Report of the 40th Scientific Advisory Committee Meeting

March 4–6, 2013, Hiroshima Laboratory

Scientific Advisors

Dr. John J. Mulvihill, Co-chairperson, Children's Medical Research Institute/Kimberly V. Talley Chair in Genetics; Professor of Pediatrics, University of Oklahoma Health Sciences Center
Dr. Shunichi Yamashita, Co-chairperson, Vice President, Fukushima Medical University
Dr. Kiyoshi Miyagawa, Professor, Laboratory of Molecular Radiology, Center for Disease Biology and Medicine, Graduate School of Medicine, The University of Tokyo
Dr. Kazuo Sakai, Director, Research Center for Radiation Protection, National Institute of Radiological Sciences
Dr. Kazuo Tajima, Director, Aichi Cancer Center Research Institute
Dr. Yoichi Gondo, Team Leader, Mutagenesis and Genomics Team, RIKEN BioResource Center
Dr. Sally A. Amundson, Associate Professor of Radiation Oncology, Center for Radiological Research, Columbia University Medical Center
Dr. Marianne Berwick, Distinguished Professor and Chief, Division of Epidemiology, Associate Director, Population Sciences, University of New Mexico
Dr. David G. Hoel, Distinguished University Professor, Department of Medicine, Medical University of South Carolina and Principal Scientist, Exponent, Inc.
Dr. Michael N. Cornforth, Professor and Director of Biology Division, Department of Radiation Oncology, University of Texas Medical Branch

Special Scientific Advisors

Dr. Hiroshi Sasaki, Professor, Department of Ophthalmology, Kanazawa Medical University
Dr. Andrew J. Einstein, Assistant Professor of Medicine, Division of Cardiology; Director, Cardiac CT Research, Columbia University Medical Center

Introduction

The Scientific Advisory Committee (SAC) met from March 4–6, 2013, in Hiroshima, Japan, to review the Radiation Effects Research Foundation (RERF) scientific programs. This year, the SAC conducted an in-depth review of the Department of Clinical Studies. To aid this review, two additional experts joined the Committee this year, Drs. Hiroshi Sasaki, Kanazawa Medical University, and Andrew J. Einstein, Columbia University Medical Center. Their insights were extremely valuable to the SAC, and it was a great pleasure for the Committee to work with these outstanding scholars. Drs. Shunichi Yamashita, Vice President of Fukushima Medical University, and John J. Mulvihill, University of Oklahoma, served as Co-chairs of the SAC. We are grateful for the opportunity to contribute, even in this small way, in the noble work of RERF and its leaders, scientists, staff, and supporters.

Dr. Toshiteru Okubo, RERF Chairman, opened the 40th meeting of the SAC on the morning of March 4, and provided a gracious welcome to all. With the Articles of Incorporation for RERF to be a public interest incorporated foundation (PIIF), the new SAC, formerly the Scientific Council (SC), will continue to review the scientific programs of RERF and report its recommendations to the Board of Directors and Board of Councilors, with the latter, in turn, expected to give feedback to the Scientific Advisors. Dr. Okubo mentioned eight retirements, with four newly hired scientists, for a net loss of four employees. Since 2004, there has been an 18% loss of general staff, leading to the present 173 people. The Department of Information Technology has introduced a virtual desktop and migration to a virtual server, increased network security, and improved access by mobile devices. At a future meeting, the SAC would be pleased to learn more about the Information Technology Department's activities, since they are so vital to the science of RERF.

Following Dr. Okubo's welcoming remarks, Dr. Roy Shore, Chief of Research at RERF, reported the status of research at RERF. He began with thoughtful and thorough responses to most recommendations made in the report of last year's SAC, with the exception of the desirability of a series of seminars on professional career development. Model programs take place at many academic medical centers. Dr. Shore went on to review RERF's major accomplishments during 2012. Among the highlights were publications in high-impact journals: *BMJ* (1), *PLoS One* (1), *Radiation Research* (9), *FASEB Journal* (1), *Radiology* (1), and *Radiation Protection and Dosimetry* (7). Of 103 items in the bibliography, 41 were in Japanese, partly due to 25 chapters written by RERF scientists for the second edition of the *Effects of A-Bomb Radiation on the Human Body*. The volume is well produced and obviously a major effort. Could its impact be augmented by translating it into English and marketing it worldwide? With the five other book chapters, we hope the review efforts did not detract from the usual priority on peer-reviewed articles of original data in the best possible journals. In that vein, one "achievement of the year" was actually printed in 2011, another was a book chapter, and several were not found in the consolidated bibliography (stroke in rats, comparative genome hybridization [CGH] arrays in F_1, and results from fallout exposures by Sakata, Grant, and Ozasa). It is especially important that any scientific evaluation of the putative effects of fallout exposure be scrupulously peer-reviewed in appropriate journals. It is commendable and great leadership that, in addition to

being frequent editors of others' manuscripts, Drs. Okubo and Shore made four first-author contributions. Work on international radiation committees and international invited lectures is highly important. We believe there is still a need for occasional updates in the best biomedical journals like the *New England Journal of Medicine, Lancet,* and *JAMA*. The new format for standardizing the tally of articles by the departments is much appreciated and should begin annual cumulative reports that, we hope, show increasing productivity. Beyond the level core funding from the principal governmental agencies—the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE), some via the U.S. National Academy of Sciences (NAS)—large funds come from the U.S. National Institute of Allergy and Infectious Diseases (NIAID) as a contract due to end in two years, the U.S. National Cancer Institute (NCI), and the Japanese MHLW and Ministry of Education, Culture, Sports, Science and Technology (MEXT). Next year's SAC hopes to hear RERF's plans for renewing the NIAID award.

Following Dr. Shore's comments, there were detailed presentations by the Department of Clinical Studies and brief reports from the Departments of Genetics, Radiobiology/Molecular Epidemiology, Statistics, Epidemiology, and the Office of Public Relations and Publications given by the department chiefs and selected staff members. Updates from four working groups and from Dr. Okubo's plan for RERF's future plans were heard. These presentations gave responses to last year's SC recommendations and reported on their major accomplishments during 2012, as well as their future plans. With regard to the future plans, the SAC is eager to help, beyond just responding as individuals to draft plans (which they will gladly do), perhaps with a sustained discussion at next year's meeting. Then, informal meetings were held between the SAC members and the RERF departments. Throughout the meeting the SAC reviewed and discussed the information provided concerning the activities of RERF, and met with a group of junior investigators over lunch on Tuesday.

Overview

The SAC feels justified in repeating last year's conclusion: "The SAC continues in its belief that the RERF is the preeminent leader in radiation risk research in the world and has the expertise, populations, and data sets to conduct fruitful investigations that cannot be carried out elsewhere. The support and assistance of the Japanese Ministry of Health, Labour and Welfare and the United States Department of Energy as well as the scientific guidance of the National Academy of Sciences continue to be critical to the mission of the RERF. Without such support and the assistance of the survivors and their families, it would not be possible for the RERF to conduct substantive research that has great impact around the world. With the rapid increase in the medical use of radiation and the worldwide expansion of nuclear power generation, now is the time for the expansion of the critical radiation health research that RERF is uniquely capable of conducting. The Advisors do, however, appreciate that the continued support from the sponsoring governmental agencies has been protected during these times of budgetary contractions."

General Recommendations

The Scientific Advisors have five general recommendations, as well as several additional specific recommendations:

1. To repeat, "More high quality publications in international English language journals are essential for the continued success of RERF" (39th SAC Report 2012). Consideration should be given to obtaining an analysis of citation impact factors for the past several years (or a decade) of publications from RERF and its individual scientists, to illustrate productivity and to show examples of exemplary work.
2. Decisions about organizational structure are becoming urgent, e.g., with regard to future hiring, purchase of large equipment, and renewal of the NIAID contract.
3. Interactions with leaders of the recovery from the Fukushima nuclear power plant accident after the Great East Japan Earthquake and *tsunami* are well justified, in our opinion, and within the mission of RERF (Article 4, Articles of Incorporation). As we approach the second anniversary of the accident, it is clear that the consequences remain huge and that RERF's knowledge, skills, and expertise are needed and might focus on public education and professional training. The SAC highly values the efforts of RERF in support of activities related to Fukushima to date. This is an ideal opportunity for delivery of the RERF "product" and "know-how" in that it represents transfer of RERF scientific knowledge and process knowledge (such as consideration of low-dose radiation health effects and long-term follow-up) to a pressing public concern. The Fukushima disaster also highlights the importance of low-dose mechanistic studies and their linkage to the Fukushima Health Management Survey. The scientific opportunities for improved understanding of radiation effects on humans are also on the increase, as development of systems and computational biology offers new opportunities for integrating basic laboratory findings into human risk assessment. Advanced statistical methods using high-speed computing also allow for greater sophistication in model development including the requisite incorporation of measurement and model uncertainties. The SAC continues to hope that the combination of increasing needs of society and increasing scientific opportunities for understanding the health effects of radiation will stimulate the Japanese MHLW and the U.S. DOE to increase or at least maintain their level of basic financial support of RERF despite the persisting environment of decreasing governmental research funds. With the sustained and outstanding senior leadership of Drs. Okubo and Shore, along with Dr. Kodama, the SAC looks forward to a bright future for science at RERF.
4. Greater attention might be made for the global impact of RERF. Good beginnings are well underway with international collaborations, participation in international policy agencies, and large research collaborations. It seems very worthwhile to pursue designation

by the International Atomic Energy Agency (IAEA) as a Collaborative Center in RERF's areas of expertise.

