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Summary of the Second Bill Morgan Memorial Symposium: An update on low dose biology, epidemiology, its integration and implications for radiation protection

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Dr. William Francis Morgan, known as Bill to many of his friends and colleagues, passed away on 13 November 2015, at the age of 62 years (Hamada et al. 2016, 2017). To commemorate the first anniversary of his passing, the first two-part Bill Morgan Memorial Symposium was held in October 2016 in Kona, Hawaii, USA, during the 62nd Annual Meeting of the Radiation Research Society (RRS) : part one was on “Biology, Epidemiology and Radiation Protection” (Held and Hamada 2017), part 2 on “Low Dose Epidemiology” (Salomaa et al. 2017). On the fifth anniversary of Bill’s passing, the second Memorial

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Symposium “Low dose biology, epidemiology, its integration and implications for radiation protection: an update” was held in October 2020 during the 66th Annual Meeting of the Radiation Research Society. The plan was to hold a face-to-face meeting in Kona, Hawaii, USA, but this was changed to a fully virtual meeting due to the pandemic of coronavirus disease 2019 (COVID-19). The symposium was co-chaired by Evagelia C. Laiakis and Nobuyuki Hamada, and consisted of three recorded presentations, a live question and answer (Q&A) session for specific questions to each presentation, and a general discussion session. The entire session was recorded and the recording was made available to all participants through the RRS annual meeting website until 20 November 2020 (https://na.eventscloud.com/website/14445/rrs20home/).

First, Gayle E. Woloschak gave a recorded presentation entitled “Effects of low dose radiation on animals” (Paunesku et al. 2021). She presented an outline of the results of work done by the International Commission on Radiological Protection (ICRP) Task Group 91 on “Radiation Risk Inference at Low-dose and Low-dose Rate Exposure for Radiological Protection Purposes” particularly emphasizing the contributions of animal studies to the work. The importance of archival datasets was highlighted especially in light of the work that Morgan had done in making the world-wide community aware of large animal studies that had been conducted by the US Department of Energy and by several groups in Europe. These archives include the European Radiation Archive and the Northwestern University Radiation Archive, both of which have put large datasets on the internet available freely to others. These databases came to fruition following multiple discussions between Morgan and Woloschak highlighting the importance of making such data freely available to the scientific community. An update on animal studies done since the Committee on the Biological Effects of Ionizing Radiation (BEIR) VII provided dose and dose rate effectiveness factor (DDREF) calculations along with determinations of dose-rate effects on cancer induction. Conclusions were (1) that raw data from archival animal studies provide important resources for a re-analysis of data with novel computational and statistical techniques and (2) that a DDREF for doses <4 Gy can be estimated close to 2 based on many differently designed rodent studies conducted worldwide. In addition, a comparison was made between animal studies in the Northwestern University Radiation Archive and recent studies done by the Institute for Environmental Sciences in Japan; comparisons of these two studies revealed marked similarities in radiation-induced toxicities in the mice with most differences occurring in respiratory system, digestive system and non-neoplastic endpoints. Interestingly the results also revealed that sham-irradiation of mice conveyed a greater risk with increasing fractionation, most likely because of the stress of taking animals to the radiation center with high frequency.

Second, Mark P. Little gave a recorded presentation entitled “Low- and moderate-dose non-cancer effects of ionizing radiation, especially circulatory and ocular diseases: a review of the epidemiology and radiobiology” (Little et al. 2021). There is a well-established association between very high doses (>5 Gy) of ionizing radiation exposure and damage to the circulatory system (Adams et al. 2003). In the last twenty years, an accumulating body of evidence suggests that lower dose exposures (<0.5 Gy) are also associated with circulatory disease, in particular in the Japanese atomic bomb survivors (Shimizu et al. 2010; Little et al. 2020) and in various occupationally-exposed cohorts (Gillies et al. 2017;

