Paper

RAPID RADIATION DOSE ASSESSMENT FOR RADIOLOGICAL PUBLIC HEALTH EMERGENCIES: ROLES OF NIAID AND BARDA

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Abstract—**A large-scale radiological incident would result in an immediate critical need to assess the radiation doses received by thousands of individuals to allow for prompt triage and appropriate medical treatment. Measuring absorbed doses of ionizing radiation will require a system architecture or a system of platforms that contains diverse, integrated diagnostic and dosimetric tools that are accurate and precise. For large-scale incidents, rapidity and ease of screening are essential. The National Institute of Allergy and Infectious Diseases of the National Institutes of Health is the focal point within the Department of Health and Human Services (HHS) for basic research and development of medical countermeasures for radiation injuries. The Biomedical Advanced Research and Development Authority within the HHS Office of the Assistant Secretary for Preparedness and Response coordinates and administers programs for the advanced development and acquisition of emergency medical countermeasures for the Strategic National Stockpile. Using a combination of funding mechanisms, including funds authorized by the Project BioShield Act of 2004 and those authorized by the Pandemic and All-Hazards Preparedness Act of 2006, HHS is enhancing the nation's preparedness by supporting the radiation dose assessment capabilities that will ensure effective and appropriate use of medical countermeasures in the aftermath of a radiological or nuclear incident.**

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INTRODUCTION

GLOBAL TERRORIST groups have expressed interest in obtaining and using nuclear and radiological materials against civilian populations, and illicit trafficking of radioactive materials is well documented. Although the U.S. Government has adopted a primary strategy of prevention and interdiction with respect to such threats, it must be ready to respond if an attack occurs, as noted by Homeland Security Presidential Directive 18 (HSPD-18). To facilitate planning using common scenarios, the federal government, in partnership with state, local, territorial, and tribal governments, developed 15 National Planning Scenarios. Among these are two for catastrophic incidents that would result in radiation exposures of the general public: The detonation of a 10-kiloton (10 KT) improvised nuclear device (IND) and the deployment of a radiological dispersal device (RDD). Models of a 10 KT detonation suggest that in a large metropolitan area, over one million individuals will desire assessment of their exposure levels, and up to two hundred thousand may receive absorbed doses over 2 Gy. An anticipated RDD incident would likely cause deleterious exposures of hundreds of people as determined by models of such incidents (Conklin 2005; Wood et al. 2008). Other scenarios of concern include the deployment of a radiological exposure device (RED), which could result in the surreptitious exposure of large numbers of civilians; accidents at or attacks on nuclear power plants or nuclear fuel reprocessing facilities; and accidents involving the loss or dispersion of industrial or clinical radiography sources.

IONIZING RADIATION—EFFECTS AND MEDICAL MANAGEMENT

The deadly effects of ionizing radiation are wide-ranging and encompass both systemic and organ-specific

damage (Fig. 1). Radiation injury to various physiological systems and tissues may result from external exposure to ionizing radiation (IR) and/or from the uptake of radioactive materials by inhalation, ingestion, skin absorption, or wound contamination, and the effects of radiation injury can be potentiated with additional trauma and/or thermal burns (combined injury) (Anno et al. 1989; Ledney et al. 1994; Cassatt et al. 2005; Flynn and Goans 2006; Bertho et al. 2008; Cassatt et al. 2008; DiCarlo et al. 2008; Okunieff et al. 2008; Zou et al. 2008). Acute effects of high-dose ionizing radiation (>2 Gy) include depletion of specific types of peripheral blood cells (Dainiak 2002), immune suppression (Chao 2007), mucosal damage, and potential injury to other sites such as bone and bone marrow niche cells, lung, kidney, and central nervous system (Okunieff et al. 2008). Even exposures to low or moderate doses (1–3 Gy) of IR can result in increased mortality if accompanied by physical injuries, opportunistic infections, and/or hemorrhage (Scott et al. 1998; Flynn and Goans 2006; Zhao et al. 2006). Long-term effects include dysfunction or fibrosis in a wide range of organs and tissues and, ultimately, a higher risk of cancer (Terzoudi and Pantelias 2006). In most cases, the deadly effects of high (>2 Gy) radiation exposure can be mitigated by early appropriate triage and treatment decisions.