5. The Articles of Incorporation and associated PIIF status now permit a route for donations and philanthropy to augment the mission and effectiveness of RERF. In fact, a notice on the website has resulted in donations. We urge thorough explorations of the use and potential of this capacity. An ad hoc committee, perhaps made up of RERF staff and members of the SAC, Board of Directors (BOD), Board of Councilors (BOC), Local Liaison Councils, NAS, and survivors groups, might review issues like purpose of the funds, recruitment of donations, and accountability, etc. The notion of establishing a legal U.S. entity, "Friends of RERF," might be considered, to gain the support of loyal alumni/ae of RERF in the U.S.

Additional specific recommendations for next year's report to the SAC from RERF:

1. Since the organizational diagram shows feedback to the SAC from the BOC, we are eager to receive that information.
2. The Information Technology Department should be on a future agenda of the SAC.
3. The new productivity summaries should be repeated with accumulation of data over time. Consider adding a field, "Extramural research funding applications submitted."
4. Although the written "Response to SAC Recommendations" (done in May or June) may contain statements like "This will be considered," the oral presentation in March 2014, should not use such language, but should say what the consideration concluded.
5. We applaud the effort to consolidate and inventory all biologic specimens.
6. A special emphasis following the last year's recommendations, as well as informal discussions with junior investigators, clearly reminds us that the young physicians need to have more formal training, which might be met with some RERF-wide program of professional career development, such as those at many academic health centers.

Individual Department Reviews

Department of Clinical Studies

Overview

In good response to last year's suggestions, the main reports including three representative presentations and seven short presentations in the breakout informal session showed hypotheses and rationales that were better articulated than before, and new crucial collaborations with clinicians have been forged. Attention has been paid not only to a specific cancer risk analysis such as thyroid, breast, stomach, 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. Furthermore, rare conditions such as short QT and Brugada syndromes as well as a common arrhythmia called atrial fibrillation are now under investigation. However, there is no dose-response relationship for most arrhythmias, and a discrepancy of data of diabetes obtained between Hiroshima and Nagasaki should be clarified. The aging effects always modify the risk and so relationship with aging should be clarified for any radiation-associated disease in A-bomb survivors.

The major platforms of the Adult Health Study (AHS), the F_1 Clinical Study, and the expanded cohort of survivors exposed in youth are continuing well. Greater interactions with the Departments of Epidemiology, Genetics, and Radiobiology/Molecular Epidemiology are encouraged, including exploratory analyses of family histories. There is clearly good teamwork, resulting in steady progress.

A landmark report appeared on radiation and cataracts, so special consideration was made. There are three main types of crystalline lens opacities—nuclear cataract, cortical cataract, and posterior subcapsular cataract (PSC)—and two methods to classify and grade them. One method is judgment by slit-lamp examination and the other is judgment from a photograph image. Recently, most cataract epidemiological studies have adopted the latter. To ensure reliability, it is very important to take high quality photographs using the same procedure throughout the study. Nuclear cataracts must be judged from slit images taken with a slit-lamp type camera, and cortical cataract and PSC must be judged from retro-illumination images taken with a retro-illumination type camera.

In previous and ongoing RERF studies, the adequacy of photographs is very poor. There are several reasons for this including: 1) lack of a standard method, for example, slit-lamp intensity, angle, and width differ among photographs; 2) the unclear focus of the photographs makes them difficult to judge; and 3) a retro-illumination camera was not used for examination of cortical cataracts and PSC. For these reasons, the methods used in the RERF study of cataract classification do not meet the latest standards for epidemiological studies, making it impossible to re-analyze the data from photographs. To utilize the data of the ongoing study, slit-lamp judgments made by the examiners must be used, despite the fact that their intra- and inter-observer agreement is questionable. Therefore, the reliability of the data is not very high. To investigate the effects of radiation, a new study using a new camera with a standard method is highly recommended.

A special emphasis following last year's recommendation clearly reminds us that the young physicians need to have more formal training, which might be met with some cross-institute program of professional career development.

Recommendations

1. The department still needs to: 1) prioritize projects; 2) improve study design and evaluation process on the current research projects especially on noncancer studies such as cataract and glaucoma; 3) encourage more peer-reviewed publications in English as first author or last author; 4) improve clinical studies by seeking active participation of world-leading experts from inside and outside Japan; and 5) intensify collaborative efforts among RERF departments and also universities and research institutes elsewhere.
2. Research on radiation and noncancer diseases should

be continued and strengthened together with leading experts in each field, as should recruitment of young researchers.

3. The descriptive findings of the different findings of radiation risk of diabetes mellitus between Hiroshima and Nagasaki should be clarified. Similar to other phenomena of aging promotion by radiation, noncancer studies should be more carefully re-evaluated and strengthened.
4. Collaboration with expert ophthalmologists should be seriously considered.
5. For the routine work of clinical evaluations and periodic contacts with survivors, there might be room for improvements and efficiencies, to make the best use of scientific and clinical skills of physicians and all the clinical assistants. A good balance is needed between daily clinical duties and research activities of junior physicians. In the next year, perhaps "clinical productivity" can be defined and assessed, addressing questions like what is the total clinical load and the available clinical personnel? Answers involve, at first glance, the numbers of subject encounters, numbers of support staff, numbers of physicians, time required, and complexity of issues, etc.
6. The research protocol (RP) to study hypertensive heart disease and heart failure in AHS participants is meritorious and important, but it would benefit from collaboration with an international leader in echocardiographic assessment of diastolic dysfunction, to ensure quality of the analysis and to incorporate more advanced echocardiographic techniques such as the speckle tracking method. Moreover, the echocardiographic equipment available for this study at the Hiroshima and Nagasaki Laboratories is not state-of-the-art, and collaboration with industry, e.g., Toshiba Corporation, to obtain access to the latest ultrasound machines should be attempted.
7. In view of the scope, number, and magnitude of suggestions, it might be wise to repeat the SAC's in-depth look at the department again next year.

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 and potential epigenetic mechanisms of disease causation. There are 12 professionals in the department, two with terms that expired before the end of 2012.

The department chief, Dr. Kusunoki, will reach retirement age within three years. Dr. Nakachi, the principal investigator (PI) on the NIAID project and the former department chief, retired five years ago, but maintains a presence in the department as a consultant. His experience and continued interactions are viewed as important to the continued success of this department and the NIAID work. However it is critical that plans for the future departmental structure and leadership be made now.

In 2012, the department reported 23 RPs, only five of which were associated with publications. Members of the department were authors on 14 papers, only one of which was in Japanese. Of these articles, all but five were associated with an RERF RP. Six of the publications had RME staff as first author, and all of those were associated with an RP. Four additional articles, three with RME first authors, and all with associated RPs, were submitted for review in 2012. This bibliography continues the trend of increasing publication numbers noted last year, although the importance of primary authorship on papers in international journals still needs to be emphasized. The department lists 29 external collaborations, all but four of which are associated with RPs. Members of this department have also given 14 presentations at domestic meetings in the past year, plus one presentation at an international meeting (the Annual Meeting of the European Thyroid Association in Italy). This activity is important for both the exchange of ideas and for maintaining domestic and international recognition for RERF and its mission.

Evaluation

Concerns raised last year over the future structure and leadership of the department were deferred in the expectation of decisions being made after the workshop on restructuring the Departments of Genetics and RME. However, a report from this workshop was not included in the written materials and no mention of any conclusions was made during the presentations this year. This issue is becoming critical, and plans for the future of the department must be addressed.

This department is comprised of small and relatively diverse groups with a finite number of investigators. The projects under study are very ambitious and complex. While all are potentially interesting, the SAC again recommends that these should be related to how the data obtained in these studies will influence the AHS, and future research should be prioritized accordingly.

Recommendations

1. As always, emphasis should be placed on maintaining and improving the publication record of the department, especially with respect to primary authorships in English language journals. Citation metrics (such as from ISI [the Institute for Scientific Information (Thomson Reuters)] or Google Scholar) would be useful for tracking impact.
2. The NIAID contract represents a significant fraction of effort in this department, but productivity appears disappointing. This is especially worrying, as the award is approaching the point when renewal plans need to be considered. A clear strategy for either renewal or restructuring to accommodate the end of this funding cycle needs to be put in place.
3. The issues of departmental restructuring and future leadership need to be resolved.
4. The increased synergistic interactions with the Statistics Department are seen as a potentially high-impact

collaboration, in terms of RME results. The idea of applying an ontology-type approach to the genome-wide association study (GWAS) data is encouraged, as a similar approach has been highly successful in extracting biological meaning from underpowered expression studies. If successful, the technique would have much broader applications to other GWAS studies. If unsuccessful, further GWAS studies should not be pursued due to lack of statistical power and sufficient numbers. Such focused close collaborations should be encouraged also with the Clinical Studies and Epidemiology Departments.

