appropriate approach to characterize the entire spectrum of radiation-induced genetic changes in the long-term. Current computational approaches can detect single nucleotide variation and small insertions and deletions with high accuracy, and the refinement and development of new algorithms will likely enable the reliable detection of structural variations of larger scale, such as translocations and inversions.
4. Finally, the committee encourages the department to explore options to outsource NGS to external commercial providers that could perform sequencing at considerably lower costs, which would enable large-scale sequencing projects that are currently cost-prohibitive with academic sequencing laboratories.

Presentations

Brief presentations were given to the SAC members in a less formal setting 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. Comments pertaining to these presentations (as well as the written report) follow:

1. Dr. Yasunari Satoh started the session with a presentation of a WGS study of irradiated human cell clones (RP-S3-11). This analysis identified a larger number of SNVs in the irradiated cell clones when compared to the control clones, and the number of mutations increased in a radiation-dose-dependent manner. Also, the validation rate of these mutations by Sanger sequencing was high, demonstrating the ability of the department to call mutations accurately with NGS. Moreover, several chromosome aberrations were identified, impressing the committee with the relatively high accuracy for calling inversions, while translocations had a high false positive rate, which is a known problem with currently available computational algorithms. The SAC recommends that the investigators

publish these results as a proof-of-concept study. The committee also encourages the investigators to utilize their WGS data to test the feasibility of detecting copy number changes as a measure of WGS read density. Next, Dr. Jun-ichi Asakawa presented results of a pilot study (RP-P2-14) using WES to detect radiation-induced germline mutations in mouse F_1 (offspring). Both the WGS and WES studies are a foray of the department into NGS approaches, and as such have provided invaluable experience and insights into the logistics of NGS and the requirements for computational analyses. However, the committee concluded that WES might not be a reliable approach to detect radiation-induced mutations (see also recommendation (3) above), which is indicated by the very low number of mutations (essentially ~1 per mouse) detected in this study.

2. Dr. Asakawa has also led RPs centered on array comparative genomic hybridization (aCGH) (RP1-10 and RP4-11), for which no presentations were given. Because of the relatively low number of deletion-type mutations detected in these studies, there have been concerns about the robustness of the analysis of the aCGH data. This is a critical point, because there is discrepancy in terms of the mutation frequency between the preliminary results of this project and the seven locus test. It would be important to verify that appropriate algorithms and statistical criteria have been applied for these analyses, and the SAC recommends that the investigators continue to work closely with the Department of Statistics to that end.
3. Dr. Yuko Hirai presented comparisons relating ESR measurements on tooth enamel with chromosome aberrations measured by fluorescence *in situ* hybridization (FISH), and updated physical dosimetry measurements of DS02. This body of work has shown that ESR vs. chromosome aberrations is better correlated than DS02 vs. aberrations, or DS02 vs. ESR measurements. This not only validates the usefulness of chromosome translocations as a biodosimeter, it further suggests that cytogenetic data could somehow be used to "modify" the best physical estimates of absorbed dose to exposed populations. The unresolved issue seems to be that the ESR/translocation data—once it is reworked in the context of the updated DS02 data—should play some role in dose reconstruction, but the committee senses (perhaps wrongly) some confusion on the part of RERF as to what that role is. That said, the investigators have initiated collaborations to develop statistical methods to integrate the physical doses and chromosome aberration data.
4. Dr. Kanya Hamasaki presented work on the transmissibility of chromosome aberrations following irradiation during different stages of development. This work has been reviewed favorably by the SAC for the last two years, and previous results have led to a publication. Based on these results, two hypotheses for the observed differences in the transmissibility of chromosome aberrations during different stages of development—differences in radiosensitivity of HSCs between fetuses and adults vs. selection by the niche that removes HSCs damaged by radiation—have been proposed and are still being tested. The committee was satisfied with the preliminary data presented and the planned experiments outlined.
5. Finally, Dr. Noda presented a project that aims to identify biomarkers of unrepairable DSBs induced by radiation. Such protein biomarkers would present in principle an alternative tool to assess radiation damage in multiple tissues. Also, assays utilizing such biomarkers may be considerably less laborious and less expensive than approaches currently used to detect persistent DNA damage, e.g., chromosome aberrations by FISH. That said, the SAC members were skeptical that there would exist specific markers for this particular type of DNA damage in the first place and, if so, whether the devised strategies could effectively identify such biomarkers. In particular, the monoclonal antibody-based screening strategy appears to be problematic, and may require the screening of hundreds of thousands of antibodies. Testing of candidate proteins based on the results of the transcriptome and proteome analyses may present a more sophisticated path forward.
6. The SAC expressed some concern about the progress for RP1-08, which was not presented in this session but has been a major project of the department for quite some time. Originally, this RP aimed to develop a fluorescent reporter system based on HR-mediated reversion ($HPRT^{dup}GFP$). This genetically engineered mouse model would have enabled the detection and quantification of mutated cell foci within tissue. However, the response of this system to ionizing radiation (IR) is not robust, largely due to the issue of high background, and it is unclear whether this problem can be overcome with the strategies proposed by the investigators. It may be prudent to discontinue this project if a refinement of the $HPRT^{dup}GFP$ system is not achieved in 2015. The committee finds it curious that a forward mutation assay based on p53 would be proposed, particularly in a mouse system, given the known instabilities involved that are likely to further exacerbate the high background problem. Nevertheless, the results would be interesting, and the SAC recommends that the investigators speed up the testing of their alternative system that can detect forward mutations in tumor suppressors (p53-GFP knock-in mice), and also re-emphasizes the need to publish at least a methods paper for the $HPRT^{dup}GFP$ mice.

