Tribute to AFRRI on Its 50th Anniversary and Perspectives on the History and Future of Radiation Biology and Health Protection

Thomas S. Tenforde

National Council on Radiation Protection and Measurements, President

AFRRI Golden Jubilee Banquet

May 12, 2011

Topics of Discussion

- **Evolution of Radiation Biology Since the Mid-20th Century**
- **Tribute to AFRRI -- 50 Years of Outstanding Scientific Achievements**
- **Major Challenges Today in Radiation Biology and in the Future**
- **Moving Towards an Understanding of the Biological Interactions and Potential Health Effects of Low-Dose Radiation Exposures**

Evolution of Radiation Biology Over the Last 50 Years

- **Mid-20th Century: Radiobiology was primarily a phenomenological science --**
  - **-- Survival of single cells irradiated *in vitro***
  - **-- Carcinogenesis in irradiated laboratory animals: rodents, dogs, monkeys, etc.)**
  - **-- Simple models of carcinogenesis (dicentric chromosome aberrations, chromatid deletions, cellular mutation, and neoplastic transformation studied *in vitro*)**

Evolution of Radiation Biology Over the Last 50 Years (cont'd)

- Radiobiology has evolved into a more sophisticated molecular, mechanism-based science, with the goal of understanding the basic causes of cancer and other diseases
- Evolution of genomics, proteomics, and metabolomics as basic components of explaining disease causation
- Use of complex models of tissue interactions with radiation and other stressors
- Increasing recognition of the importance of understanding potential health effects of radiation exposure, including very low doses

Tribute to AFRRI – Early Foundations of a National Resource

- **1958 – DoD Bureau of Medicine and Surgery proposed to Air Force Special Weapons Project, later named Defense Atomic Support Agency (DASA), that a facility be established to study human radiation effects**
- **1960 -- Congress approved DASA-sponsored construction of a 14,905 ft^2 laboratory and 2,500 ft^2 animal facility in Public Law 86.5000**

Tribute to AFRRI – Establishment in the 1960s

- Ground breaking began in November, 1960, and the research facility was occupied in January, 1962 and fully operational by September, 1963
- AFRRI was formally established by DoD Directive 5154.16 on May 12, 1961
- Special facilities were provided at AFRRI, including a TRIGA reactor (initial criticality attained on June 28, 1963), a high-dose ^{60}Co facility, a 54-MeV linear accelerator, and a low-level ^{60}Co irradiation facility

Tribute to AFRRI – Threat to Its Existence in Early 1990s

- With the end of the "Cold War" in 1991 questions were raised about the need to continue funding of AFRRI
- However, a strong evaluation of AFRRI research by the American Institute of Biological Sciences, coupled with the development of nuclear weapons capabilities in other nations (*e.g.*, India and Pakistan) and nuclear power plant accidents at TMI and Chernobyl, led to strong support from DoD officials for continuation of AFRRI funding

Tribute to AFRRI – Moving With the Times in Extending the Sophistication and Goals of Biomedical Research on Radiation Effects

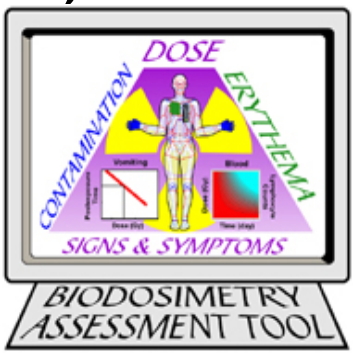
- AFRRI's primary mission over 50 years has been research on biomedical effects of ionizing radiation to which both military personnel and the civilian population might be exposed in the event of a nuclear detonation or accident
- Greatly increased emphasis over the past decade on countermeasures to deliberate acts of nuclear or radiological terrorism

Tribute to AFRRI – Moving With the Times in Extending the Sophistication and Goals of Biomedical Research on Radiation Effects (con't)

- In late 1970s the staff performing biomedical research was expanded significantly, along with the range of programs designed to address military concerns related to problems such as combined injury (*e.g.*, radiation plus CNS trauma, burns, chem/bio toxic exposures, and infection), and performing effective procedures for the diagnosis and treatment of radiation injuries