Azizova et al. 2018a). As summarized by Little, there is reasonably consistent evidence of most major types of circulatory disease, in particular ischemic heart disease and stroke; however, excess relative risks per unit dose in low- and moderate-dose epidemiological studies are somewhat variable, possibly a result of confounding and effect modification by well known (but unobserved) risk factors. Radiation doses of 1 Gy or more have been known for over 70 years to be associated with increased risk of posterior subcapsular cataract, in particular in the Japanese atomic bomb survivors and a few other groups exposed at high dose and high dose rate (Neriishi et al. 2012; Worgul et al. 2007). There is accumulating evidence of excess risks at lower doses and low dose rates in the Chernobyl liquidators, US Radiologic Technologists and Russian Mayak nuclear workers (Little et al. 2021). In general most of these studies suggest that cortical cataracts may also be associated with ionizing radiation, although there is less evidence (in two out of five studies with information on this endpoint) that nuclear cataracts are radiogenic. A linear dose-dependence was assumed, and the subsequent analysis yielded a linear dose-response with a positive slope, indicative of detrimental effects. For other ocular endpoints, specifically glaucoma and macular degeneration, there is very little evidence of effects at low doses (Little et al. 2018; Bragin et al. 2019). Glaucoma has the characteristics of a tissue reaction (formerly deterministic effect), with a relatively large threshold dose (>5 Gy) below which no excess is observed (Little et al. 2018; Hamada et al. 2019). There is some evidence of neurological detriment following low-moderate dose (~0.1–0.2 Sv) radiation exposure in utero or in early childhood (Otake and Schull 1998; Hall et al. 2004; Little et al. 2021), but little consistent evidence of any other type of non-cancer disease (Little et al. 2021).

Third, Vinita Chauhan provided a recorded presentation entitled “The integration of the adverse outcome pathway framework to radiation risk assessment” (Chauhan et al. 2021). In chemical toxicology, an approach is used that offers a means to capture available mechanistic knowledge in the literature and link it to outcomes of relevance to chemical toxicity, namely the adverse outcome pathway (AOP). AOPs are a conceptual framework for organizing scientific knowledge on the causal linkage between a molecular initiator of a specific biological event, and a consequent adverse outcome considered relevant to regulatory decision-making. In 2012, the Organisation for Economic Co-operation and Development (OECD) launched the AOP framework to improve efficiency for chemical safety assessment. The AOP approach is a collaborative tool that maps measured key events at all levels of biological organization to an adverse outcome of regulatory significance (Ankley et al. 2010; OECD 2016). AOPs begin with a molecular initiating event and are empirically supported through evidence using the Bradford Hill (B-H) viewpoints (Hill 1965; Becker et al. 2014; Villeneuve et al. 2014). Bringing this approach to the field of radiation research would help to better organize current knowledge on radiation effects. In the session, the AOP framework was discussed in the context of the chemical field including how it can be applied to the area of radiation research; a vision for integration was provided. It was highlighted that AOPs could be adopted as a method to inform issues of high to low dose extrapolation, have utility in supporting low dose radiation risk assessment, and create a paradigm within which radiation research priorities may be developed. However, for this approach to be successful, the radiation research community would need to come together to assess the literature and help harness these data in a systematic manner for incorporation

into the AOP framework. Steps towards integration would involve knowledge transfer to the scientific community by engagement of journals, societies and international governing bodies. Networking and focused workshops jointly with the chemical community would also be an important element to a path forward. A starting point could be a horizon style scanning survey that aims to identify global the applicability of the AOP framework to address scientific and regulatory needs of the radiation protection community. This could pose a possibility for a collaboration between the radiation and chemical research communities that could identify the opportunities and challenges for a successful implementation of AOPs into the radiation field.