DEPARTMENT OF RADIOBIOLOGY/ MOLECULAR EPIDEMIOLOGY

Overview

Formerly its own department, the Department of Radiobiology/Molecular Epidemiology became part of the Department of Molecular Biosciences (tentative name) after its merger with the Department of Genetics. Dr. Kusunoki (previous Chief of the Department of Radiobiology/ Molecular Epidemiology) serves as interim Chief, and Dr. Hayashi has been appointed as Associate Chief of the new department. The Cell Biology and Immunology Laboratories will conduct research projects that were associated with the

Department of Radiobiology/Molecular Epidemiology.

The Department of Radiobiology/Molecular Epidemiology was large, with 11 staff involved in a wide variety of research topics, and includes a contracted study from NIH/NIAID. The primary focus is to clarify the molecular basis of radiation-associated malignant and non-malignant diseases and the effect of radiation on aging, focusing on immune responses. The responses to the previous SAC recommendations indicate sound leadership. Most of these were successfully incorporated by personnel in the department, as well as through collaboration. The department lists three publications in international journals (including in press) and eight papers of other types, including those in various stages of preparation. It is credited with 26 scientific presentations, including six presentations at international meetings, which represents an increase in scientific presence compared to recent previous years.

Evaluation and Critique

As previously ascertained by the SAC, there is the need for planning the future structure and leadership of the department. Much of the proposed research is both potentially interesting and ambitious, involving cancers of different types and various common diseases, all to be investigated at the levels of DNA, RNA, and protein (antigen). For example, given that DNA/chromatin methylation varies with cell type, age, and developmental stage, it has been hypothesized that methylation will change in response to micro-environmental cues, such as those associated with low nutrient concentrations and stroma cell contacts. The SAC believes that the personnel in this department have the necessary expertise to isolate cells of specific types required for these types of studies. In this context, the need for a structured approach is worth reiterating, since the new Department of Molecular Biosciences (tentative name) will involve an even higher level of diversity as it relates to Working Groups and projects. The need for prioritization of protocols is made all the more important given the unresolved state of continued funding through the NIAID contract.

Specific Recommendations

1. The finding that the EML4-ALK fusion gene was detected in PTC cases among A-bomb survivors is very interesting, as is the fact that the fusion gene was frequently detected in immortalized human thyroid epithelial cells after irradiation. It is of importance to examine whether or not the Tg mice that express the fusion gene after treatment develop PTC with a high frequency. It is possible that the fusion gene is merely a product resulting from a passenger mutation (translocation) or that it causes apoptosis in normal thyroid cells, but not in the immortalized cells used. In either case, the department is planning to examine effects of radiation on PTC development *in vivo*. While this is an important study, it may prove difficult to examine using wild-type mice. Here, the SAC recommends quickly assessing whether the developed Tg strain(s) actually develops tumors when the transgene is expressed in thyroid cells.
2. Aging is likely related to impairment of the immune system, such as decreases in the number and function of T cells and other immune-related cells. One project proposes to examine T cell receptor diversity in CD4 and CD8 T cell samples that were obtained from humans of different ages. This project is sound and in fact shows some immune system impairment. One concern, however, is the aging effect on the ratio of memory and naive T cells, since memory T cells exhibit restricted diversities whereas naive T cells exhibit comparable diversities to thymic T cells. Another project is to determine changes in the DC number and cytokine production. Several interesting and noteworthy changes were observed. However, these changes have not yet been related to chronic or persistent inflammation, which is the basis for the development of cancer and other common age-related diseases. Further study of this issue in that context is encouraged.
3. The NIAID-contract immune senescence studies are ongoing. The only real concern in this area relates to the unsettled status of the renewal of the contract, and the impact that uncertainty will have on resources.
4. The correlation between radiation and telomere shortening was demonstrated by an assay using peripheral leukocytes in A-bomb survivors. This is interesting from the viewpoint of irradiation promoting aging, although the consequence of the telomere shortening was not investigated. We question whether or not the "smear pattern" of telomere lengths is a good marker for aging. Another concern is in the use of leukocytes in bulk. It may be important to look at which granulocytes or lymphocytes (or specific immune cells or stem cells) are affected.
5. Age- and radiation-related changes in the number and function of circulating HSCs and HPCs were extensively examined, and decreases in the number of $CD34^+$ HSCs and T cells (but not leukocytes) have been demonstrated. This is interesting because the results suggest that subsets of HSCs, and possibly altered HPCs, dominate in A-bomb survivors. The characterization of those HSC or HPC subsets is encouraged.
6. It is an intriguing finding that some SNPs located near the promoter region of the IL7R gene show genetic association with hepatocellular carcinoma (HCC) development in A-bomb survivors. Somewhat surprisingly, the association was detected even when the elevated relative risk was as low as 1.5 (RERF report). Replication of this study with an independent set of samples, and functional analysis of each of the SNPs, may be important in order to warrant publication. Generally speaking, an association study may seem relatively straightforward, but can involve a lot of hard work. Our recommendation is to use already published functional SNPs (or SNVs) for the association study, avoiding much of the effort involved in searching for new SNPs.
7. It was surprising to learn that radiation increases the incidence of stroke due to brain hemorrhage, and that it shortens the latency in SHRSP rats. These results are of potentially high impact to RERF, and therefore

require careful handling for public consumption. There are some concerns with this study: one is how the result obtained using a specific model is interpreted; another is that only one model of early stroke onset was used. Another model may be necessary to substantiate this important finding. In addition, investigation as to mechanism is encouraged.

8. The Department of Radiobiology\Molecular Epidemiology plans to conduct omics studies in longitudinal samples. In principle, this is viewed as a move in the right direction, but the SAC would like a clearer explanation as to practical experimental approaches involved and a more precise description of the technologies to be used.