5. More attention should be paid to dose dependence in all studies. Dose-response relationships should be a major focus in experimental design.
6. The identification of anaplastic lymphoma kinase (*ALK*) gene rearrangements in thyroid and lung cancers strongly suggests that chromosome rearrangements may play a crucial role in carcinogenesis. However, to clarify the mechanism underlying radiation-induced carcinogenesis, large numbers of exposed and non-exposed cases should be recruited in the study. An opportunity seems available with the Clinical Studies Department's effort on thyroid nodules.
7. Methylation analysis in the subset of genes selected is based on a hypothesis that radiation may affect aging-related epigenetic changes. To explore the impact of epigenetic changes on radiation-induced disease onset, a more defined rationale for experiments in terms of epigenetic dynamics associated with aging and radiation exposure will be required.

Department of Genetics

Overview

The Department of Genetics, headed by Dr. Kodama, is comprised of two laboratories: the Cytogenetics Laboratory and the Biochemical Genetics Laboratory. With seven professionals, the department has four members past retirement age, including the department chief and the chief of the Biochemical Genetics Laboratory.

Publications appearing in 2012 number nine, with two more in press, for a total of 11. Seven of these publications have department members as first authors, three are in Japanese, and all of this year's publications are linked to at least one RP. The number of full RPs has been decreased slightly since last year, from 18 to 14, six of which were associated with publications in peer-reviewed journals this past year. Seven external funding awards partially supported the work, including awards from MEXT, the National Institute of Radiological Sciences (NIRS), and the Japan Chemical Industry Association (JCIA). The department lists eight external collaborations, all of which are associated with at least one RP. Members of this department have also given 11 presentations at domestic meetings in the past year, plus two presentations at international meetings (one at the Environmental Mutagen Society meeting in Washington, DC, and one at the European Radiation Research Society meeting in Italy). Such presentations are important for both the exchange of ideas and for maintaining domestic and international recognition for RERF and its mission. The SAC continues to encourage the development of a stronger presence at international radiation meetings.

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

Evaluation

The SAC was pleased to see that productivity, particularly in terms of English-language publications in peer-reviewed journals, had increased significantly over that from last year. Work briefly presented during the individual department session seemed more cohesive compared to last year, and one got the impression that this group was beginning to operate as a team once again.

Two issues were raised during the previous review. The first related to concerns about changes in leadership. The SAC would have been more comfortable if direct discussion had been forthcoming to show that concerns in this area were being taken seriously regarding, for example, long-term planning in the context of impending retirements. Since four senior members including Dr. Kodama, the department chief, have already retired and are under renewal status, it is considered vital that good geneticists be either promoted or recruited to continue productivity with respect to mid- and long-term perspectives. The retirement of Dr. Nakamura is understandably regrettable, although his input, if only on a part-time basis as a consultant, adds a reassuring measure of continuity. Having said this, in light of recent improvements in the department's performance, and judging by the individual RP presentations given, Dr. Kodama has demonstrated that he is more than competent to direct the activities of this team.

The second area of concern involved prioritization of efforts directed toward embracing emerging technologies, particularly whole genome sequencing (WGS). During last year's assessment, it was suggested that perhaps an RERF workshop could be devoted to radiation research in the post-genomic era, or to a more focused theme, such as germ cell mutation detected through genomic sequencing. The SAC was heartened to find that such a workshop is scheduled to convene following this review, which we take as a positive response to that suggestion. The SAC would be interested to see how this meeting affects the department's stance on WGS, perhaps in the form of a brief statement encapsulating its position. Moreover, the presentation by Dr. Asakawa left the clear impression that the department was seriously weighing the relative benefits of WGS in the context of budgetary constraints. For both of these responses to the SAC's recommendations and concerns, the department should be commended. A competent WGS-specialized bioinformatician will be necessary if the WGS approach is embraced and used in routine analyses. It would consequently be necessary to encourage him/her to interact with other scientists within and outside RERF. One idea was to consider recruiting such a person to the Statistics Department.

Recommendations

Insofar as genetics largely forms the basic foundation of all of biology, medicine, and biomedical research, it is

important for the Genetics Department to realize they exert major influence in the way that RERF is viewed by the outside world. Ideally, they should be proactive in educating other departments and bringing them the cutting-edge tools of genetics. They find themselves now at a critical crossroads with respect to adopting so-called next-generation sequencing approaches, and decisions in this area will probably have significant impact on RERF as a whole.

Regarding the topic of WGS, the SAC makes the following observations and recommendations.

- The striking incongruity between the WGS analysis of cell lines originally done by the Beijing Genomics Institute (BGI) and then later by the Japanese research organization RIKEN is quite troublesome and yet, at the same time, rather informative about the state of affairs surrounding WGS. It underscores the absolute need for trustworthy bioinformatics, which the researchers involved fully recognize. But it raises the issue as to expense required to achieve high-quality bioinformatics input, which is almost certainly going to be large compared to sequencing proper.
- It is the opinion of the SAC that the brief foray into WGS by this department has made it acutely aware of this situation. What is unclear is whether RERF leadership, which seems committed to WGS, appreciates the resources required to make this commitment viable. The suggestion to train Dr. Satoh for the purpose of eventually providing needed bioinformatics expertise is understandable, but there is some doubt as to whether this is the best solution. As to whether the department should purchase their own sequencing machine, this would seem superfluous compared to the costs associated with bioinformatics analysis. It was the opinion of more than one SAC member that RERF should consider developing a centralized facility for the purpose of implementing WGS technology. Such a facility should also enhance the application of WGS technologies to cancer genomics, metagenomics, and transcriptomics, etc. in the other departments. A couple of other SAC members were perplexed by the choice of Epstein-Barr virus (EBV)-transformed cells for this initial pilot study in connection with genetic alterations that the immortalization process would likely produce.
- The decision as to whether RERF is willing to consider internal reapportionment of resources (as opposed to independent sources of funding) can be postponed, but not indefinitely. Otherwise, RERF may miss a golden opportunity to demonstrate scientific leadership to the scientific community about a question of significant importance, namely transmission of genetic alterations in the F_1 and subsequent progeny.
- Specific recommendations by the SAC at this time include continuing to explore the potential use of WGS as current resources allow. In so doing, they will gain experience invaluable for the purpose of more sharply focusing their expectations regarding WGS, framing essential scientific questions, and providing more accurate assessment of concomitant costs. They shouldn't waste any time doing this. We take it that the brief presentations given to the SAC represent projected areas of research emphasis for the near future. We make the following observations and/or recommendations regarding those presentations.
- The SAC was uniformly impressed by the micrographic images shown by Dr. Asao Noda that resulted from his green fluorescent protein (GFP) reporter system. One member contemplated the relevance of the approach, which is designed to detect mutations deriving from homologous recombination, when most data for ionizing radiation, including the rather convincing and interesting preliminary work by Dr. Kodaira on F_1 mice, indicate that breakpoint junctions are nonhomologous in nature. It was also commented that results using this otherwise potentially interesting and powerful system need to be more widely published.
- The work by Dr. Satoh, which utilized the same cell system and experimental approach described by Dr. Asakawa, studied single nucleotide polymorphisms (SNPs) and INDELs (insertions and deletions) in EBV-transformed lymphocytes following exposure to X rays. Until proper zero-dose controls are run, it is not possible to draw any meaningful conclusions about this approach. As it stands now, the data would seem to indicate that this system is unlikely to provide useful information, for one because there is no indication of a dose response.
- The presentation by Dr. Hamasaki builds upon observations previously made concerning transmissibility of chromosome aberrations in mice irradiated *in utero*. Similar to results found in rat mammary epithelial cells, preliminary evidence indicates that there is also transmissibility of fetal damage in mouse thyroid epithelial cells. This finding is of significance because this group had previously demonstrated that there was essentially no fetal transmission of aberrations in the blood cells of humans or spleen cells of the mouse. Hence, fetal transmissibility is probably both species- and tissue-specific. This is important work and should be continued. The comment was made that efforts might be enhanced through the use of combinatorial painting by multicolor fluorescence *in situ* hybridization (mFISH) or spectral karyotyping (SKY), although it is recognized that implementing these advantaged methods are also associated with higher costs.

Department of Epidemiology

Overview

The Department of Epidemiology continues to be central to RERF and its efforts to characterize and quantify the role of radiation and subsequent health conditions. Careful follow-up of three major cohorts is conducted by established procedures. The Epidemiology Department has developed close relationships with community hospitals and pathology laboratories to collect tissue samples for RERF studies. 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; the F_1 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.

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 that is critical for cancer and for noncancer endpoints, such as cardiovascular, liver, and thyroid diseases. Mail survey data are essential to provide information regarding potential confounders and effect modifiers. These data will assist with more accurate estimates of risk by dose, and are particularly critical for those who were exposed *in utero* or when young at the time of exposure.

It is very gratifying to see that the clear trajectory of accomplishment evidenced under the leadership of Dr. Ozasa last year has continued this year. The Epidemiology Department in conjunction with RERF has developed excellent relationships with Fukushima Medical University and the population around Fukushima, which they have carried out diplomatically and energetically. RERF can be proud of the professionalism and usefulness of the Epidemiology Department.

The department has engaged in multiple activities during the past year. There has been a continuation of the prior impressive increase in publications (33 in international journals: 22 published, eight in press, and three submitted). Many of these publications have been mid-tier journals, and have a broad audience. Another 25 publications have appeared in Japanese-language journals. Furthermore, there have been 36 presentations at multiple meetings during the past year by members of this department, a very big increase; these presentations were in Japan, Puerto Rico, Ireland, Scotland, San Diego (U.S.), Maine (U.S.), Finland, and Oxford (U.K.).