In the live Q&A session following these three presentations, questions addressed to Woloschak regarding future directions focused on introduction of artificial intelligence (AI) in data analysis for low dose radiation effects on human health and whether such datasets exist to initiate such efforts. Machine learning based approaches have previously been used to analyze DDREF inferred from data on 120,000 animals from the US and Europe. Work done on supercomputers at the Argonne National Laboratory has previously used AI approaches and they are available if needed for animal studies. In addition, discussion on generating an omics-based dataset for low dose radiation results, similar to National Aeronautics and Space Administration's (NASA's) GeneLab (Berrios et al. 2020), reiterated the need to develop a centralized data hub, while funding for low dose radiation programs still remains at an all-time low level in the US (Cho et al. 2019), even though the amount of data that has been generated could easily justify the need. Mark Little expanded on cataracts, mentioning that whereas cortical cataracts have been seen in several radiation-related cohorts (Hamada et al. 2020), nuclear cataracts are the typical age-related cataracts and have been observed in only a few radiation studies (e.g. in the Mayak workers, Azizova et al. 2018b). Chauhan was asked about the challenges that could be expected while implementing an AOP for a less deterministic endpoint, such as cognitive detriment. Chauhan explained that the whole premise of the framework is to better organize existing and new studies to help direct future research. In building a qualitative AOP, the steps are similar irrespective of whether or not the adverse outcome is less deterministic such as cognitive effects. The greatest challenge will come when quantifying the AOP where inconsistencies in the literature arise, and less deterministic events may be difficult to predict. Chauhan further highlighted that while data are diverse, another premise of an AOP is to highlight the universality of a biological response across different stressors, and that events, which are mechanistically well-defined, can then be more predictive of disease progression.

Finally, three shorter live presentations were given within the general discussion session. The first two presentations dealt with the US National Council on Radiation Protection and Measurements (NCRP) Report No. 186 "Approaches for integrating information from radiation biology and epidemiology to enhance low-dose health risk assessment" (NCRP 2020), first by Michael M. Weil from a biology viewpoint and then by Mark P. Little from a modeling viewpoint. The development of biologically based dose-response (BBDR) models for cancer will require input from experimental studies. Of particular importance will be the identification of key events in radiation carcinogenesis, the target cells in which those events must occur, and how each event impacts cell proliferation or loss and the likelihood of subsequent events. Several murine models of radiation carcinogenesis are

sufficiently developed to be useful in parameterizing and testing BBDR models, in particular radiation-induced acute myeloid leukemia and thymic lymphoma. Among BBDR models for cancer, multiple pathway models are thought to be a particularly likely way of describing the biology, which can be to some extent experimentally tested. Most BBDR models for circulatory disease are for atherosclerosis, the process underlying most major types of circulatory disease (e.g. ischemic heart disease, stroke). A generalized model, a form of multi-stage clonal expansion model that incorporates multiple pathways (Little et al. 2008, 2010), would be appropriate for integrating most data for cancer from epidemiology and radiation biology. However, this modeling framework is less well understood for circulatory disease. The AOP framework on the other hand is still likely to be appropriate for these biological endpoints. Finally, Vinita Chauhan gave an overview of the new Canadian project to develop AOP for space flight non-cancer health outcomes, such as ocular, circulatory, and neurological diseases. Relevant studies that are consistent with the modified B-H viewpoints for causality were identified from a preliminary screening of the literature using well-defined search criteria. Studies were retrieved using typical search engines and literature databases sourced from NASA, the Canadian Space Agency, and authoritative reports (e.g., ICRP publications and NCRP reports/commentaries). The current AOP Wiki was also screened to identify any existing AOPs that could be leveraged. These studies guided the development of an AOP network for adverse outcomes of cardiovascular disease, impaired learning/memory, bone loss, and cataracts. Recommendations from field experts were taken into consideration for finalizing the key events for each of the individual adverse outcomes. Preliminary screening identified over 400 studies that met components of the B-H viewpoints. Most available literature was derived from cell, animal and human space research. Evidence was extracted from the 30 years of long-duration missions and from ground-based studies. Radiation studies were predominantly used to identify the key events, however other space stressors (microgravity and environment) were also considered. The proposed qualitative AOP network contained a total of 19 key events, beginning with “deposition of energy” as the molecular initiating event. Shared key events across some of the adverse outcomes were identified at the macro-molecular level. Further complete screening of the literature will be needed to finalize the overall weight of evidence for key event relationships in the AOP. The proposed AOP network can help in the development of strategies to mitigate risks from space travel, inform standards, and identify biomarkers that may be useful for the development of countermeasures. A scoping review is ongoing to confirm the overall weight of evidence for all the proposed key event relationships.