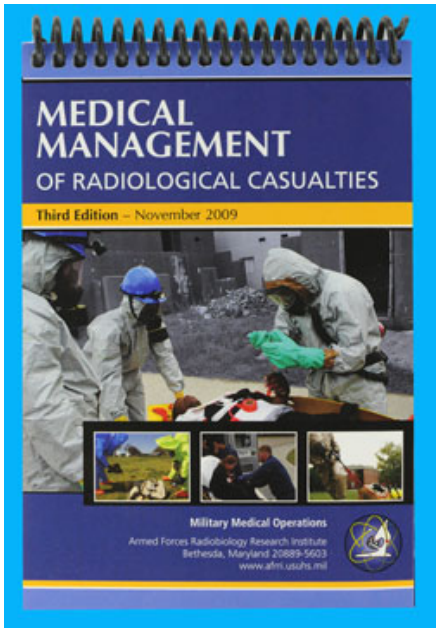
Tribute to AFRRI – Moving With the Times in Extending the Sophistication and Goals of Biomedical Research on Radiation Effects (con't)

- Use of molecular methods for radioprotection and countermeasures to radiation injury (*e.g.*, free radical scavengers and the use of cytokines to counteract diminished hematopoietic functions)
- Development of an integrated multiassay strategy for radiation dose assessment