DEPARTMENT OF EPIDEMIOLOGY

Overview

The work of the Department of Epidemiology is the critical backbone for RERF risk estimation and characterization of the effects of radiation exposure from the atomic bombings of Hiroshima and Nagasaki. Three major cohorts are followed extensively: the Life Span Study (LSS) of 120,000 individuals; the *in utero* cohort of 3,600 individuals; and the F_1 cohort of children of atomic bomb survivors, consisting of approximately 77,000 individuals. Follow-up is ongoing, based on questionnaire, vital statistics data for deaths throughout Japan, and cancer incidence in Hiroshima and Nagasaki prefectures. As the cancer registry system in Japan will be changing in the future, it may be necessary to take that situation into account while gathering cancer incidence data.

The focus of the department on developing accurate data to derive dose-response information from radiation exposure, while accounting for potential confounders and effect modifiers (e.g., smoking and alcohol use) has produced surprising new insights into male and female differences in the radiation dose-response curves. The extensive work done by the Department of Epidemiology and the Department of Statistics is thorough and exemplary; further, this work is the essence of excellent collaboration within RERF.

The department continues to be ably led by Dr. Kotaro Ozasa, Chief, Department of Epidemiology, with assistance from Dr. Grant. Twelve high-quality publications have been produced (*The Lancet Oncology*, for example) but the productivity in terms of publications appears to be somewhat less in this past year. On the other hand, the SAC felt that the ongoing work is highly productive, and there may be multiple papers coming out in the near future that are of extremely high quality and utility for the understanding of radiation health effects. There are six full-time, one cross-appointment, and two part-time doctoral-level scientists, plus two pre-doctoral level scientists. Multiple presentations have been given at national and international meetings during the year—six in Japan, five in Nevada, and one each in Spain, Texas, Maryland, Alaska, and California.

General Comments

A number of continuing activities are generally routine but form the basis of much of the research conducted at RERF. Large projects, such as the maintenance of active cohorts; continued maintenance of data from the tumor and tissue registries in Hiroshima and Nagasaki; and primary analyses of mortality and incidence from the cohorts, are defined in Platform Protocols. As these develop, it is clear that new analyses will demonstrate enhanced understandings of the associations of radiation exposure with risk for cancers and other chronic diseases. The inclusion of lifestyle factors in analyses will continue to be important, and these are beginning to be examined as part of the major radiation risk analyses.

Accomplishments

Most of the recommendations from last year have been followed up. For example, a new genomic study of papillary thyroid cancer in collaboration with the U.S. National Cancer Institute and Japan's RIKEN is planned in order to take advantage of new advances in genomics and of the resources at RERF. A study of breast cancer and serum hormone biomarker levels is being conducted with Oxford University, again taking advantage of the unique RERF resources.

Analyses of solid cancer incidence through 2009 using new dosimetry and including potential confounding factors such as smoking and alcohol use are being prepared for publication.

Studies of site-specific cancer incidence with histological reviews are ongoing and will take some time to prepare, due to the intensive nature of pathologic review. The U.S. National Cancer Institute is collaborating on some of these, and RERF epidemiologists are taking the lead on others.

Work with the Department of Statistics has produced important new methods for imputation of missing values, so that when analyzing the "black rain" issue, or including confounders such as smoking, the analyses can use all the data, not just those that are non-missing.

Future Plans

The plans for 2015 are exciting, although the critical routine activities of maintenance of data appear to have received little emphasis in the presentations; yet these are critical to the mission of RERF: the collection of incidence data, mortality data, and tissue resources.

In addition, the collaborations with the National Cancer Institute in the U.S., RIKEN in Japan, and others in the evaluation of solid tumors and the effect of new radiation dosimetry will be interesting. For example, the analysis showing that estradiol mediates the effect of radiation on breast cancer is an important new finding and has public health implications. Another example is the different dose-curves for solid tumors for males and females. The updated dosimetry at this point has not changed risk estimates but has in fact made them more precise. New studies are planned with collaborators, such as the Asia Cohort Consortium and the Institute of Cancer Research in the UK.

Specific Recommendations

1. In addition to continuing the ongoing and critical current work, it will be important to establish a system to preserve pathological specimens from the LSS and *in utero* and F_1 cohorts.

2. The department maintains much of the infrastructure for RERF, and as such, they require more personnel to assist with and direct the ongoing tasks. A way to develop new hires would insure the continuity and excellent work that has been ongoing.
3. The department plans to evaluate additional lifestyle risk factors in analyses of cancer and other chronic disease incidence in the LSS cohort. Important lifestyle factors might include obesity, as BMI indicators can be easily used to analyze obesity.
4. Adjustment of lifestyle factors for a dose-response relationship will be more influential when the dose range is limited to low doses. In this case, a nonparametric approach may be better to describe relationships.
5. It may be informative to analyze cancer survival among A-bomb survivors and compare them to other groups domestically and internationally. Survival is not a direct indicator for radiation risk, but when comparing the risks based on cancer mortality and incidence, it will be helpful. Recently, the CONCORD-2 study revealed that the cancer survival rate for leukemia (adults) is low in Japan and those for stomach, liver, and lung are high, compared with U.S. and European countries. Such analyses, of course, need to consider lead time bias.
6. Recent advances have been found in the LSS solid cancer analyses taking lifestyle data and improved dosimetry into account. Ongoing re-analyses of the previous work provide revisions that are more reliable. Interestingly, it was found that a statistically significant dose-response curvature of solid cancers exists among males. This result will have strong impact on not only radiation research but also on cancer research in general. It is suggested that a paper be submitted as soon as possible to a high impact journal.
7. The risk analysis of *in utero* exposure seems to be very amenable to radiation protection and risk communication, because a gap exists between the RERF study and the Oxford study. A key point for analysis might be confounding by birth weight, and thus RERF should analyze birth weight when evaluating *in utero* exposure.