The LSS mail survey completed in 2009 has now been cleaned and is being prepared for analysis. In collaboration with the U.S. NCI, manuscripts on cancer incidence are in preparation. Updates are ongoing by using migration data from the AHS subjects to estimate time, age, gender, and city for incidence data, as it is no longer possible to obtain address information from Japan's *koseki* family registry system.

Site-specific studies with histological review are active regarding skin cancer (336 cases from 1948–1996), thyroid cancer (371 cases from 1958–2005), and breast cancer (1,732 cases) in relation to "intrinsic" subtypes by estrogen and progesterone receptors and human epidermal growth factor receptor 2 (Her2), in collaboration with a pooled analysis at Oxford University.

Data to evaluate the effects of "black rain" have been analyzed with the Department of Statistics and the Subcommittee to Review Residual Radiation Exposure and are continuing to be reviewed. Mortality data for 1950–2008 for the *in utero* cohort have been updated and analysis is ongoing. Analysis of mortality between 1946 and 2005 for the F_1 cohort is also ongoing. At this time, there appears to be no significant increase in mortality for cancer or noncancer diseases in relationship to individual parental gonadal dose.

Two years ago this department was intensively reviewed. Suggestions included (1) prioritization of projects, (2) more accurate characterization of the denominator for incidence studies, (3) a table detailing dose distributions for the various cohorts, (4) more first- or last-author publications, (5) detailed consideration of methodology, such as focus on genetic risk, comparison of incidence and mortality rates with other Japanese populations, and evaluation of exposure to medical radiation, and (6) more intensive collaborative efforts among departments. Again, the improvement hoped for is continuing. The department is currently working on 22 full-scale studies and 10 preliminary or pilot studies. These have all been thoughtfully considered, and collaborators with other institutions have assisted in bringing these studies to fruition or developed. In addition, there is clear evidence of more collaboration among the Epidemiology Department and other departments such as the Departments of Statistics and Clinical Studies.

Other collaborations have continued to be fruitful and include those with Fukushima Medical University, the University of Washington, the Asia Cohort Consortium, the U.S. NCI, Kurume University, Hiroshima University, Nagasaki University, and local hospitals.

Evaluation

The department has been generally impressive in responding to last year's critique. Collaborations are maturing and productivity continues to increase.

1. Based on the progress seen, it would appear that projects have been prioritized and consolidated.
2. The Epidemiology Department has been very productive and deserves congratulations for their efforts.
3. The collaborations developed and followed through by the Epidemiology Department are international and have a strong impact.

Recommendations

1. More staff would help this department in conducting the follow-up and day-to-day operations; this would free the scientists to complete more analyses and develop new biological hypotheses in conjunction with other scientists within RERF.
2. The F_1 and *in utero* analyses are particularly relevant and important to publish as soon as possible.
3. Finally, as recommended last year, the Epidemiology Department collaborations with other departments to develop genetic and molecular epidemiology within RERF in order to study gene-environment interactions and develop relevant genetic analyses are strongly encouraged.

In summary, there has been a continued increase in productivity, fulfilling previous promise. The SAC anticipates a continued upward trajectory.

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 six statisticians and an offer has been made to a seventh statistician. The department also has the support of two research assistants.

There is one full-scale RP on shielding and dosimetry, as well as eight type-A RPs and pilot studies, one of which has been terminated. Eighteen papers were published in English-language journals, seven of which were first-author publications—a great improvement from last year with only one first-author paper. Finally, of the 18 published papers, three were in the critical area of A-bomb dosimetry and eight were carried out jointly with the Department of Epidemiology, which has been greatly encouraged.

The Statistics Department has been responsive to most of the suggestions from the previous review. They have further developed collaborations with other research groups both in internal departments and external institutions in Japan and other countries in order to optimize their productivity.

Evaluation

Organizationally, the department appears to be functioning smoothly. It had to adjust for the loss of two senior statisticians who were not productive from a publishing standpoint. Basically, the department should continue on its trajectory and continue to follow the recommendations from last year.

- Continue to emphasize statistical collaboration, especially with the Department of Epidemiology.
- Continue the good research productivity in statistical methodological research as it relates to RERF research areas.
- Continue support of academic outreach. This should include the continued collaborations with experts in other institutions as well as making presentations at scientific meetings.
- Continue support for consulting, mentoring of junior investigators, and the career development of staff.

One of the most important departmental research activities is the work on the department's RP on shielding survey and dosimetry study. The entire RERF organization depends on having the best available dosimetry information. It is very encouraging to see the number of publications that the department has been producing in this critical area and it is important to continue giving dosimetry a high priority. The non-RERF reports on "black rain" dosimetry have made these efforts all the more important, and therefore dosimetry should be given the highest priority at RERF.

Overall, the Statistics Department has been productive in both collaborative research and basic methodology development that applies to RERF research topics. Dr. Cullings has been an effective leader of the department, and it is expected that the department will continue on its successful path. The addition of two statisticians should greatly help with the department's high level of productivity.

Recommendations

1. As previously recommended, the denominators for population incidence studies adjusting for outmigration have been updated. This information including methodologies used needs to be made generally available as do the uncertainties in these estimates. Therefore, a technical report should soon be made available.
2. The dosimetry changes and their impact on the basic LSS cancer risk estimates should be completed as soon as possible so that questions about their possible effect can be settled. Also, it is critical that the results of the research work and politics of the "black rain" issue receive support from the Public Relations and Publications Office.
3. Because of the increased demands of dosimetry, Fukushima, and intramural collaborations, additional staff should be added.
4. Continued training in bioinformatics in anticipation of collaborative support is encouraged. How soon actual statistical support in this area is needed, however, is not clear at this point in time.

Public Relations

RERF scientific activity resulted in numerous important findings in the past year, published in leading peer-reviewed journals such as the *British Medical Journal, Radiology, FASEB Journal,* and *Radiation Research*. The foundation's Public Relations and Publications Office responded with press releases for nine of these papers. These releases generated media coverage in the Japanese press, enhancing the position of RERF. Over the course of 2012, there were 21 TV stories about RERF, 123 print media stories, including 11 in the Yomiuri Shimbun and 19 in the Asahi Shimbun, and 760,000 visitors to the RERF website. It appears that there was no overseas media coverage during 2012.

At the same time, it was a challenging year in terms of public relations, with the Tokyo Broadcasting System Television, Inc. (TBS) broadcast of a critical news program entitled "First-ever coverage of the unknown reality of the RERF" on July 28, 2012. RERF believes this program misinformed the audience that ABCC had "buried" research on internal radiation exposure in the mid-1950s, and unfairly criticized RERF studies as having served no useful purpose for the A-bomb survivors as well as the people of Fukushima. RERF's response was to send a formal letter of protest to TBS on July 31; although a follow-up meeting was held in January 2013, no response was received.

The PR group does best when RERF scientists reveal novel findings in top peer-reviewed journals, so RERF scientists should strive for major publications every year and a comprehensive review every four years in a major biomedical journal. Each full-time equivalent researcher should be expected to serve as first or senior author on at least two papers each year, and effort should be taken to publish in leading general scientific and medical journals, not just radiation-specific journals.

Recommendations

- Given the challenges with media coverage of RERF in the past year, it is essential for the foundation to be proactive with the media, to consistently craft a message that reinforces the complimentary perceptions that RERF is the leading center worldwide for radiation research, and that RERF is focused on advancing the health of survivors.
- Towards this end, RERF should engage the services of a Japan-based media consulting firm and of a public relations firm.

- A response (or non-response) to any negative publicity received by RERF should be crafted in conjunction with these consultants. This will be important in light of the continuing interest in "black rain" health effects.
- Meetings and events for which there is a concern that RERF will receive significant criticism should be attended by a representative of the Public Relations and Publications Office.
- RERF should seek to enhance the perception of it as the leading radiation research organization worldwide, by obtaining coverage in leading international media outlets, including television, print media, wire services, and electronic media. RERF should be a voice for responsible, informed, unsensational information, and analysis about radiation and its relationship to public health and safety. Examples include ABC, Al-Jazeera, BBC, CBS, CCTV, CNN, NBC, PBS; *Le Monde, The New York Times, The Times, The Wall Street Journal, The Washington Post*; Associated Press (AP), Reuters, and Xinhua.
- Media coverage should be tracked for each paper, including number of media cites and media reach for each cite. A monthly media report in Japanese and English should summarize the month's coverage and be posted on the website. An annual media report should be prepared for and presented at the SAC and BOC meetings. Total media reach for 2013 should be much greater than that for 2012.
- Consideration should be given to have official participation of survivors at most RERF meetings, including the SAC meetings.
- "Model curricula, including slides for 15-minute and 50-minute lectures on the health consequences of radiation, might be prepared and mounted on the website in various languages for medical students, practicing physicians and other health care professionals, and physicians in training for radiology, radiation therapy, and general medicine, as well as graduate students in biomedical sciences. There might be merit in exploring the possibility of awarding continuing educational credits for self-directed tutorials for web-based instruction aimed at health professionals who need such credit" (39th SAC report, 2012). Fees could be charged for professional education.
- The museum display might be translated and sent to overseas museums (at their expense).
- Social media, such as LinkedIn, might be mobilized to disseminate the message and mission of RERF. Innovative approaches like QR-codes for cell phones might also be useful.
- The annual meeting of the Japan Radiation Research Society (JRRS) might be an occasion to reach students at local universities and even secondary schools with the grandeur and excitement of radiation research. Public lectures for adult learners might be offered in other major cities besides Hiroshima and Nagasaki.
- Consideration should be given to a two to four-week elective course for final year medical students in Japan and from abroad on medical care of the radiation survivors, probably in partnership with an acute care teaching hospital.
- The film "Black Sun of Hiroshima" might be given English or other language subtitles for regional distribution worldwide, by television, cinema, or DVD.
- Advantage might be taken of the new PIIF status to receive and even solicit philanthropic and charitable donations from personal and corporate friends, even alumni(ae), of RERF. A development office should be established to facilitate and optimize such donations.
- An American "Friends of RERF" organization should be established to permit tax-deductible contributions to RERF from U.S. residents.

