I. Introduction: Radiobiology and Radiobiologic Methods Course from the Center for Medical Countermeasures Against Radiation (CMCR) Consortium

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I. Introduction:

Since the discovery of the radioactivity of Uranium by Antoine-Henri-Bacuerel in 1896, and radium by Marie and Pierre Curie in 1897, and the discovery of x-rays in 1895 by William Conrad Roentgen, scientists and clinicians have been fascinated by the physical and biological effects of ionizing irradiation (1). This fascination has led to both highly positive and significantly negative consequences. The first therapeutic usesof ionizing irradiation were both for imaging the body and treating cancers. These uses led to the discovery that diagnostic images of internal organs, principally bone, could be adapted for the care of patients. The publicized x-ray photograph taken in 1895 of the hand of Pierre Curie showing his ring, has been reproduced in radiology textbooks and lectures throughout the world (1). The Fields of Diagnostic Radiology, Nuclear Medicine, and Radiographic Imaging have guided physicians and healthcare professionals to decades in the management of millions of patients worldwide.

In Therapeutic Radiology (Radiation Oncology) implantation of ionizing irradiation sources including radium was based on the discovery that gamma rays (photons) emitted by radium and beta rays (electrons) could be utilized for brachytherapy approaches to the management of head and neck, uterine, cervical, and endometrial cancers and to deliver irradiation to prostate cancer, as well as to metastatic lesions from a wide variety of tumors.

In recent decades, highly focused x-ray beams have been utilized to treat benign diseases including vascular malformations, cranial nerve abnormalities, such as Trigeminal Neuralgia, and benign tumors of nerves within the skull including: acoustic neuromas. Most recently, novel radiation therapy techniques including Proton beam radiotherapy, Carbon ion radiotherapy, and neutron beams have come into clinical use. The advances in both diagnostic radiology including new imaging techniques and therapeutic radiology (Radiation Oncology) have provided great medical benefits to society.

Understanding the physical properties of ionizing irradiation as distinct from ultraviolet irradiation, radio waves, and thermal irradiation are indispensable for an understanding of the safe uses and dangers of therapeutic radiation (1).

In addition to medical uses of ionizing radiation, radiocarbon dating by measuring radio-isotope decay has provided valuable insight into the fields of paleontology and anthropology. In the field of Cosmology an understanding of ionizing radiation emissions from deep space has allowed mapping of the origins of the universe. In biological sciences, new approaches toward understanding the evolution of organisms on Earth have also been aided by study of early organism adaptation to ionizing irradiation, which penetrated the primordial planetary atmosphere of Earth. Irradiation measurement techniques have provided valuable information to studies of both the origin of life and the evolution of species.

Unfortunately, there are profoundly negative consequences of ionizing irradiation. At the turn of the 20th Century, scientists and clinicians using early x-ray machines and radioisotopes, learned the painful consequences of over-exposure (1). Ionizing irradiation toxicity to normal tissues was observed in the first patients (and physicians) to have radio-isotope implants or prolonged and multiple external radiographic irradiation exposures. Both scientists and the clinicians suffered significant normal tissue damage (radiation burns) and the late effect of carcinogenesis including solid tumors and leukemias. Ionizing irradiation was shown to induce chromosome breaks (visible by microscopy), depletion of white blood cells, principally immunocytes (T-cells, B-cells, NK cells), and a variety of organ specific radiation damage events. Dose response curves for death and toxicity were shown to differ between animal species and some microorganisms (insects) were shown to be highly radioresistant (1).

The discipline of Radiation Safety developed as a result of early reports of toxicity to humans, and came into use in the mid-20th Century. Based on early experiments showing severe toxicity to the unborn fetus and consequences of radioisotope uptake by the mother, there developed an understanding of the half-life (T1/2) of inhaled or ingested individual radioisotopes. The extreme longevity was reported for the biologic effects of some transuranium isotopes (Uranium^{235}) deposited in bones and other organs.

Nowhere, have the deleterious effects of ionizing irradiation been more obvious than in the consequences in the discovery of nuclear fission and fusion. Devastating consequences was observed with the original victims of the 1945 atomic bombings in Hiroshima and Nagasaki, Japan were widely reported. The genotoxic effects observed in several subsequent generations of the Japanese Atomic Bomb survivors led to an expansion of the developing field of Radiation Biology. Since the fission bomb explosions in 1945, and subsequent thermonuclear fusion bomb tests in the late 1940s and 1950s, there have also been concerns over atmospheric dispersal of radioisotopes (1). The harnessing of nuclear fission for power generation and the build-up of both nuclear power plants and nuclear weapons facilities, spent nuclear fuel dumps and nuclear-weapons stockpiles have led to several reports of nuclear accidents. A compilation of data from these accidents, including most recently that in Chernobyl, 1986 and in Fukushima in 2011 utilized new and sophisticated radioisotope and radiation measurement techniques. These data have increased our understanding of the consequences of environmental radiation contamination, particularly the consequences of having radiation-emitting long-lived radioisotopes in the human body or in the environment. Nuclear power plants and nuclear bomb detonation sites are monitored for these isotopes (2).