DEPARTMENT OF CLINICAL STUDIES

Overview

Dr. Waka Ohishi is the Chief of the Department of Clinical Studies, consisting of six clinicians/scientists located in Hiroshima, and Dr. Ayumi Hida is the Acting Chief of the Department of Clinical Studies in Nagasaki, consisting of three clinician/scientists. The clinicians provide patient evaluations and entry of patients on clinical studies for individuals in the Adult Health Study (AHS) and F_1 clinical studies. These physicians have been effective in working with and retaining patient participation in the studies of RERF. The prior SAC comments have been addressed and a conservative plan for the next year has been presented.

Responses to the 2014 SAC comments and recommendations:

1. With regard to the cataract study, following consultation with experts in ophthalmology and the purchase of a slit lamp and a retro-illumination type camera for evaluation and grading of cataracts, the protocol for the ophthalmologic study of A-bomb survivors has been improved and should provide useful data.
2. Cardiovascular studies comprise a significant commitment to investigate non-cancer effects on the health of A-bomb survivors. The design of clinical studies will include consideration of stress and psychosocial stress.
3. Longitudinal studies of neurocognitive function include consideration of age in the analysis of findings. The AHS cohort provides an extremely valuable resource for studies of proteomics, metabolomics, and lipidomics for discovery of biomarkers of neurocognitive degenerative diseases, in addition to effects of radiation exposure.
4. A formal mentoring program has been established to encourage the development of future clinicians with interest in radiation.

Achievements in 2014

1. Publications include eight peer-reviewed and published in English language journals and ten co-authored papers in international journals.
2. Important accomplishments include studies of thyroid nodules in a younger A-bomb survivors cohort and continuation of the F_1 offspring study.

Assessment of future plans and recommendations

Milestones for 2015 include progress in studies of cancers and non-cancer diseases in the AHS cohort. There is a rationale to address radiation effects on cardiovascular diseases (CVD) and to identify risk factors. The rationale is less strong for studies of valvular diseases and atrial fibrillation.

The cataract studies will have the necessary resources and expertise to support completion of this project and provide additional useful data. Thyroid studies provide important data on nodule development, but the thyroid function studies appear to involve a negative result and should be completed and reported.

Cognitive studies offer a novel patient population with longitudinal clinical data and clinical specimens. The analysis of the cohort experiencing dementia may offer an opportunity for biomarker development, but is not likely to correlate to radiation exposure.

Specific Recommendations for Clinical Studies

1. Although the research structure is well organized with internal and external collaborations (following the SAC 2014 recommendation), several suggestions are provided to review the current research topics with the intent to focus the scope of the studies on cause-and-effect disease mechanism in general.
2. The relationship of clinical findings to radiation exposure and cancer/non-cancer diseases needs more profound consideration of disease mechanism in addition to reliance merely on statistical analysis. Alternatively, from the standpoint of other evidence or

fundamental research results, close collaboration with world-leading academic societies is desired.
3. To consider findings for mechanistic understanding of radiation-associated or -induced cancer/non-cancer diseases, a closer relationship with other groups (radiobiology and molecular epidemiology) is encouraged, especially for the young clinicians.
4. The clinical studies on arteriosclerosis and cardiac diseases are ongoing and integrate inflammatory biomarkers and modern ultrasound imaging. However, good monitoring of data collection is needed to assure quality of data and standardization of diagnostic steps.
5. Following the SAC 2014 recommendation, a new cataract study has been prepared, which apparently needs careful and precise diagnostic and epidemiological participation with individual dose evaluations to avoid misleading conclusions and to determine any possible interactions related to aging and lifestyle confounding factors.
6. The gastric cancer study group needs to integrate with other research groups (such as the Department of Molecular Biosciences [tentative name]) and to share biomaterial samples.
7. Recruitment and exchange of young investigators from other research groups, such as from universities, should be seriously considered to strengthen and improve the current activities of the Clinical Studies Department.

DEPARTMENT OF STATISTICS

Overview

The Department of Statistics is perhaps the most collaborative of the departments at RERF, as it is needed for consultation and collaboration on most projects undertaken. In addition, this department conducts independent research on statistical methods. The department is ably led by Dr. Harry M. Cullings and consists of seven statisticians, although Dr. Reid D. Landes is leaving in June, which will bring the department down to only six statisticians. Twelve papers were published in English language journals, six in Japanese and four in press, with another 14 submitted. Meeting presentations numbered 42, with 17 in Japan, 18 in the U.S., and one each in Spain, Austria, Korea, France, Taiwan and two in Italy. The department members have participated in short courses on missing data analysis, efficient Bayesian computation methods, competing risks and multi-state modeling. There is one full-scale research protocol on shielding and dosimetry, as well as six Type-A (smaller) research protocols, one of which will be terminated. Of these seven protocols, an outside investigator is the principal investigator on three of them, one of which is the one to be terminated.

The Statistics Department has been responsive to the recommendations from last year's review. Importantly, they are collaborating with other research groups both internal to RERF departments and external institutions in Japan and other countries. This is evidenced by their publications both in international and Japanese journals.

Evaluation

Organizationally, the department is running smoothly under the able direction of Dr. Cullings. Importantly the department needs to recruit additional statisticians in order to provide the scientific support to other RERF researchers. There is the risk of the department being "spread too thin" because of the many consulting and research demands for the size of the department. The department should continue on its current path as recommended last year 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 very impressed with the completion of the new dosimetry that has now been incorporated into the basic LSS database and especially the new solid cancer incidence data analysis which will be published this year. This has been a complex and difficult effort that has produced critically important results. Working together with the Epidemiology Department led to a second noteworthy accomplishment, namely, the publication of an analysis of the effects of "black rain." This should greatly help to effectively limit the criticism of the RERF dosimetry and its radiation risk analyses. The department has also published on methods for dealing with incomplete smoking data in risk analyses and also on the use of non-parametric methods in low dose risk estimation.