Hematopoietic recovery depends on prompt treatment, to preserve or enhance the ability of the residual stem cells and progenitor cells to proliferate and differentiate sufficiently to reconstitute the immune and hematopoietic systems early enough to prevent otherwise lethal infections and hemorrhage (Herodin and Drouet 2005; Singh et al. 2008). Other radiation injuries may not manifest immediately. The severity of radiation injury is generally a function of the dose received and variables such as dose rate, heterogeneity of partial-body exposures, and radiation quality (e.g., high vs. low linear energy transfer). This latency and dose-dependency afford an opportunity to administer appropriate mitigating and therapeutic agents prior to the full expression of acute tissue injury, potentially improving outcomes.

The Strategic National Stockpile (SNS) contains a number of emergency medical countermeasures for effects of radiological and nuclear incidents, and the Department of Health and Human Services (HHS) is pursuing development and acquisitions that will further enhance its capability to counter the range of acute and long-term injuries that can result from such incidents, whether accidental or intentional. However, because current and foreseeable medical countermeasures for radiation injuries are often expensive, labor-intensive and time-consuming to administer (and monitor), limited in availability, and occasionally associated with serious toxicities, they should be administered only to persons who will likely benefit from their use. Fast, accurate radiation dose assessment will greatly facilitate identification of exposed people who could benefit from early intervention. Clinical and diagnostic evaluation of those individuals receiving radiation doses sufficient to cause acute injury is critical for the optimal management of such patients (Fliedner et al. 2001, 2008).

Significant radiation accidents are rare; however, historically they have prompted substantial anxiety in populations at risk of exposure, even in those without obvious injury or illness. The public response to the accidents at Three Mile Island and Chernobyl, and the dispersion of ^{137}Cs sources in Goiânia, Brazil, illustrate

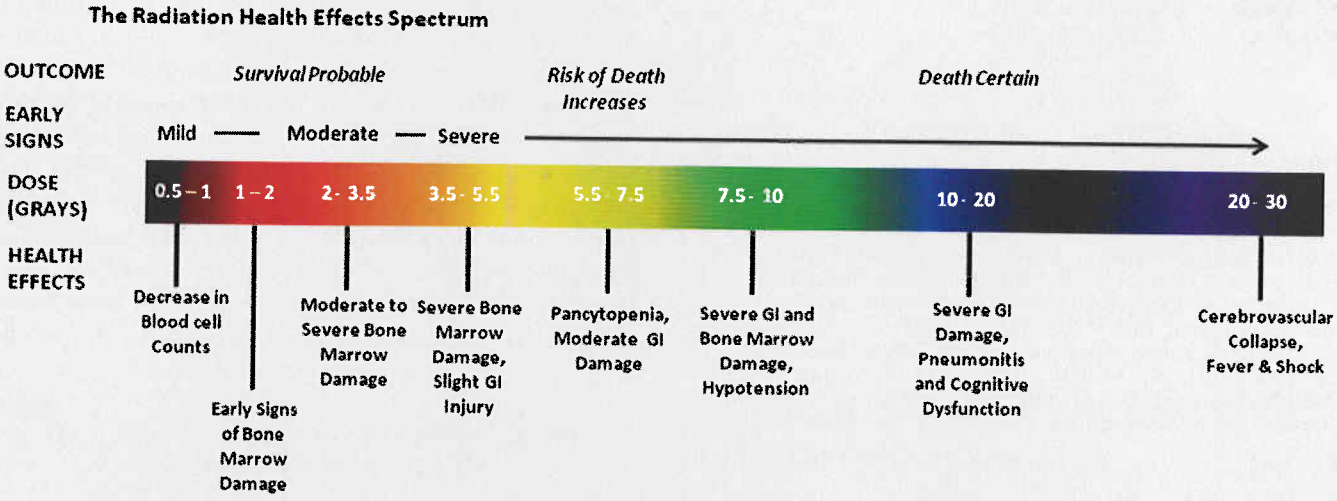

Fig. 1. Spectrum of effects associated with absorbed doses of ionizing radiation. Outcomes indicated are for a continuum of radiation effects alone (not combined with other injuries), with supportive care.