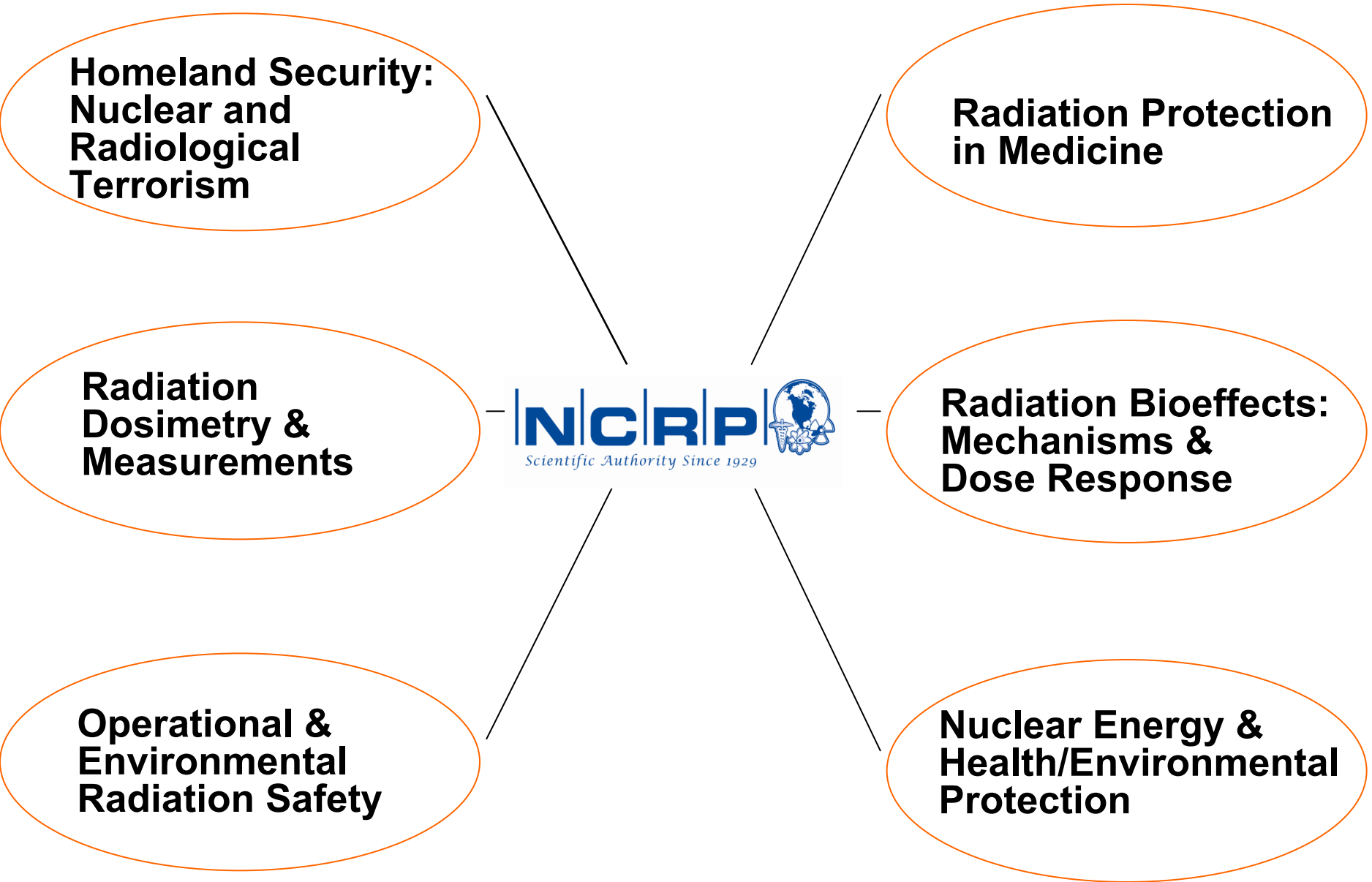


Tribute to AFRRI – 50 Years of Excellence

- **Over its history, AFRRI has placed a high value on publishing the results of its work in journals, books and reports available in the open literature (hundreds of papers and reports that provide guidance on assessing and managing radiation exposures and bioeffects)**
- **In addition, AFRRI is widely recognized as a major resource for symposia and medical training related to ionizing radiation exposures and effects [*e.g.*, the Medical Effects of Ionizing Radiation (MEIR) course]**



Focal Areas of NCRP Reports and Conferences and Interests in Common With AFRRI



AFRRI Collaborations and Scientific Contributions to NCRP

- **Although its primary mission is to conduct research in radiobiology and related matters essential to operational and medical support of DoD and the military services, AFRRI has had many productive collaborations with other government agencies (*e.g.*, CDC and FDA) and non-government organizations such as NCRP**
- **AFRRI staff have collaborated in the preparation of NCRP publications and the organization and conduct of conferences**

AFRRI Collaborations and Important Scientific Contributions to NCRP (con't)

Several examples of recent AFRRI staff collaborations with NCRP are:

-- Former Scientific Director Dr. E. John Ainsworth (1989-1998) served on the Scientific Committee that prepared Report No. 138 on *Management of Terrorist Events Involving Radioactive Material* (2001)

-- Dr. Eric Kearsley, former AFRRI Scientific Director, worked with NCRP as a staff consultant from 1998-2001