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 a productive and effective leader of the department and the SAC believes that it will continue to be a critical component of RERF.

Specific Recommendations

1. The updating of residence probabilities for estimating the effect of out-migration from tumor registry catchment areas has been completed and should be published.
2. The work on a SIMEX (simulation-extrapolation) approach for adjusting for random errors in dose estimation seems interesting and is encouraged.
3. 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.
4. The methodological research is important and should continue; it is somewhat of a concern that bioinformatics work seems to be evolving slowly. This may be due to the need for decisions on the specific types of experimental data that the Molecular Biosciences Department (tentative name) will be generating.
5. The work on the shape of the cancer dose-response functions with an emphasis on the incorporation (e.g. Markov Chain Monte Carlo) of the dose uncertainties

associated with DS02 including the new dosimetry adjustments should be of a high priority. The possible effects of the inclusion of covariates such as smoking are especially important and their inclusion is greatly encouraged.

6. The new work on nonparametric risk estimates of low-dose cancer effects is important and encouraged. These estimates at low doses should then be compared with those of the traditional linear-quadratic dose-response models and those of more biologically models such as the Moolgavkar-Knudsen two-stage model.

RERF International Symposium: Application of "Omics" to Radiation Research

December 2–3, 2014, Hiroshima Laboratory

Robert L. Ullrich, Associate Chief of Research

On December 2–3, 2014, an international symposium titled "Application of 'Omics' to Radiation Research" was held at Hiroshima RERF. This symposium was made possible through funding from the Japan Ministry of Health, Labour and Welfare (MHLW) international exchange program. Many of the participants were from overseas and the working language of the symposium was English, with all presentations, including those of Japanese scientists, made in that language.

The purposes of this symposium were twofold: first, to provide the opportunity for RERF scientists to become familiar with the latest cutting-edge "omics" technologies, including proteomics, proteogenomics, and metabolomics, and how they could be applied to identify biomarkers and molecular changes associated with mechanisms of radiation-induced disease in the survivors of the atomic bombings; second, to familiarize the outside participants with the opportunities through collaborative research programs to better understand radiation risks, develop new tools to facilitate the early diagnosis of disease processes important to the survivors, and improve treatment approaches.

Such collaborative studies using these new technologies have the potential to make a major impact on understanding of disease processes such as cancer and cardiovascular disease that is likely to result in improvement of the lives of people throughout the world.

Topics in the symposium included presentations from RERF scientific staff on the current status of the Adult Health Study (AHS), transcriptomic and proteomic analysis, lipidomics and integrated "omics" approaches, and metabolomics. Four internationally known Japanese scientists and three leading scientists from the United States were invited speakers. The symposium was attended by the RERF scientific staff, who also acted as discussants or moderators, by a number of scientists from academic and research institutions in Japan, as well as by international observers from Europe and the United States. Session I, involving the current status of RERF AHS studies, was chaired by Dr. Yoshiaki Kodama, Chief, RERF Department of Genetics. The session was opened by Dr. Kazunori Kodama, Chief Scientist, Director, Biosample Center, who introduced RERF's Life Span Study (LSS) and AHS biosamples and their significance to radiation research. Dr. Waka Ohishi, Chief, Department of Clinical Studies, went into further detail about AHS studies, as a follow-up to Dr. Kodama's presentation. Dr. Tomonori Hayashi, Assistant Chief, Department of Radiobiology/Molecular Epidemiology, gave a general summary of RERF AHS immunology and National Institute of Allergy and Infectious Diseases (NIAID) immunosenescence studies. A discussion ensued, followed by a group photo session and lunch at Hijiyama Hall.

Session II, with the theme transcriptomics (study of all RNA molecules and their functions) and proteomics (study of all proteins produced by an organism), began in the afternoon, and Dr. Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology, chaired the session. Dr. Sumio Sugano, Professor, Division of Biosciences, Department of Medical Genome Sciences, Graduate School of Frontier Sciences, University of Tokyo, spoke about single cell transcriptome analysis using next generation sequencers, followed by Dr. David R. Goodlett, Professor and Isaac E. Emerson Chair of Pharmaceutical Sciences, University of Maryland School of Pharmacy, who spoke on label free proteomics for clinical analysis.

After a short break, Session III, relating to the fields of lipidomics (study of pathways and networks of cellular lipids in biological systems) and integrated "omics," was chaired by Dr. Ohishi, with Dr. Kazutaka Ikeda, Senior Researcher, Laboratory for Metabolomics, Center for Integrative Medical Sciences, Riken, giving a presentation on the topic of multi-lipidomics platforms for focusing globally on lipo-quality. Dr. Mark R. Emmett, Professor, Department of Biochemistry and Molecular Biology, Sealy Center for Molecular Medicine, University of Texas Medical Branch, then spoke on uses of integrated "omics" in cancer research. The day's events concluded with a reception hosted by RERF that was held at Andersen, a popular European-style bakery/restaurant in downtown Hiroshima.