RERF International Workshop: Heavy Structural Shielding

February 4–5, 2013, Hiroshima Laboratory

Harry M. Cullings, Chief, Department of Statistics

On February 4 and 5, 2013, an international workshop was held at RERF on radiation dose calculation for survivors who had heavy structural shielding. Heavy structural shielding refers to concrete buildings or underground air-raid shelters. Nearly all of the air-raid shelters were located in Nagasaki and consisted of tunnels dug into the side of a hill, or other, similar underground spaces. The dosimetry systems DS86 and DS02 do not contain modules for calculating the structural shielding of survivors in such situations, and those survivors have therefore been considered to have unknown doses, which represent missing values for dosimetric variables in RERF analyses. The calculation of shielding for heavy or underground structures involves special problems that do not occur with light wooden structures such as houses, for which the shielding is calculated by DS86 and DS02. In light of this situation, the RERF Dosimetry Committee decided to hold a workshop to discuss these problems and the feasibility of calculating doses for such survivors.

Opening remarks were given by Dr. Kazunori Kodama of RERF, and Dr. Stephen D. Egbert of Science Applications International Corporation provided a key lecture for the workshop. Dr. Satoru Endo of Hiroshima University and Dr. Tetsuji Imanaka of Kyoto University served as discussants. Presentations were also made by a number of RERF researchers and staff, including Mr. Tadaaki Watanabe, Mr. Tomoaki Yamashita, Mr. Takashi Oda, Mr. Hiroshi Fuchi, and Dr. Harry M. Cullings. The workshop concluded with detailed discussions and a hands-on demonstration of the models and tools used at RERF in the 1960s to produce "Globe" (spherical coordinates) data on the shielding of survivors in concrete buildings.

Mr. Watanabe reviewed the categories of survivors with unknown doses, Mr. Oda reviewed detailed data on concrete buildings, and Mr. Fuchi reviewed detailed data on air-raid shelters. Of 7,070 survivors in the Life Span Study (LSS) with unknown dose, an estimated 3,729 were in either concrete buildings (2,114) or air-raid shelters (1,615). There were at the time 24 concrete buildings in Hiroshima and 37 in Nagasaki, but many buildings contained only a few survivors, whereas a few contained many survivors. In regard to feasibility of dose calculation, almost all of the concrete buildings in Hiroshima have floor plans available, but very few of the survivors in those buildings have shielding histories that depict their location within the buildings: 979 of 1,272 survivors in concrete buildings in Hiroshima were in buildings with floor plans, but only 218 of those 979 have shielding histories. In Nagasaki, a larger fraction of survivors have shielding histories but far fewer of the concrete buildings have floor plans: 255 of 842 survivors were in buildings with floor plans, and 166 of those 255 have shielding histories. In the case of air-raid shelters, detailed floor plans and architectural drawings may not be necessary for dose calculation, but few survivors have shielding histories depicting their location within the shelter: 1,488 of the 1,615 survivors in air-raid shelters were in Nagasaki, and only 247 of those 1,488 have shielding histories. The table gives details for individual buildings in terms of the existence of floor plans and the numbers of survivors with and without shielding histories.

Doses in concrete structures vary greatly depending on the exact position of survivors within the structure for which the doses are calculated. In order to calculate doses to survivors in a heavy-shielding structure, the dosimetry system would need to calculate "shielded fluences": numbers of neutrons and gamma rays in categories of energy and direction, at various locations in the structure. There are two main problems, essentially matters of practicality, in calculating shielded fluences within concrete buildings. One problem is that heavy shielding requires a more difficult calculation: because so few of the neutrons and gamma rays impinging on the building pass through to create dose in the more heavily shielded interior locations of interest, it may require very large amounts of computer time, accurate geometries, and sophisticated biasing (putting more effort on those portions of the incident fluences that lead to the majority of the shielded fluences in the locations of interest) to do calculations with acceptable accuracy and precision. The other problem is that, unlike the Japanese houses considered by the dosimetry systems, each concrete building and each air-raid shelter is unique, which means it is necessary to build a detailed computational model and do a suite of calculations for each building or shelter. Furthermore, because the shielded fluences in a heavy structure depend so acutely on the exact survivor location within the structure, additional problems, discussed below, arise in calculating dose estimates for survivors.

Dr. Egbert gave an extensive review of the kinds of computational programs and related software that are available for such calculations. He began by illustrating the dosimetry method used in the current system and then reviewing two important papers from 1992 in which doses were calculated for the occupants of two concrete school buildings in Nagasaki.[1,2] These papers used methods much like those that would be used in a contemporary calculation and illustrated a number of important principles that would apply directly to the problems under consideration by RERF.

There are two basic computational approaches to the shielding calculation: Monte Carlo and discrete ordinates. Monte Carlo works by creating "particle histories" of neutrons and gamma rays, using rules of probability to propagate individual, imaginary neutrons or gamma rays through the shielding. Because neutrons can be captured or scattered in interactions that produce gamma rays, neutron scattering may give rise to new gamma rays according to certain probabilities. Monte Carlo is "an approximate solution to an exact problem": it can handle a very detailed model of the building, but very few histories end up

Table. Details of occupants in concrete buildings

Bldg No.	Hiroshima			Nagasaki		
	Floor plan*	SH**	No SH	Floor plan	SH	No SH
1	1	3	0	0	38	6
2	1	2	1	1	13	1
3	1	3	5	0	1	0
4	1	7	10	1	10	3
5	1	1	1	0	2	0
6	1	1	1	1	6	0
7	1	25	21	1	2	1
8	1	33	16	0	2	1
9	1	50	41	1	4	1
10	0	2	5	1	2	0
11	1	5	15	0	2	1
12	1	2	2	1	2	3
13	1	13	147	0	2	0
14	1	4	9	0	4	2
15	1	0	4	0	6	3
16	0	0	2	0	1	0
17	1	6	87	0	50	7
18	0	0	10	0	39	15
19	0	2	33	0	7	0
20	1	1	86	0	1	0
21	1	49	207	1	74	61
22	1	1	97	0	19	22
23	1	0	23	0	6	4
24	0	0	118	0	11	6
25				0	4	1
26				1	33	15
27				0	1	0
28				0	26	5
29				0	45	20
30				1	4	3
31				1	7	0
32				1	6	1
33				1	3	0
34				0	1	4
35				0	2	20
36				0	6	36
37				0	11	45
"Others"	0	8	113	0	2	100
Total	**19**	**218**	**1,054**	**13**	**455**	**387**

*1 = floor plan available, 0 = no floor plan; **Shielding history (gives location within building)

delivering dose at the location of interest, and it is difficult to obtain enough such histories at any location, let alone to map out the dose environment in the entire building. The discrete-ordinates approach works by partitioning the building into imaginary cells that constitute a "spatial mesh" and calculating differential flows of neutrons and gamma rays through the mesh. It is "an exact solution to an approximate problem": it provides solutions in every location defined by the center of a cell in the spatial mesh, but it is difficult to make the mesh fine enough to include sufficient detail of the building's structure and it is also difficult to avoid computational artifacts such as "ray effects." Dr. Egbert reviewed software packages of each method and also hybrid approaches that combine them.

Dr. Cullings reviewed several concerns relating to the statistical properties of dose estimates that appear to be possible for survivors in heavy shielding, particularly in concrete buildings, assuming that the computational problems can be solved, i.e., assuming that sufficient funding is available for acceptably precise estimates at *known locations* within a building. Many of the concrete buildings were at distances from the bombs where the unshielded dose was well above lethal levels, such that shielded doses inside the buildings could span a large range from sublethal to supralethal levels. For example, the doses inside the Chinzei School calculated by Rhoades *et al.*[1] ranged from 0.2 Gy or less at positions deep in the first floor to well above 30 Gy near the windows on the second floor, and the dose gradients as a function of location within the building are correspondingly steep. As a consequence, the fact of survival contains information about the survivor's likely position within the building and the corresponding dose: the more lethal the dose in a given location, the less likely it is that a person who survived was in that location.

For survivors who lack shielding histories to document their position (location within the building), it may be difficult or impossible to obtain a reliably unbiased estimate of dose—for example, a simple spatial average over a building containing lethal or supralethal doses in some areas would clearly be a biased overestimate. Even for survivors with shielding histories, the positional uncertainty may result in substantial dose uncertainty. In the case of the doses calculated by Rhoades *et al.*,[1] who had extremely good position information, the estimated positional uncertainty was between 30 and 90 cm in each of two horizontal directions, and the corresponding dose uncertainty was between about 3% and 56%, although almost all estimates had uncertainty of less than 30%.