the stress that such incidents produce in civilian populations and frame much of the government's thinking about the requirements for responses to future accidents or terrorist incidents (Collins 2002; Chernobyl Forum 2006). The Goiânia, Brazil, ^{137}Cs incident evolved to present a widespread civilian fear of radiation risk—more than 100,000 people requested to be evaluated using the then-current technologies, which proved to be slow and cumbersome (Lipsztein et al. 1991; Maletskos and Lushbaugh 1991; Melo et al. 1994; De Oliveria et al. 2001; Anjos et al. 2002; Thongpraparn et al. 2002; Steinhausler et al. 2005). Assuaging the anxiety of individuals and providing a basis for categories of "no exposure," "exposed with immediate need," or "exposed with a requirement for long-term risk estimation" will be among the most important roles in early triage and diagnostics. Rapidly addressing individual exposure to IR will potentially reduce the immediate demand for medical services and enable providers to concentrate on the acutely injured.

HHS GOALS FOR RADIATION DIAGNOSTICS AT THE POINT OF CARE

Unfortunately, no rapid point-of-care single-time-point diagnostic that can reliably discriminate levels of IR exposure currently exists. The complete blood count, particularly the absolute lymphocyte count, is useful, but optimally requires at least two samples preferably spaced 6–12 h apart to estimate dose. The diagnostic "gold standard" in the field of radiation biodosimetry, the dicentric chromosome assay, is labor-intensive and slow, and its use in mass casualty situations would be problematic. The overarching technical requirement is for a dose assessment architecture, or system of platforms, that contains both diverse and integrated elements, each of which possesses a sensitivity and specificity appropriate for the diagnostic problem at hand.

The rationale for developing improved radiation diagnostics is five-fold. Such tools will (1) identify patients requiring urgent medical assessment (the target population for therapies); (2) provide assurance to anxious individuals who received radiation doses below the threshold for immediate concern; (3) improve risk assessment for the delayed or late effects of radiation exposure; (4) improve patient tracking efficiency for repeated observation or therapeutic administration; and (5) potentially have a role in the monitoring of therapy and long-term follow-up (for example, biomarkers of damage and recovery to assess pharmacologic effect and potential long-term cancer risk). Collectively, these benefits will enhance the medical and operational responses to radiation incidents of all types.

The dosimetric and diagnostic tools must be sufficiently accurate and precise to enable appropriate triage and treatment decisions. For large-scale incidents, rapidity and ease of screening are essential. Tools for primary triage decisions must be suitable for use in the field, including appropriate portability and ease of use. Secondary and tertiary triage, as well as long-term follow-up, can be done at specialized care facilities with diagnostic tools compatible with those settings.

The PHEMCE

The HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) leads and coordinates, in collaboration with other agencies, the HHS mission to develop and acquire medical countermeasures that will improve public health emergency preparedness, to prevent and mitigate the adverse health consequences associated with chemical, biological, radiological, or nuclear (CBRN) and naturally occurring threats (Fig. 2). The 2007 HHS *PHEMCE Implementation Plan for CBRN Threats* (www.hhs.gov/aspr/barda/phemce/enterprise/strategy) identified the top priorities for medical countermeasure research, development, and acquisition programs that