Session IV, held the next day, December 3, was chaired by Dr. Hayashi under the theme metabolomics (study of metabolites present within an organism, cell, or tissue). Dr. Albert J. Fornace, Professor, Molecular Cancer Research Chair at Lombardi Comprehensive Cancer Center, and Professor, Department of Biochemistry and Molecular & Cellular Biology and Department of Oncology, Georgetown University, opened the session with his description of ongoing developments in radiation metabolomics. Dr. Mitsuhiro Yanagida, Professor, G0 Cell Unit, Okinawa Institute of Science and Technology Graduate University (OIST), spoke on the issue of the science of blood metabolomics in humans. After a short break, Dr. Daisuke Miura, Associate Professor, Metabolic Profiling Research Group, Innovation Center for Medical Redox Navigation, Kyushu University, discussed a matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS: a soft ionization technique used in mass spectrometry for analysis of biomolecules)-based imaging technique and its application to pathological analysis.

Session V, which was time set aside for general discussion, marked the conclusion of the meeting and was finished with closing remarks by Dr. Robert L. Ullrich, Associate Chief of Research and the organizer of the event. Japanese *o-bento* lunches for the speakers rounded out the itinerary.

This "omics" symposium focused on a new research field for RERF and has already led to new research projects being developed by RERF scientists. In addition, the

symposium has stimulated important scientific discussions between RERF scientists and leading scientists in Japan, as well as enhanced overseas researchers' interest in RERF as a laboratory with which they can become involved in collaborative research into radiation effects.

— Program —

Opening Remarks: Roy E. Shore (RERF)
Introduction of participants: Robert L. Ullrich (RERF)
Aims and outline of the symposium: Robert L. Ullrich (RERF)

Session I. Current status of RERF AHS studies
Chair: Yoshiaki Kodama (RERF)
"RERF LSS and AHS biosamples"
Kazunori Kodama (RERF)
"RERF AHS studies"
Waka Ohishi (RERF)
"RERF AHS immunology and NIAID immunosenescence studies"
Tomonori Hayashi (RERF)

Session II. Transcriptomics and proteomics
Chair: Yoichiro Kusunoki (RERF)
"Single cell transcriptome analysis using next generation sequencers"
Sumio Sugano (University of Tokyo)
"Label free proteomics for clinical analysis"
David R. Goodlett (University of Maryland School of Pharmacy)

Session III. Lipidomics and integrated omics
Chair: Waka Ohishi (RERF)
"Multi lipidomics platforms for focusing globally on lipo-quality"
Kazutaka Ikeda (Riken)
"An integrated omics approach in cancer research"
Mark R. Emmett (University of Texas)

Session IV. Metabolomics
Chair: Tomonori Hayashi (RERF)
"Ongoing developments in radiation metabolomics"
Albert J. Fornace (Georgetown University)
"Blood metabolomics of human individuals"
Mitsuhiro Yanagida (OIST)
"MALDI-MS-based metabolomic imaging technique and its application to pathological analysis"
Daisuke Miura (Kyushu University)

Session V. General discussion
Chair: Robert L. Ullrich (RERF)
General discussion
Closing remarks: Robert L. Ullrich (RERF)

Participants

Dr. Albert Joseph Fornace, Professor, Molecular Cancer Research Chair at Lombardi Comprehensive Cancer Center; Professor, Department of Biochemistry and Molecular & Cellular Biology and Department of Oncology, Georgetown University

Dr. David Goodlett, Professor and Isaac E. Emerson Chair of Pharmaceutical Sciences, University of Maryland School of Pharmacy

Dr. Mark Emmett, Professor, Department of Biochemistry and Molecular Biology, Sealy Center for Molecular Medicine, The University of Texas Medical Branch

Dr. Daisuke Miura, Associate Professor, Metabolic Profiling Research Group, Innovation Center for Medical Redox Navigation, Kyushu University

Dr. Kazutaka Ikeda, Senior Researcher, Laboratory for Metabolomics, Center for Integrative Medical Sciences, Riken

Dr. Mitsuhiro Yanagida, Professor, G0 Cell Unit, Okinawa Institute of Science and Technology Graduate University (OIST)

Dr. Sumio Sugano, Professor, Division of Biosciences, Department of Medical Genome Sciences, Graduate School of Frontier Sciences, The University of Tokyo

<Observers>

Dr. David Simar, Senior Lecturer, Inflammation and Infection Research, School of Medical Science, the University of New South Wales

Dr. Romain Barres, Associate Professor, The Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen

Dr. Romanas Chaleckis, Post Doctorial Scientist, G0 Cell Unit, Okinawa Institute of Science and Technology Graduate University (OIST)

<RERF>

Dr. Toshiteru Okubo, Chairman
Dr. Roy E. Shore, Vice Chairman and Executive Director
Mr. Takanobu Teramoto, Executive Director
Dr. Robert L. Ullrich, Associate Chief of Research
Dr. Kazunori Kodama, Chief Scientist, Director, Biosample Center
Dr. Waka Ohishi, Chief, Department of Clinical Studies, Hiroshima
Dr. Yoshiaki Kodama, Chief, Department of Genetics
Dr. Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology
Dr. Kotaro Ozasa, Chief, Department of Epidemiology
Dr. Harry M. Cullings, Chief, Department of Statistics
Dr. Hiroaki Katayama, Chief, Department of Information Technology
Dr. Tomonori Hayashi, Assistant Department Chief, Department of Radiobiology/Molecular Epidemiology
Dr. Ayumi Hida, Acting Department Chief, Department of Clinical Studies, Nagasaki

RERF International Workshop: Meeting on Dosimetry Issues

March 25–26, 2015, Hiroshima Laboratory

Harry M. Cullings, Chief, Department of Statistics

On March 25–26, 2015, an international workshop was held at Hiroshima RERF on dosimetry issues related to calculation of doses for the atomic bomb survivors. This workshop was the third in an annual series of meetings. The plan for this workshop was to begin by summarizing the recently completed work on dosimetry at RERF, followed by discussions related to a new plan for improved organ dosimetry. Following these topics was a discussion of particular categories of survivors with "unknown doses," which made up the majority of the agenda.