-- Dr. William F. Blakely was chairman of the Program Committee for the 2004 NCRP Annual Meeting on *Advances in Consequence Management for Radiological Terrorism Events*, and he and other AFRRI staff were speakers at the meeting [Proceedings published in *Health Physics* 89, 415-588 (2005)]

-- Former Scientific Director Dr. Terry C. Pellmar (2002-2008) is serving as an NCRP Technical Consultant and had a significant role in preparation of Commentary No. 21 on *Radiation Protection in the Application of Active Detection Technologies* (2011)

Challenges in Radiation Safety and Health Protection That Lie Ahead

- Many issues need to be addressed in regard to radiation exposures and countermeasures in medical procedures, nuclear power plant operations and nuclear waste management, potential acts of nuclear/radiological terrorism, space exploration, and commercial applications of radiation sources and radioactive materials
- A full discussion of these issues is beyond the scope of this talk
- Goal will be to point out some difficult challenges facing the radiation health protection, radiobiology, and biomedical science communities over the coming decades

Challenges in Radiological Medical Procedures

- **Improved dose controls in diagnostic procedures (especially CT and nuclear medicine) – selection of appropriate doses and equipment settings, online dose monitoring, avoidance of unnecessary imaging procedures**
- **Dose management in image-guided interventional procedures [NCRP Rep. No. 168 (2010) has 31 recommendations]**
- **Establishment and use of consistent set of diagnostic reference dose levels (NCRP report in progress)**
- **Effective patient communication**