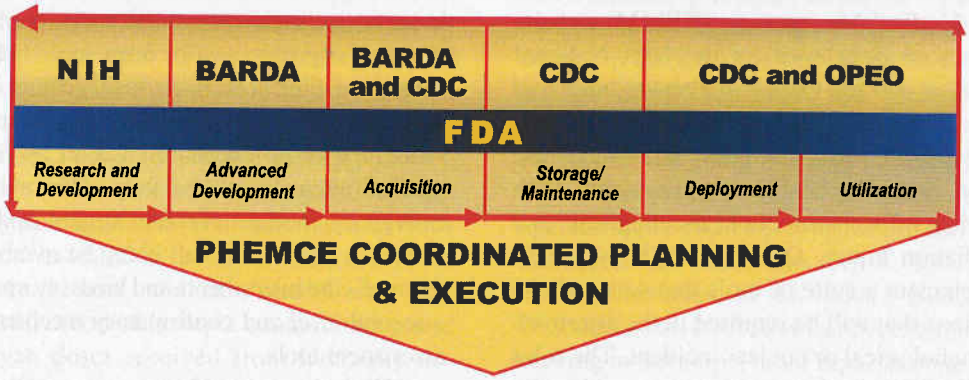

Fig. 2. PHEMCE coordination of the HHS pathway, from research and development of medical countermeasures through their deployment and utilization.

HHS has determined, in collaboration with interagency partners, to have the greatest potential to improve public health emergency preparedness. Biodosimetry and bioassay capabilities, including both rapid biodosimetry assays for on-scene triage and a laboratory system capacity, were called out as high priorities in this report.

Research and development toward improved, high-throughput systems for the diagnosis of radiation injury include cytogenetic, genomic, proteomic, metabolomic, immunologic, and physiochemical approaches predictive of radiation injury (Blakely et al. 2003; Grace et al. 2002; Megid et al. 2007; Okunieff et al. 2008, Bertho et al. 2008; Chaudry 2008; Tyburski et al. 2008). Funding for such efforts has been provided by a variety of governmental agencies, including, among others, HHS's National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health (NIH; www3.niaid.nih.gov/research/topics/radnuc/program/radiationBiodosimetry.htm) and Biomedical Advanced Research and Development Authority (BARDA; www.hhs.gov/aspr/barda); and the DoD's Defense Threat Reduction Agency (DTRA; www.dtra.mil) and Defense Advanced Research Projects Agency (DARPA; www.darpa.mil). Radionuclide bioassay capabilities are supported at the Centers for Disease Control and Prevention (CDC; www.bt.cdc.gov/radiation).

Given the high consequence but lower probability of an IND incident and the number of different possible radiation exposure scenarios, platforms that can serve more than one purpose make the most economic sense. HHS is taking this approach with therapeutic products where feasible. For example, an agent useful for ARS can also have potential use for organ-sparing and recovery of non-target injuries from radiotherapy treatments or from radiotherapeutic pharmaceuticals, such as tumor-targeting radiolabeled monoclonal antibodies.

Enhancing the use of the current and evolving physical or biological dosimetric techniques is the goal of the Radiation Emergency Assistance Center/Training Site (REAC/TS; orise.orau.gov/reacts), as well as the Radiation Event Medical Management (REMM) website (www.remm.nlm.gov) developed by the NIH National Library of Medicine and the Office of Preparedness and Emergency Operations (OPEO) within the Office of the Assistant Secretary of Preparedness and Response (ASPR). REMM provides health care providers with accurate, up-to-date information about the diagnosis and treatment of radiation injury. One PHEMCE goal is to develop and implement a suite of tools that can perform diagnostic functions that will be required in the aftermath of a significant radiological or nuclear incident. The roles of NIAID and BARDA in this mission are specifically described in more detail below.

The roles of NIAID and BARDA

HHS assigned NIAID the leadership role in managing basic research efforts to develop medical treatments and diagnostics for CBRN threats. BARDA was established by the Pandemic and All-Hazards Preparedness Act of 2006 to coordinate and administer civilian programs for the advanced development and acquisition of emergency medical countermeasures for the SNS. NIAID and BARDA collaborate, working closely with the Food and Drug Administration, to promote product development of promising candidate emergency medical countermeasures and radiation dose assessment tools. In general, NIAID supports early research and development, and BARDA supports advanced development. Sustained research and development efforts, in close collaboration with cutting-edge research being conducted in the private sector, will ensure a robust pipeline that is aligned with HHS PHEMCE requirements for radiation dose assessment capabilities. This pipeline is sustained in BARDA by diverse funding sources, including those authorized under the Project BioShield Act of 2004 and the Pandemic and All-Hazards Preparedness Act of 2006. NIAID has been funding some projects jointly with BARDA under a memorandum of understanding.