After a brief greeting, Dr. Harry M. Cullings, Chief, RERF Department of Statistics, began the meeting with a summary of recent changes to survivors' DS02 dose estimates, as a result of the various projects included in the recent work at RERF during 2010–2014. This work included cross-checking, prioritization, and selection of the best U.S. Army map coordinates for each survivor based on all available original source documents, as well as restoration of digits (tens of yards) that had been truncated for many survivors due to limitations in early data processing systems. In addition, geometrically corrected pre-bombing aerial photographs were prepared and assembled into photographic maps of Hiroshima and Nagasaki called "orthophotographic mosaics," and these were used to correct distortions in the U.S. Army maps, resulting in more accurate location information for survivors.

A major improvement in terrain shielding input data was achieved by using high-resolution digital terrain elevation data. Finally, the upgrade included a number of miscellaneous improvements such as a "fix" to the DS02 code for combining the shielding of houses and terrain features, and a change in the way that neutron and gamma-ray components of dose are handled when total shielded kerma exceeds 4 Gy.

Dr. Cullings showed various histograms of the new dose estimates, scatter plots of new vs. old doses, and tables related to changes in dose estimates. There were no major changes in the frequency distributions of dose estimates for the LSS. The overall effect of the changes on risk estimates is expected to be small, although some relatively subtle matters such as curvature in the dose response may be affected. The effects on major risk estimates for the LSS are currently being evaluated. A manuscript combining three previous manuscripts on the new dose estimates is being prepared and is expected to be submitted to an appropriate journal.

In the next presentation, Dr. Cullings described a new plan for a binational working group on organ dosimetry to be created and funded by RERF. The plan is to combine the existing DS02 shielded fluences with newly created computational phantoms (models of the human body) to derive new calculations of doses to tissues and organs. The new phantoms would replace simple models of the human body developed in the 1980s, based on geometrical shapes such as cones and cylinders, and would have more anatomical detail and body sizes. These would include a pediatric series, male- and female-specific adolescent and adult phantoms, and trimester-specific fetal phantoms. In addition to the 15 organs originally included in DS86, additional organs including the esophagus, heart, kidney, major blood vessels, prostate, and thymus, as well as various teeth would be calculated. Finally, there would be new combined "body + workbench" and "body + machine tool" phantoms for factory workers that were behind a workbench or free-standing machine tool to allow correct calculation of partial-body shielding. The binational working group held its first meeting May 20–21, 2015, at Hiroshima RERF.

In the next presentation, Dr. Stephen D. Egbert discussed a number of factors that the organ dose working group would need to consider in its work, particularly in regard to how the radiation transport calculations would be performed. He began with a history of organ dose calculation, noting that modifications of the T65D dosimetry system were the first calculations of organ doses by use of transmission factors (ratio of organ dose to dose in air at the same location) that were not assumed to depend on any other factors such as distance or house shielding. Then in 1985 the DS86 leakage tables were created for 15 organs in 3 sizes of phantoms. These tables could be used with any shielded fluence calculated by DS86 (and later, DS02) and have been used for 30 years.

Next, Dr. Egbert discussed basic possible parameters for the new effort, and in particular he recommended several target values of statistical precision for the new tables, starting with 1% standard error due to sampling statistics, for total organ dose. He compared the advantages and disadvantages of a forward Monte Carlo transport code (Monte Carlo N-Particle, or MCNP) and an adjoint (backwards calculation in time) code (Monte Carlo Adjoint Shielding, or MASH). Key points were that MCNP was more modern and up-to-date than MASH in its inputs such as scattering probabilities ("cross sections") but is extremely inefficient for this problem, and leakage tables would have to be developed by *post hoc* processing of the results. Another important point was that conversion factors for converting fluence to dose would have to be developed in some cases and should be improved in others, particularly for heterogeneous organs and tissues involving an interface between two media, such as red bone marrow (soft tissue interface with bone), skin and lens of eye (soft tissue interface with air), and tooth enamel (small, sharply defined inclusions of enamel interfacing with dentin/pulp, soft tissue of the mouth, and bone in the jaw).

Following Dr. Egbert's presentation, the focus shifted to a discussion of survivors in two DS02 categories of shielding, namely categories "10" and "11," for which there is no DS02 module to calculate survivors shielding. The purposes of this discussion were to illuminate the detailed shielding situations of a large fraction of the survivors who currently

have "unknown" doses and to suggest possible situations that might be amenable to dose calculation with modest effort, as well as to examine the assumptions under which survivors at long enough distances have their doses calculated in the current implementation of DS02 using averaged transmission factors (TF).

Several members of the Master File Section provided details on what is known about the shielding of survivors in these categories. Mr. Tadaaki Watanabe, Master File Section, Department of Epidemiology, began by presenting some detailed information and tables. Of 7,070 survivors with "unknown" doses, DS02 categories 10 and 11 comprise 5,863 (about 83%), of whom 5,448 are in category 11. Only about 27% of the survivors in these categories have shielding histories, but virtually all of them have some substantial information about their shielding on other early forms. Although DS02 category 10 is commonly referred to as "average outside," only about 69% of the survivors involved were outside, and the other 31% were actually inside at the time of the bombing. Similarly, although DS02 category 11 is commonly referred to as "average inside," only about 68% of the survivors involved were inside, and the other 32% were actually outside at the time of the bombing. Mr. Watanabe showed a detailed table, reproduced below, of the types of shielding for all survivors in DS02 categories 10 and 11.