In some sense a concrete building is a microcosm of the entire city, given the range of doses possible in the building and the dose uncertainty due to positional uncertainty, and there would be a need for a method to account for that dose uncertainty as is currently available for other survivors with "known" doses. There are few if any buildings that have enough surviving occupants with shielding histories to allow the dose estimates of the survivors in a building to serve as a useful estimate of the frequency distribution of doses among all possible survivors in that building. Furthermore, such estimates would be clouded by the positional uncertainty of the survivors with shielding histories, and the need to assume that the survivors with shielding histories would have the same spatial distribution as the full complement of all survivors from a building in which the occupants, including those who did not survive, were evenly distributed throughout all occupiable parts of the building. As these are likely to be untenable conditions and assumptions, one would need to consider something such as a Bayesian approach for the survivors without shielding histories. Both that approach and the method of accounting for dose uncertainty among those *with* shielding histories would have to rely on additional information such as the median lethal dose estimated by Levin *et al.*,[2] with the attendant concerns about the accuracy of that estimate and the caveat that it applies only to survivors without any concomitant injury from heat or blast trauma.

Mr. Watanabe and Mr. Oda provided a demonstration of the spherical-coordinates projector and related tools that were used in the 1960s, with scale models of the buildings and shelters, to collect "Globe" data on the shielding in various directions for survivors in heavy shielding. Those data were used in the tentative dosimetry system T65D to calculate doses, although they were considered "rough estimates" by Dr. J. S. Cheka of Oak Ridge National Laboratory in the U.S.,[3] who was a leading dosimetry physicist associated with the effort, and were considered not to be reliably accurate by Mr. Seymour Jablon.[4] The ensuing discussion clarified that, unfortunately, there is no apparent way to use the Globe data for survivors in concrete buildings, because each such building is unique. Therefore, we cannot do something analogous to what was done in DS86 and DS02 in using Globe data for survivors who were outside but near wooden houses. To devise a similar method for concrete buildings, we would calculate the doses for various positions in a model concrete building and then use the Globe data for those positions and for survivors in actual concrete buildings to relate the cases of the actual survivors to positions in the model building. However, we cannot make a model concrete building that capably represents all of the various buildings of interest.

A further general discussion on feasibility of dose calculation was held. Dr. Egbert pointed out that calculations would require detailed structural data for a building, including the thickness of walls and floor slabs, the dimensions and locations of windows, the details of any other massive structures such as pillars and beams, and the elemental compositions of all the related materials. It appears that work on the heavy shielding problem may continue with performance of calculations for some example buildings to evaluate feasibility.

I would like to thank the participants of the workshop, especially Dr. Egbert, and Dr. Douglas E. Peplow of Oak Ridge National Laboratory for granting permission for Dr. Egbert to use his instructional materials on shielding calculation, the members of the RERF Master File Section who prepared detailed materials and excellent illustrations of the available data, and the members of the Departments of Statistics and Epidemiology, as well as others at RERF who supported the workshop. Dr. George D. Kerr, an important investigator in this area, was unfortunately not able to attend the workshop, but we would like to recognize his contributions to work on this problem over the years, starting with work he did with Globe data and T65D.

References

1. Rhoades WA, Childs RL, Ingersoll DT. Radiation exposure inside reinforced concrete buildings at Nagasaki. Health Phys. 63: 510–21; 1992.
2. Levin SG, Young RW, Stohler RL. Estimation of median human lethal radiation dose computed from data on occupants of reinforced concrete structures in Nagasaki, Japan. Health Phys. 63: 522–31; 1992.
3. ABCC Interoffice Memorandum dated 22 September 1970, from Mr. M. Usagawa of the Statistics Department to Mr. Yoshida, re revision of CD#575: code for globe operation for subjects exposed inside concrete building on class of estimating dose.
4. Jablon S. ABCC Technical Report No. 23–71: Atomic bomb radiation dose estimation at ABCC. Atomic Bomb Casualty Commission, Hiroshima and Nagasaki, Japan, 1971.

— Program —

February 4, 2013

Greetings and introduction
Toshiteru Okubo (RERF)
Opening remarks
Kazunori Kodama (RERF)
"Overview of survivors with unknown doses"
Tadaaki Watanabe (RERF)
"Available data on survivors in concrete buildings"
Hiroshi Fuchi (RERF), Takashi Oda (RERF)
"Available data on survivors in air-raid shelters (Nagasaki)"
Hiroshi Fuchi (RERF), Tomoaki Yamashita (RERF)
"Available Monte Carlo codes for calculating shielding in

heavy structures”
Stephen D. Egbert (Science Applications International Corporation)
“Statistical issues and related requirements for dosimetry of survivors with heavy shielding”
Harry M. Cullings (RERF)
“Status of survivors with misclassified factory shielding and survivors in factory buildings not fitting current DS02 models”
Tadaaki Watanabe (RERF), Hiroshi Fuchi (RERF)
“Demonstration of ‘Globe’ spherical coordinate projector”
Takashi Oda (RERF), Tadaaki Watanabe (RERF)
Summary of first day’s discussion
Harry M. Cullings (RERF)

February 5, 2013
Discussion of possible updates to DS02 structural shielding calculations
Closing remarks
Roy E. Shore (RERF)

Participants

Stephen Egbert, Senior Scientist, Science Applications International Corporation, USA
Tetsuji Imanaka, Assistant Professor, Research Reactor Institute, Kyoto University
Satoru Endo, Associate Professor, Institute of Engineering, Hiroshima University

<RERF>
Toshiteru Okubo, Chairman
Kazunori Kodama, Chief Scientist
Harry M. Cullings, Chief, Department of Statistics
Kotaro Ozasa, Chief, Department of Epidemiology, Hiroshima and Nagasaki
Eric J. Grant, Assistant Chief, Department of Epidemiology, Hiroshima
Tadaaki Watanabe, Department of Epidemiology, Hiroshima
Tomoaki Yamashita, Department of Epidemiology, Nagasaki
Fumiko Nakamura, Department of Epidemiology, Hiroshima
Sachiyo Funamoto, Department of Statistics
Keiko Marumo, Department of Information Technology
Hiroshi Fuchi, Department of Epidemiology, Nagasaki
Takashi Oda, Department of Epidemiology, Hiroshima

RERF International Workshop: Radiation and Cardiovascular Disease

February 5–6, 2013, Hiroshima Laboratory

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

The RERF Department of Clinical Studies, with the help of the Cardiovascular Disease (CVD) Working Group, hosted a two-day international workshop titled "Radiation and Cardiovascular Disease" on February 5 and 6, 2013, in the Auditorium of the Hiroshima RERF.

Recent results of the Life Span Study (LSS) have showed that increased mortality risk from heart disease and stroke is associated with radiation dose. Looking at the risk by subtype showed no significant association with ischemic heart disease, cerebral infarction, cerebral hemorrhage, or subarachnoid hemorrhage, whereas significant associations between radiation dose and hypertensive heart disease, rheumatic heart disease, and heart failure were observed. In addition, increased risk of myocardial infarction has been observed in the Adult Health Study (AHS), for example, among female survivors exposed to over 2 Gy at less than 40 years of age. Although no consistent trend has been observed with regard to stroke, recent reports indicate that the risk of hemorrhagic stroke increases with radiation dose in both males and females.

Based on this background, experts in relevant fields in Japan and abroad, along with RERF research scientists, made presentations at the workshop to discuss the following questions: What is consistent or inconsistent in the study results for radiation-associated CVD? What mechanisms are important for radiation-associated CVD at high- and low-dose exposures? What are the measurable indicators for evaluation of radiation-associated CVD? Which statistical methods are useful for evaluating radiation-associated CVD risk?

On the first day of the workshop, Dr. Fred A. Mettler, Jr. (University of New Mexico) offered a broad-based review of findings and problems pertaining to radiation risk and cardiovascular disease. He spoke from the viewpoint of general concepts and studies of radiation therapy, radiation workers, A-bomb survivors, and animal experiments. Subsequently, Dr. Kotaro Ozasa (Chief, RERF Department of Epidemiology) gave a lecture titled "Epidemiological studies of cardiovascular disease in the LSS"; Dr. Peter Jacob (Helmholtz Zentrum München) presented "Radiation dose responses of LSS cardiovascular disease mortality"; and Dr. Nobuhiko Ban (Tokyo Healthcare University) offered "Considerations for dose response of radiation-related cardiovascular disease." The session sparked active discussion about the importance of dose-response evaluation by subtype and period, and about how to assess dose response by taking risk factors into consideration.

During the afternoon session, Dr. Steven E. Lipshultz (University of Miami) delivered a lecture titled "Cardiomyopathy following radiation exposure in the childhood cancer survivor cohort." He explained study results (including his own) based on vast amounts of data from long-term follow-up of a childhood cancer survivor cohort (considering, for example, heart disease risk by subtype and the effects on growth hormones by cranial irradiation). Dr. Ikuno Takahashi (Research Scientist, RERF Department of Clinical Studies) then presented "Overview of studies on cardiovascular disease in the AHS" and Dr. Fiona Stewart (Netherlands Cancer Institute) considered "Biological mechanisms of radiation-induced cardiovascular disease." Discussion during this session focused on different biological mechanisms of radiation-induced cardiovascular diseases for high-dose exposure as opposed to low-dose exposure, whole body exposure as opposed to local/cranial exposure, and various cardiovascular disease subtypes. Participants emphasized that more appropriate markers (examinations and biomarkers) need to be selected, taking the aforementioned biological mechanisms into consideration, in order to correctly assess radiation-induced cardiovascular disease risk.