Challenges in Nuclear and Radiological Safety and Security – Nuclear Power

- **Harvest "lessons learned" from Fukushima crisis to develop improvements in reactor designs and safer operating procedures**
- **Evaluate safety of Gen 3+ and Gen 4 reactor designs and operational features**
- **Evaluate use of compact modular reactors in networks rather than large GW_e^+ reactors**
- **Develop national plan for spent fuel management or long-term storage**

Challenges in Nuclear and Radiological Safety and Security – Nuclear Power (con't)

- **Significant and urgent requirement for an expanded nuclear workforce**
- **Extended training opportunities needed for nuclear engineers, radiation safety officers, and operations and maintenance staff (community college and university capabilities should be expanded)**
- **Many AFRRI and NCRP reports provide excellent and up-to-date reference material for advanced training opportunities**

Challenges in Nuclear and Radiological Safety and Security – Terrorism Threats

- Challenges are great in detection and deterrence of radionuclides for Improvised Nuclear Devices or Radiological Dispersal Devices, countermeasures to a terrorism incident, and post-incident recovery & cleanup
- AFRRI and NCRP have provided significant guidance in these areas of response to IND or RDD incidents [*e.g.*, NCRP Rep. No. 165 (2011) on information for decision makers after an RDD or IND incident]

Other Challenges in Radiation Safety and Security Today and in the Future

- Improved radiation shielding designs are essential for astronaut protection in NASA lunar and interplanetary space missions
- Safety of terahertz security screening systems and remote special nuclear materials detection systems for preventing nuclear terrorism threats need to be given attention
- Advanced medical diagnostic systems such as 10-tesla MRI equipment should be developed
- Understanding of potential health effects of low-dose radiation exposures should be given a high priority and emphasized for funding by government agencies such as DOE

Biological Interactions and Potential Health Effects of Low Radiation Doses

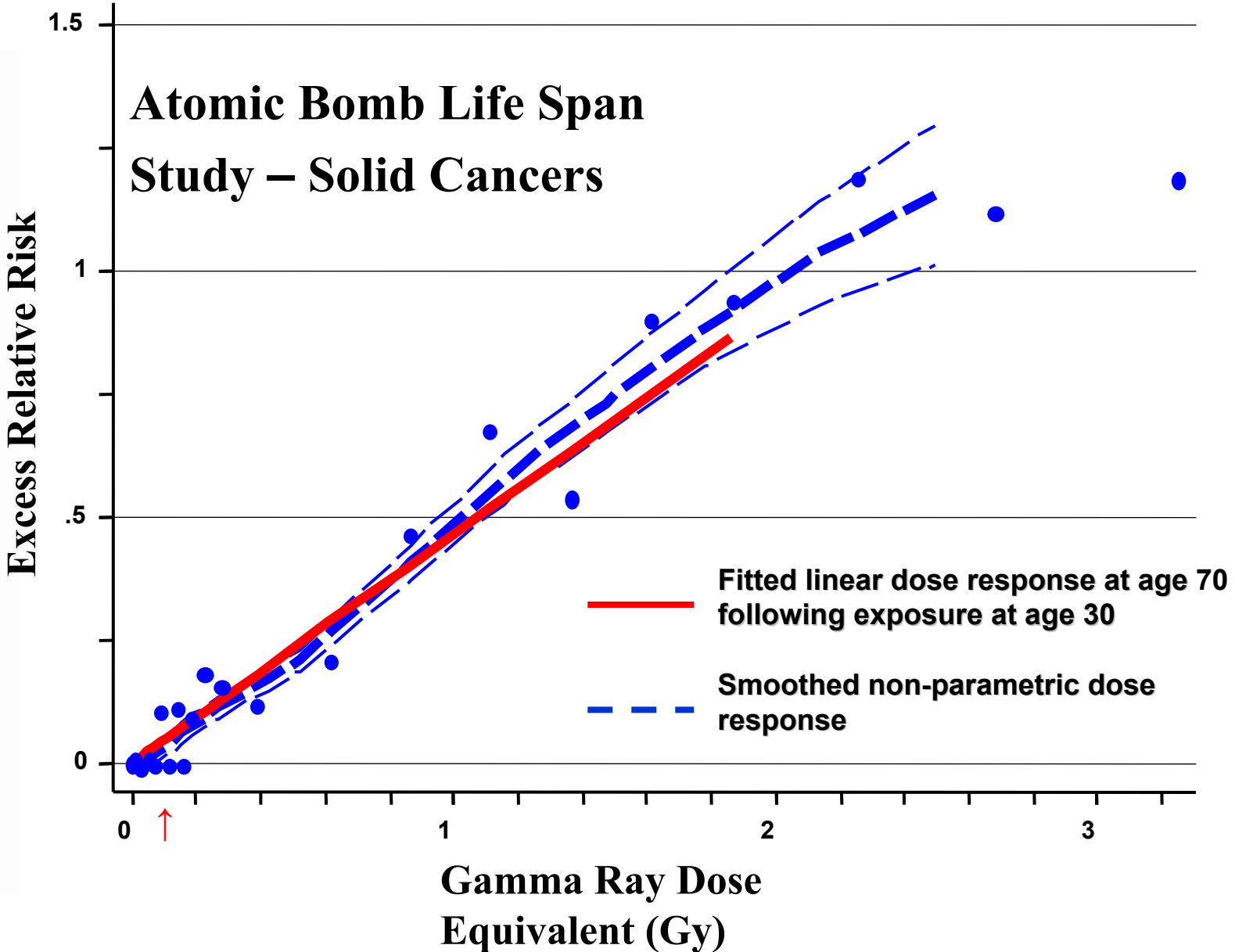
What is Considered to be a Low Dose of Radiation?