A final question in the session was directed towards identifying the differences between AOPs and the classic multistage clonal expansion models of cancer. Little addressed this by noting that the generalized multistage clonal expansion models developed for cancer are another way of integrating the biological data and it is well consistent with AOP framework. Chauhan further added that the two indeed complement each other very well: the AOPs allow for the assembly of knowledge to defined key events that are measurable and essential to achieve the adverse outcome which can then be used to validate model parameters in the biologically-based model approach.

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Biographies

Evagelia C. Laiakis, Ph.D, is an Associate Professor in in the Department of Oncology at Georgetown University. She received her Ph.D. degree from the University of Maryland at Baltimore under the mentorship of Dr. William F. Morgan. She is an elected Council Member to NCRP and has been serving at PAC-1 since 2016. She is also a Councilor-at-Large of the Radiation Research Society, the recipient of the 2019 Jack Fowler Award, and a dedicated mentor to students and postdocs.

Vinita Chauhan, Ph.D, is a research scientist at the Consumer and Clinical Radiation Protection Bureau of Health Canada. She graduated with a Ph.D in Biochemistry from the University of Ottawa and has been employed at Health Canada for the past 20 years. She is a member of the High Level Group on Low Dose Research and Extended Advisory Group on Molecular Screening and Toxicogenomics of the OECD.

Mark P. Little, D.Phil, joined NCI Radiation Epidemiology Branch (REB) in 2010, and was promoted to a Senior Investigator in 2012. Previously (2000-2010), he worked in Imperial College London, and before that (1992-2000) at UK National Radiological Protection Board (now part of Public Health England). He is a member of Council of NCRP, and has served as consultant to UNSCSEAR, to IAEA, to ICRP (in particular as member of ICRP Task Group 91), to the UK COMARE, and to NCRP SC 1-21 and 1-26. In REB, Dr. Little is working on assessment of leukemia risk in persons exposed at low doses and dose rates, cancer risk in various groups exposed as result of the Chernobyl accident, on risks of various health endpoints in the US radiologic technologists, and on treatment-related second cancer risks in various populations. He has particular statistical interests in machine learning algorithms and dose measurement error models. He has over 280 publications in the peer-reviewed literature.

Gayle E. Woloschak, Ph.D, is a Professor of Radiation Oncology and Professor of Radiology at Northwestern University’s Feinberg School of Medicine. She is currently Chair of NCRP PAC 1, a member of ICRP Committee 1, and a member of the US delegation to UNSCEAR.

Michael M. Weil, Ph.D, is a Professor of Cancer Genetics at Colorado State University. He is the Director of the NASA Specialize Center of Research on Carcinogenesis and a member of NCRP PAC1.

Nobuyuki Hamada, RT, Ph.D, is a Senior Research Scientist at CRIEPI Radiation Safety Research Center and a Visiting Professor at Hiroshima University Research Institute for Radiation Biology and Medicine. He serves on ICRP Task Groups 102 and 111, NCRP PAC 1, IRPA Phase 3 Task Group on the implementation of the eye lens dose limits, Consultation Committee on AOP development for space flight health outcomes (Canadian project), and Scientific Committee for the 2021 MELODI Workshop on AOP for radiation effects. He has published >125 papers in peer reviewed international journals.

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