Recently BARDA released a Sources Sought Notice (RFI-BARDA-08-21A; https://www.fbo.gov/?s=opportunity&mode=form&id=997f67c8155b32dfa03e01951dfa77cc&tab=core&_cview=0) to gather information on technologies and manufacturing capabilities to meet specified radiation dose assessment requirements. Technologies cited by respondents included proteomics, metabolomics, lipidomics, genomics, electron paramagnetic resonance, optically stimulated luminescence, and many others. The technologies included some field-ready approaches.

Proposed biodosimetry architecture

Fig. 3 presents a schematic representation of a notional system for radiation dose assessment. After a radiation incident, point-of-care diagnostics will be needed. In particular, rapid-assessment tools for immediate determination of exposure will be immensely helpful in screening, triage, and clinical facilities management in a mass casualty incident. Persons having a rapid-assessment tool that reveals little or no exposure (<2Gy) are less likely to seek medical attention immediately. This will help relieve the emergency medical services system and eventually other medical systems that will likely be overburdened. Hospital point-of-care instruments and bioassay systems will serve as a second level and confirmatory mechanism for the rapid-assessment tools.

High-throughput bioassay systems that will measure absorbed dose, rather than simple exposure (incident IR),

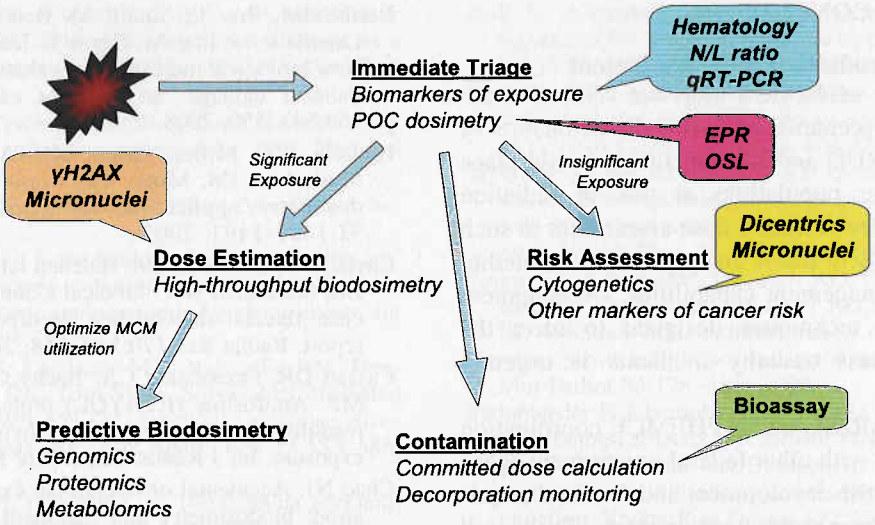

Fig. 3. Proposed radiation dose assessment architecture showing the use of exemplar dosimetry, including biomarker assays, from immediate assessment through determination of contaminating radionuclide burdens and effect of decorporation therapy. γH2AX—phosphorylation of histone H2AX on serine 139 at sites flanking DNA double-strand breaks (DSBs) can provide a measure of the number of DSBs within a cell; Bioassay—biological assay; Dicentrics—chromosomes having two centromeres; EPR—electron paramagnetic resonance also known as electron spin resonance (ESR); MCM—medical countermeasure; Micronuclei—Small masses of nuclear material that are a hallmark of genetic toxicity; N/L ratio—neutrophil/lymphocyte ratio; OSL—Optical Stimulated Luminescence; POC—Point-of-Care; qRT-PCR—quantitative reverse-transcriptase polymerase chain reaction.

will enable segregation of exposed or concerned individuals among these groups: (1) those with significant absorbed doses that will need immediate attention; (2) those who will need attention in the next few weeks; and (3) those who received limited or no exposure and may only require longer-term monitoring (due to increased risk of cancer or other disease). Organ-specific radiation injury may be determined using "predictive biomarkers" (sometimes called "predictive biodosimetry") that can be assessed following organ or tissue injury. These biomarkers may allow the identification of persons at risk for specific injuries (partial body organ irradiation, for example) and will facilitate optimal use of available medical countermeasures.