BEIR VII published by NAS/NRC in 2006 defines "low dose" as less than 100 mSv per year (based on lack of comprehensive epidemiology and laboratory data below that level)

Why Study Biological and Health Effects of Exposure to Low Radiation Doses?

Nearly all public and occupational annual radiation exposures are "low"

Limits on Precision of Epidemiology Data at Low Radiation Doses



Limits on Precision of Epidemiology Data at Low Radiation Doses (con't)

Statistical Power:

-- Studies at low dose levels require a *much larger* sample size to attain adequate statistical power to define dose-response characteristics

-- confidence intervals on estimates of excess relative risk per Gy become much wider at low dose levels

-- studies at low dose levels have a greater percentage of "false positive" and "false negative" results, with "false positive" results often giving significant overestimates of risk

Limits on Precision of Epidemiology Data at Low Radiation Doses (con't)

***Dosimetry Uncertainties*:**

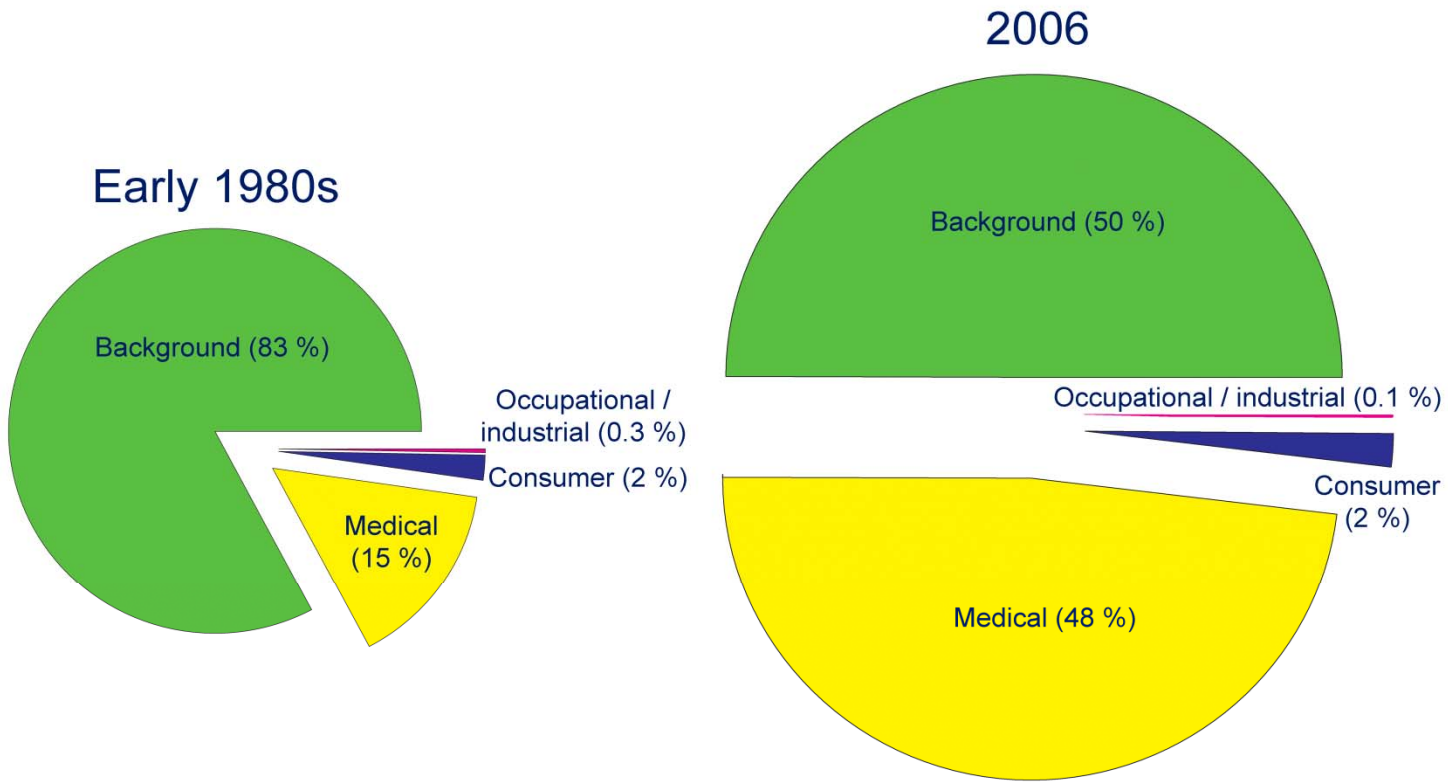
-- Many sources of errors in measured and calculated external, internal and organ doses that influence dose-response modeling

-- *Classical errors*: influence estimates of average for exposed group; shared by all members of group

-- *Berkson errors*: lead to variations among estimates for individual members of exposed group

***Response Modifying Factors*: National origin, age at exposure, attained age, gender, inherent genetic susceptibility, exposure to cancer promoters and other environmental risk factors, general health status, lifestyle factors (diet, drugs, tobacco use, intake of antioxidants …)**

NCRP Report No. 160, *Ionizing Radiation Exposure of the Population of the United States*