Next, Mr. Takashi Oda, Master File Section, Department of Epidemiology, reviewed detailed information about three of the categories for persons who were outside: "in open," "behind a wall," and "behind a tree." Although the DS86 and DS02 implementation manuals and associated materials suggest that DS02 category 10 includes a number of survivors who were "in open" but did not have flash burns, and persons who were "in open with flash burns" are supposed to be categorized as DS02 category 0 ("in open"), there were 108 survivors in both DS02 categories 10 and 11 who were actually "in open" and more than half had flash burns, suggesting it might be feasible to reclassify them as DS02 category 0 with calculated doses. Persons who were classified as being "behind a wall" appeared similar to those who were found to be behind more massive earthen barriers in other recent work at RERF. That is to say, it might be possible to perform dose calculations for them based on their drawings in the cases where drawings exist.

Mr. Hiroshi Fuchi, Master File Section, Department of Epidemiology, then reviewed the details of persons in DS02 categories 10 and 11 who were inside of a building, i.e., in either factories or "barracks" type buildings. Some of the survivors who were in factories appeared to have actually been in the modeled parts of modeled buildings in Nagasaki, making reclassification possible for them. Others were clearly in other types of factory buildings or in sheds on the sides of larger buildings. Of the barracks type buildings, many cases shown were small buildings such as sheds, toilet buildings, and guard shacks. It is not clear whether the materials and construction of these barracks type buildings, especially the small ones in light of their small size compared to "9P" houses, would allow the use of the 9P house model for them with suitable adjustments.

Next, Dr. Cullings gave a talk that reviewed aspects of the history of the DS02 categories 10 and 11, the rules for when they are calculated with averaged transmission factors (TFs) as opposed to being classified as "unknown dose," and how the averaged transmission factors are calculated. A point that emerged from these detailed presentations is that the "average outdoor" and "average any" TFs are based on assumptions that are not completely consistent with the actual makeup of the shielding situations to which they are being applied, and may not be accurate estimates of the true mean TFs of the survivors to whom they are being applied. Furthermore, it may be possible to estimate better averaged TFs, and if it is, it may be reasonable to apply them at proximal as well as distal distances.

Dr. Cullings closed by reviewing criteria for possible calculation of currently "unknown" dose estimates, including cost and feasibility, and the precision and potential bias of feasible estimates. Finally, he pointed out that computational methods and resources have changed dramatically since the time 30 years ago when DS86 was created.

Dr. Eric J. Grant, Assistant Chief, Department of Epidemiology, gave a closing talk that provided an illustration of the power of modern computational methods. He considered survivors who were classified as "in open," but may have had nontrivial shielding from nearby buildings and other structures, or tree canopy. He pointed out that technologies exist to create three-dimensional imagery or mathematical models from sources such as aerial photographs and/or survivors' shielding history diagrams. After showing some examples gleaned from the Geographical Information System (GIS) used for map work at RERF, he picked an example neighborhood and showed panoramic views from a three-dimensional model that he created in Google Sketchup™. He pointed out some advantages for survivors in DS02 categories 10 and 11 that are categorized as "in open":

- Most were interviewed and have shielding histories.
- Many were located at close ranges and have high doses.
- They could add to the statistical power of RERF studies.
- They would alleviate concerns regarding biases due to "unknown doses" and help us maximize the use of our data.

He pointed out, however, that implementing his idea might require developing some new models or methods for situations not well represented by RERF's current GLOBE models (e.g., the model house cluster of DS86) and methods.

With that the meeting ended on a positive note, with tangible ideas for possible future improvements to the dosimetry of survivors without shielding histories and ways to reduce the number of survivors with "unknown" doses, as well as a preview of upgrades being considered for organ dose calculation.

— Program —

March 25, 2015 (1st Day)

Update for Dr. Egbert on recent changes to survivors' input data, handling of neutron dose in truncation of doses > 4 Gy total shielded kerma, resulting changes to doses, etc.

Harry M. Cullings, RERF

Table: Details of DS02 categories 10 and 11

City	ds02cat	Outside				Inside					Other	Total
		In open	Behind wall	Behind tree	Terrain	Factory	Barrack	Tram or train	Concrete building	Earth covered shelter		
H	10	58	6	6	0	20	18	1	1	3	6	119
	11	50	87	7	19	65	31	192	56	17	42	566
N	10	15	0	132	57	30	47	1	2	1	11	296
	11	37	21	16	111	109	13	3	11	254	49	624
Total		160	114	161	187	224	109	197	70	275	108	1,605

Note: H: Hiroshima; N: Nagasaki

Organ dosimetry: plan for improved organ dose calculations, including partial-body shielding of factory workers who were behind workbenches or machine tools, etc.
Harry M. Cullings, RERF

Organ dosimetry: needs for new working group re alteration of DS02 code to accept leakage tables for new computational phantoms, etc.
Stephen D. Egbert, LEIDOS

Details of shielding situations included in DS02 shielding categories 10 & 11: "Average Outside" and "Average Inside/Outside"
Tadaaki Watanabe, Takashi Oda, Hiroshima RERF
Tomoaki Yamashita, Hiroshi Fuchi, Nagasaki RERF

History of DS02 categories 10 and 11, current rules for known vs. unknown dose and formulation of averaged transmission factors, how these might be improved.
Harry M. Cullings, RERF

Discussion of urban canopy, arboreal canopy, possibility of whole-city 3D modeling and large forward transport calculations, general discussion and wrap-up
Eric J. Grant, RERF

March 26, 2015 (2nd Day)
Discussion

Participants

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

<RERF>
Toshiteru Okubo, Chairman
Takanobu Teramoto, Executive Director
Robert L. Ullrich, Associate Chief of Research
Kazunori Kodama, Chief Scientist
Harry M. Cullings, Chief, Department of Statistics
Kotaro Ozasa, Chief, Department of Epidemiology, Hiroshima and Nagasaki
Yoshiaki Kodama, Director, Biosample Center
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