Persons receiving whole body absorbed doses below the threshold for serious acute effects (<2 Gy) will still need accurate dose estimation for risk assessment of long-term complications such as cancer and cardiovascular disease, and this information will inform the need for further population monitoring and/or specific therapeutic intervention (Terzoudi and Pantelias, 2006). Finally, in circumstances that result in individuals becoming internally contaminated with radionuclides (fallout contamination or RDD), radiochemical assays of blood, urine, sputum, hair, and skin/wound sites will facilitate the identification of isotopic contamination and estimation of organ doses received from internally deposited nuclides. These assays will also enable monitoring of the effectiveness of decorporation (chelation) therapy (Hogan and Kellison, 2002; orise.orau.gov/reacts/dose-est-compendia.htm; www.internaldosimetry.com).

Another major goal in designing and creating new biomarker methodologies or instruments for point-of-care use is establishment of the relationship to the current standard metric. As mentioned above, cytogenetic analysis (i.e., dicentrics and translocations) is the longstanding "gold standard" assay for assessment of the absorbed IR dose. This assay was developed for, and has been successfully applied to, dose exposures exceeding 0.1 Gy, up to 5 Gy (Lloyd et al. 1992, 2000; Ramalho et al. 1998; Wilkens et al. 2008). Application of cytogenetic assays for mass screening, however, would be difficult and costly, as chromosome analyses are time-consuming and require highly skilled personnel. In addition, some technical considerations constrain estimation of doses below 0.1 Gy (Lloyd et al. 1992, 2000; Ramalho et al. 1998; Wilkens et al. 2008). Developments in modern molecular biology techniques have brought novel biomarkers into consideration that might uncover a new "gold standard." Toward this end, sentinel biomarkers are being investigated from conserved cellular signal transduction pathways that govern DNA repair, apoptosis, cell-cycle arrest pathways, and genomic stability (Blakely et al. 2003; Grace et al. 2002; Marchetti et al. 2006; Dressman et al. 2007; Bertho et al. 2008; Okunieff et al. 2008; Paul and Amundson 2008). HHS is seeking to develop a more rapid, biomarker-related "gold standard" that validates all new point-of-care absorbed-dose bioassays.

CONCLUSION

Path forward for radiation dose assessment

Radiation dose assessment tools are critical to address mass casualty scenarios involving the detonation of an IND. Although RDD and RED incidents would place substantially smaller populations at risk of radiation injury, the demand for radiation dose assessment in such incidents is still likely to strain, and probably overwhelm, current medical management capabilities. Development of new and rapid techniques designed to meet the requirements of mass casualty incidents is urgently needed.

NIAID and BARDA, under PHEMCE coordination and in collaboration with other federal government agencies, are supporting the development and eventual acquisition of radiation dose assessment products. These will enable appropriate triage and medical treatment in a mass casualty radiological incident. NIAID development of new dosimetric tools and products is a primary conduit for the advanced development and acquisition that is the responsibility of BARDA. Together with the FDA's Center for Devices and Radiological Health (CDRH; www.fda.gov/CDRH), and working in collaboration with partners such as DARPA and DTRA, BARDA and NIAID provide the main development pathway for mass casualty dosimetry within the USG. Within the PHEMCE process, feedback is provided to this development pathway from the ultimate "end users" within the federal government and at the state, local, and tribal levels. This coordinated process ensures that the dose assessment tools, techniques, and systems developed will enhance the nation's preparedness for radiological or nuclear incidents.

AUTHORS' ADDENDUM

In February 2009, HHS/BARDA issued a Broad Agency Announcement (BAA-BARDA-09-36) for point-of-care and high-throughput biological assays or systems for determining absorbed ionizing radiation doses and expects to award one or more contracts in 2009.

HHS/BARDA also issued BAA-09-34 open to accept white papers and Quad Charts for biodosimetry tools as well as medical countermeasures to treat and assess various aspects of acute radiation syndrome.

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