On the second day, following a lecture by Dr. Toru Nabika (Shimane University) on "Genetic analysis of stroke-prone spontaneously hypertensive rats (SHRSP)—a genetic model rat of stroke," Dr. Norio Takahashi (Consultant, RERF Vice Chairman's Office) presented "Animal study for radiation and cardiovascular disease in RERF." Dr. N. Takahashi's study uses SHRSP hypertensive rats at RERF and is conducted in collaboration with Dr. Yasuharu Niwa (Associate Senior Scientist, RERF Department of Radiobiology/Molecular Epidemiology). A significant finding from the study indicated that a correlation was observed between radiation exposure (1–4 Gy) and cardiovascular disease development based on the SHRSP rat model, with characteristic histopathology in the brain, heart, and other organs of the irradiated rats. This result served to focus attention on the importance of research at lower dose ranges.

The concluding session was an overall discussion debating future directions for RERF's cardiovascular disease studies. The two-day discussions were summarized by Drs. Kazunori Kodama, Kotaro Ozasa, Masazumi Akahoshi, and Roy E. Shore. The speakers, chairpersons, and others are now preparing a meeting report, which will be submitted to an international journal.

— Program —

February 5, 2013

Opening remarks
Toshiteru Okubo, RERF

Session I. Update on assessment of radiation risks of cardiovascular disease

Chair: Kazunori Kodama (RERF)

Introduction of participants
Kazunori Kodama (RERF)

Aims and outline of the workshop
Waka Ohishi (RERF)

"Review of studies on radiation risks of cardiovascular disease"
Fred A. Mettler, Jr. (University of New Mexico)
"Epidemiological studies of cardiovascular disease in the LSS"
Kotaro Ozasa (RERF)
"Radiation dose responses of LSS cardiovascular disease mortality"
Peter Jacob (Helmholtz Zentrum München)
"Considerations for dose response of radiation-related cardiovascular disease"
Nobuhiko Ban (Tokyo Healthcare University)

Session II. Clinical research on radiation and cardiovascular disease

Chair: Fiona Stewart (The Netherlands Cancer Institute)
"Cardiomyopathy following radiation exposure in the childhood cancer survivor cohort"
Steven E. Lipshultz (University of Miami)
"Overview of studies on cardiovascular disease in the AHS"
Ikuno Takahashi (RERF)
"Biological mechanisms of radiation-induced cardiovascular disease"
Fiona Stewart (The Netherlands Cancer Institute)

Discussion (Sessions I and II)

February 6, 2013

Session III. Animal models for radiation and cardiovascular disease

Chair: Norio Takahashi (RERF)
"Genetic analysis of stroke-prone spontaneously hypertensive rats (SHRSP)—a genetic model rat of stroke"
Toru Nabika (Shimane University)
"Animal study for radiation and cardiovascular disease in RERF"
Norio Takahashi (RERF)

Discussion (Session III)

Session IV.

Chairs: Roy E. Shore (RERF), Masazumi Akahoshi (RERF)
Overall discussion (Commentators: Kazunori Kodama [RERF], Masazumi Akahoshi [RERF], Kotaro Ozasa [RERF])
Discussion
Summary
Recommendations for projects on cardiovascular disease at RERF
Others

Closing remarks
Roy E. Shore (RERF)

Participants

<Speakers> (presentation order)
Fred A. Mettler, Jr., Clinical and Emeritus Professor, Department of Radiology, University of New Mexico, New Mexico Federal Regional Medical Center
Peter Jacob, Acting Director, Institute of Radiation Protection, Helmholtz Zentrum München
Nobuhiko Ban, Professor, Tokyo Healthcare University
Steven E. Lipshultz, Professor, Department of Pediatrics, Leonard M. Miller School of Medicine, University of Miami
Fiona Stewart, Associate Professor, the Netherlands Cancer Institute
Toru Nabika, Professor, Department of Functional Pathology, Shimane University School of Medicine
(RERF)
Kotaro Ozasa, Chief, Department of Epidemiology, Hiroshima and Nagasaki
Ikuno Takahashi, Research Scientist, Department of Clinical Studies, Hiroshima
Norio Takahashi, Consultant, Vice Chairman's Office

<Observers>
Satoshi Maruyama, Deputy Director, General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare

<RERF>
Toshiteru Okubo, Chairman
Roy E. Shore, Vice Chairman
Takanobu Teramoto, Executive Director
Kazunori Kodama, Chief Scientist
Nori Nakamura, Consultant, Department of Genetics
Waka Ohishi, Acting Chief, Department of Clinical Studies, Hiroshima
Yoshiaki Kodama, Chief, Department of Genetics
Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology
Yasuharu Niwa, Associate Senior Scientist, Department of Radiobiology/Molecular Epidemiology
Harry M. Cullings, Chief, Department of Statistics
Hiroaki Katayama, Chief, Department of Information Technology
Masazumi Akahoshi, Chief, Department of Clinical Studies, Nagasaki
Michiko Yamada, Chief, Division of Health Examinations, Department of Clinical Studies, Hiroshima
Yukiko Shimizu, Part-time Professional, Department of Epidemiology, Hiroshima

RERF International Workshop: RERF Radiation Research in the Post-genomic Era

March 7–8, 2013, Hiroshima Laboratory

Yasunari Satoh, Research Scientist, Laboratory of Biochemical Genetics, Department of Genetics
Yasuharu Niwa, Associate Senior Scientist, Laboratory of Cell Biology, Department of Radiobiology/ Molecular Epidemiology

An international workshop was held on March 7 and 8, 2013, at the RERF Hiroshima Laboratory, under the theme "RERF Radiation Research in the Post-genomic Era."

In recent years, research based on next-generation sequencing (NGS) has been flourishing in the fields of medical science and biology. NGS enables the collection of enormous amounts of experimental data never before possible. Although next-generation sequencers have not yet been introduced at RERF, it is essential for RERF to use NGS technology in its future research. The goal of the workshop was to discuss possible uses of NGS in determining radiation-induced mutation rates in human germ cells, and in studying radiation effects related to carcinogenesis, immune function, and epigenetics. Both of these research areas are important aspects of RERF's mission, and nine researchers well known in these fields in Japan and abroad were invited to participate in the workshop to talk about recent progress in NGS-based research and future research possibilities at RERF using NGS.

Dr. Yoshiaki Kodama (Chief, RERF Department of Genetics) inaugurated the event by introducing the workshop's aims and speakers. Dr. Jun-ichi Asakawa (Senior Scientist, RERF Department of Genetics) followed with a presentation titled "Brief notes on transgenerational effects of A-bomb radiation."

The workshop consisted of five sessions. In the first, "*De novo* mutations in germ cells," Dr. Yoichi Gondo (RIKEN; RERF Scientific Advisor) gave a lecture on "High-resolution detection of germline single nucleotide variations in the mouse by next-generation re-sequencing." He reported that 1) NGS was used to detect base substitutions in the genome of F_1 mice produced by mating C57BL/6J male mice exposed to N-ethyl-N-nitrosoures (ENU), a chemical mutagen, with ENU-untreated DBA/2J female mice; 2) whole-exome sequencing was used to sequence approximately 50 Mb of the mouse genome that encompasses virtually all of the mouse coding regions; 3) about 100 ENU-induced base substitutions per F_1 mouse were detected; and 4) two of the strengths of this method were that a reliable mouse genome sequence—the sequence of the C57BL/6J mouse strain decoded in the Mouse Genomes Project—was used as the reference sequence, and that the information about 600,000 known single nucleotide polymorphisms (SNPs) existing between the two strains of C57BL/6J and DBA/2J was used as the positive control.

The next speaker of the first session was Dr. Katie Campbell (University of Washington), who presented a talk titled "Estimating the human mutation rate using autozygosity in a founder population," reporting on a study of large Hutterite families living in the United States. She reported that the aim of the study was to estimate the natural mutation rate in humans by examining almost identical regions of two chromosome strands of paternal and maternal origins that resulted from having a distant common ancestor on the paternal and maternal sides. The analysis showed a mutation rate of 1.21×10^{-8} mutations per base pair per generation, which increased 9-fold for bases within CpG dinucleotides (9.72×10^{-8}).

In the second session, "Detecting genetic variation and mutation using next-generation sequencer," Dr. Ryan Mills (University of Michigan) gave a talk titled "Mapping structural variation by population-scale genome sequencing," in which he presented the results of the 1,000 Genomes Project Consortium. He first reported on the results of the pilot phase of the project, which analyzed the whole genome sequences of 179 individuals across four ethnic groups: about 22,000 distinct deletions and 6,000 insertions and tandem duplications were detected. He also reported on the results of a subsequent phase of the project that analyzed an additional 1,092 individuals across 14 ethnic groups.