During the decades following 1945, sometimes referred to as the “Cold War” (1945 – 1998), there was increased production and stock-piling of hundreds of nuclear weapons. The fission core of a thermonuclear weapon consists of a fission bomb. Original fission bombs used Uranium 235 and then prominently Plutonium 239 for the fission reaction causing detonation. Plutonium was also stockpiled for creation of “breeder reactors” to produce more weapons grade fissionable isotopes, but also led to peaceful uses of plutonium in nuclear power plants. The breeder reactors led to large quantities of fissionable material, and during the “Cold War”, the production of hundreds of fission core devices for detonation of fusion reactions in thermonuclear weapons (Hydrogen bombs) has created a potential large supply of these original materials. At the end of the “Cold War” with the decreased threat of global nuclear war, there has appeared a new danger. The nuclear fission cores for thermonuclear weapons may, in the wrong hands, produce three categories of devastating radiation terrorist devices: 1) nuclear fission bomb, 2) dirty bomb (conventional bomb disperses the isotopes in the fission core), and 3) willful dispersal (without an explosion) of the fission core radioisotopes into the environment.

Efforts to address these potential problems have include a need for planning a response to each type of event.

The Center for Medical Countermeasures (CMCR) Program was initiated 2005 by the National Institutes of Health, as part of an overall counter-terrorism program. Started originally in response to the 9/11 “Twin Towers”, Pentagon, and rural Pennsylvania terrorist attacks, the Department of Homeland Security through the National Institutes of Health, created a radiation counter-terrorism program (See Chapter XXXVI of the web-based textbook). This collaboration was started between the National Institute of Allergy and Infectious Diseases (NIAID) and the National Cancer Institute (NCI), and included a targeted funding for two main areas of research: 1) the development of new physical and biological dosimeters, so that large numbers of possible casualties of a radiation terrorist event could be appropriately triaged based on dose of radiation experienced; and also for 2) the development of radiation medical countermeasures to treat casualties.

For countermeasures discovery and development three concepts were established: 1) *radiation protection* (agent given before exposure), 2) *radiation mitigation* (agent given after exposure, but before onset of illness), and 3) *treatments* for visible and physically apparent radiation injuries (2). Perhaps most importantly, the development of better radiation biology, radiation physics, and triage methods for medical management of irradiated humans, became a National priority. After the “Cold War”, concern for irradiated casualties was focused on an expected smaller number of potential victims. Radiation biologists, radiation physicists, physicians, and other medical personnel, who utilized radiation in their clinical practice worked on understanding the parameters of over-exposure. The CMCR Program now in its 13th year, consists of four Consortium participant centers throughout the United States, and has led to exciting new discoveries in multiple areas of radiation biology, radiation dosimetry, and radiation countermeasures. The CMCR Program has evolved into a consortium of four centers, and a central management team at NIAID, which functions as an integrated program through which to manage the discovery, development and implementation of new and significant discoveries.

A primary task of the CMCR consortium is education. Therefore, we have designed and implemented this web-based Radiobiology Methods teaching tool. It is the purpose of this "virtual textbook" to provide to the general scientific and educational community a clear overview of radiation biology and radiation dosimetry, and to carry out ongoing updates in the chapters and interact with readers during the evolution of new advances by programs of the CMCR Consortium. This educational tool has been designed to provide basic information for students at all levels: 1) in primary to secondary education, 2) graduate students, 3) post-doctoral fellows, 4) medical students, and 4) established scientists, physicians, and healthcare personnel at all levels. This tool has also been designed to lead users to more advanced information in each area, and encourage readers to contact the authors of each section with questions and for discussions.

There is already an existing availability of a number of radiobiology textbooks. It is not the goal of the present web-based document to provide an overview of radiobiology, rather we seek to emphasize methods currently in use for study of each of several different topics of relevance to the CMCR mission. The Table of Contents lists specific topics relative to the CMCR Program and is the focus of educaiton.

To prepare this tool, the CMCR Consortium has utilized the expertise of its own members from the four centers (Columbia University, UCLA, Duke University, and the University of Pittsburgh), as well as a spectrum of experts in physics, general medicine, radiation biology, radiation dosimetry, veterinary medicine, immunology, hematology, and related fields to provide a comprehensive and dynamic teaching approach.

The table of contents indicates topics, authors, and their expertise, and will be an evolving, edited, and updated web-based tool. Each section is designed to provide basic information and more detailed information, appropriate primary references, and ways to contact each author. Most importantly, the sections are designed to be updated by the authors frequently. Those who utilize this tool are encouraged to contact the authors of each section (Email addresses are attached to each author in Table of Contents) for more detailed information and for discussions.

References:

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