Dr. Mills' talk was followed by a presentation from Dr. Akihiro Fujimoto (RIKEN) on "Comprehensive analysis of genetic variation by whole genome sequencing." Dr. Fujimoto reported on the results of the first whole genome sequencing (WGS) of a Japanese individual, and of WGS of 27 hepatocellular carcinoma (HCC) cases. He reported 1) that about three million SNPs and 5,000 deletions were found in the WGS of the Japanese individual; 2) that a list of recurrently mutated genes in HCC was generated from the latter (27 HCC cases) WGS; 3) that multiple chromatin regulators were mutated in about half of the tumors in the HCC WGS; and 4) that hepatitis B virus genome integration in the telomerase gene or the *MLL4* gene was frequently observed in HCC associated with hepatitis B.

In the third session, "Some data and ideas for future studies," Dr. Yasunari Satoh (Research Scientist, RERF Department of Genetics) talked about a study, "Model experiments using irradiated human cultured cells," being conducted in the Department of Genetics.

In the fourth session, "Applications of high-throughput sequencing to the immune system," Dr. Harlan Robins (Fred Hutchinson Cancer Research Center) presented a talk on "Profiling the adaptive immune system with high-throughput sequencing." He reported the results of detailed analyses using NGS of the immune system reconstructed by hematopoietic cell transplantation and the T-cell receptor repertoire in tumor-infiltrating lymphocytes. Dr. Ituro Inoue (National Institute of Genetics) then presented "Comprehensive analyses of *HLA* genomic region," reporting on methods of human leukocyte antigen (*HLA*) genotyping with NGS.

In the fifth session, "RNA sequencing and epigenetics," Dr. Yongli Xiao (U.S. National Institute of Allergy and Infectious Diseases) presented "High throughput RNA sequencing of an autopsy tissue sample from the 1918 influenza

pandemic." He reported that his team, using NGS, had sequenced the flu virus genome and transcripts extracted from formalin-fixed and paraffin-embedded (FFPE) lung tissue samples from two influenza pandemics, in 1918 and 2009. They succeeded in almost completely recovering the genome sequences of both flu viruses, 1918 and 2009, and identified an immune-related gene expressed in lung tissues as well as bacterial sequences associated with secondary bacterial infections. He also reported on the effectiveness of application of duplex specific nuclease (DSN) for minimizing ribosomal RNA effects.

Dr. Haruhiko Siomi (Keio University) followed with a talk titled "Small RNA-mediated transposon silencing," reporting on PIWI, an element involved in the silencing of retrotransposons in the gonad. The presentation also described discovery of new functions of retrotransposons in genome evolution, and of such molecular complexes as small temporal RNAs. Dr. Akira Watanabe (Kyoto University), addressing the topic "Genome and epigenome analysis of iPS cells for regenerative medicine," talked about the use of NGS to construct genomic and epigenomic databases with the aim of producing clinically applicable induced pluripotent stem (iPS) cells. He reported that his team found a slight variation in the gene structure among iPS clones, and determined that a genomic and epigenetic match between iPS cells and the donor's somatic cells is essential in the clinical application of iPS cells. The presentations in this session made everyone realize anew the importance of epigenetics in the post-genomic era.

The symposium concluded with a roundtable discussion chaired by Dr. Yoichiro Kusunoki (Chief, RERF Department of Radiobiology/Molecular Epidemiology). Symposium participants also toured the facilities and learned more about RERF's research.

RERF benefited greatly from the symposium because RERF researchers were able to actively communicate with the visiting speakers and obtain their expert advice and cooperation concerning ongoing research at RERF as well as studies in the planning stages. These include model experiments using irradiated human cells in culture, studies of transgenerational radiation effects using mice, methods for detection of mutations and estimation of mutation rates, analysis of T-cell repertoires and epigenomics using archived lymphocytes that have been donated by A-bomb survivors on an ongoing basis, and RNA sequencing using autopsied tissue samples from A-bomb survivors.

— Program —

March 7, 2013

Opening remarks
Toshiteru Okubo (RERF)

Introduction
Aims of this workshop and introduction of speakers
Yoshiaki Kodama (RERF)
"Brief notes on transgenerational effects of A-bomb radiation"
Jun-ichi Asakawa (RERF)

Session#1: *De novo* mutations in germ cells
Chair: Yasunari Satoh (RERF)
"High-resolution detection of germline single nucleotide variations in the mouse by next-generation re-sequencing"
Yoichi Gondo (RIKEN)
"Estimating the human mutation rate using autozygosity in a founder population"
Katie Campbell (University of Washington)

Session#2: Detecting genetic variation and mutation using next-generation sequencer
Chair: Katie Campbell (University of Washington)
"Mapping structural variation by population-scale genome sequencing"
Ryan E. Mills (University of Michigan)
"Comprehensive analysis of genetic variation by whole genome sequencing"
Akihiro Fujimoto (RIKEN)

Session#3: Some data and ideas for future studies
Chair: Jun-ichi Asakawa (RERF)
"Model experiments using irradiated human cultured cells"
Yasunari Satoh (RERF)

Round-table discussion

Session#4: Applications of high-throughput sequencing to the immune system
Chair: Tomonori Hayashi (RERF)
"Profiling the adaptive immune system with high-throughput sequencing"
Harlan Robins (Fred Hutchinson Cancer Research Center)
"Comprehensive analyses of HLA genomic region"
Ituro Inoue (National Institute of Genetics)

March 8, 2013

Session#5: RNA sequencing and epigenetics
Chair: Ituro Inoue (National Institute of Genetics)
"High throughput RNA sequencing of an autopsy tissue sample from the 1918 influenza pandemic"
Yongli Xiao (U.S. National Institute of Allergy and Infectious Diseases)
"Small RNA-mediated transposon silencing"
Haruhiko Siomi (Keio University)
"Genome and epigenome analysis of iPS cells for regenerative medicine"
Akira Watanabe (Kyoto University)

Round-table discussion
Chair: Yoichiro Kusunoki (RERF)

Closing remarks
Roy E. Shore (RERF)

Participants

<Speakers> (Presentation order)

Yoichi Gondo, Team Leader, Mutagenesis and Genomics Team, BioResource Center, RIKEN Tsukuba Institute

Katie Campbell, Senior Fellow, Eichler Lab, Department of Genome Sciences, University of Washington

Ryan E. Mills, Assistant Professor, Department of Computational Medicine and Bioinformatics, University of Michigan Medical School

Akihiro Fujimoto, Senior Scientist, Laboratory for Medical Informatics, Center for Genomic Medicine, RIKEN

Yokohama Institute
Harlan Robins, Associate Member, Program in Computational Biology, Fred Hutchinson Cancer Research Center
Ituro Inoue, Professor, Division of Human Genetics, National Institute of Genetics
Yongli Xiao, Staff Scientist, Taubenberger Lab, Viral Pathogenesis and Evolution Section, Laboratory of Infectious Diseases, U.S. National Institute of Allergy and Infectious Diseases
Haruhiko Siomi, Professor, Department of Molecular Biology, Keio University School of Medicine
Akira Watanabe, Assistant Professor, Genome/Epigenome Analysis Core Facility, Center for iPS Cell Research and Application, Kyoto University
(RERF)
Jun-ichi Asakawa, Senior Scientist, Laboratory of Biochemical Genetics, Department of Genetics
Yasunari Satoh, Research Scientist, Laboratory of Biochemical Genetics, Department of Genetics

<RERF>
Toshiteru Okubo, Chairman
Roy E. Shore, Vice Chairman
Nori Nakamura, Consultant, Department of Genetics
Yoshiaki Kodama, Chief, Department of Genetics
Yoichiro Kusunoki, Chief, Department of Radiobiology/Molecular Epidemiology
Waka Ohishi, Acting Chief, Department of Clinical Studies, Hiroshima
Kotaro Ozasa, Chief, Department of Epidemiology, Hiroshima and Nagasaki
Harry M. Cullings, Chief, Department of Statistics
Mieko Kodaira, Chief, Laboratory of Biochemical Genetics, Department of Genetics
Tomonori Hayashi, Assistant Chief, Department of Radiobiology/Molecular Epidemiology
Kiyohiro Hamatani, Chief, Laboratory of Cell Biology, Department of Radiobiology/Molecular Epidemiology
Yasuharu Niwa, Associate Senior Scientist, Laboratory of Cell Biology, Department of Radiobiology/Molecular Epidemiology
Kengo Yoshida, Research Scientist, Laboratory of Immunology, Department of Radiobiology/Molecular Epidemiology

<Observers>
John J. Mulvihill, Children's Medical Research Institute/Kimberly V. Talley Chair in Genetics; Professor of Pediatrics; Head, Section of Genetics, University of Oklahoma Health Sciences Center
Evan B. Douple, Former Associate Chief of Research, Radiation Effects Research Foundation
Isaf Al-Nabulsi, Japan Program Manager and Senior Technical Advisor, Office of Health, Safety and Security, U.S. Department of Energy
Toshiya Inaba, Professor, Department of Molecular Oncology and Leukemia Program Project, Research Institute for Radiation Biology and Medicine, Hiroshima University
Hirotaka Matsui, Associate Professor, Department of Molecular Oncology and Leukemia Program Project, Research Institute for Radiation Biology and Medicine, Hiroshima University
Akinori Kanai, Assistant Professor, Department of Molecular Oncology and Leukemia Program Project, Research Institute for Radiation Biology and Medicine, Hiroshima University