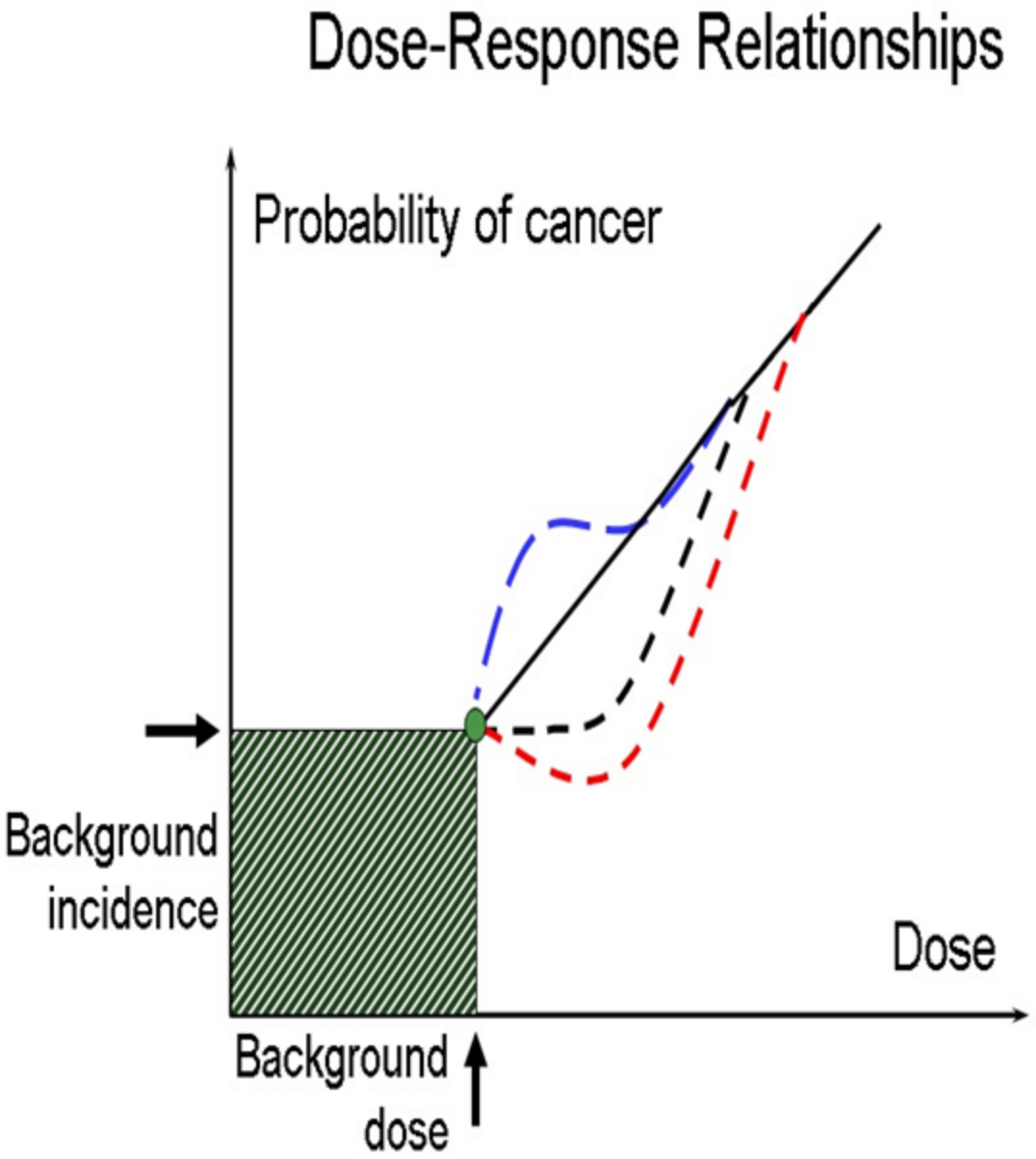
	Early 1980s	2006
Collective effective dose (person-Sv)	835,000	1,870,000
Effective dose per individual in the U.S. population (mSv)	3.6	6.2

Low-Dose Radiation Exposures in Occupational Settings (Effective Doses in Addition to Average from Other Sources of ~6.1 mSv)*

Occupation	Average Annual E (mSv)
Medical	0.8
Aviation	3.1
Commercial Nuclear Power	1.9
Industry and Commerce	0.8
Education and Research	0.7
Government, DOE, and Military	0.6

* From NCRP Rep. No. 160 (2009): *Ionizing Radiation Exposure of the Population of the United States*

Low-Dose Radiation Biological Effects



Primary Goals in Low-Dose Radiation Studies:

- **Determine dose-response properties for cellular, tissue and whole-animal biological effects**
- **Evaluate validity of LNT (linear nonthreshold) model**
- **Integrate data on dose-response properties into reliable predictive model(s) of potential human health effects**

Scientific Approaches to Defining Dose-Response Characteristics for Low-Dose Radiation Effects

NCRP

- **Lack of precision in epidemiological studies for characterizing responses to low radiation doses has led to a research focus on studies with controlled laboratory experimental systems**
- **More than ten years of research supported by U.S. Department of Energy, NASA, and other organizations worldwide has led to important insights into, and modeling of, low-dose radiation effects:**

-- molecular and cellular effects on DNA and cytogenetic control mechanisms and damage repair pathways

-- direct and indirect (non-targeted) effects on cellular and tissue/organ functional properties and regulatory controls

-- evaluation of important factors influencing radiation response, including dose rate, radiation quality (LET), and biological modifiers of radiation response

Molecular Pathways of Low-Dose Radiation Damage and Repair to DNA and Chromosomes

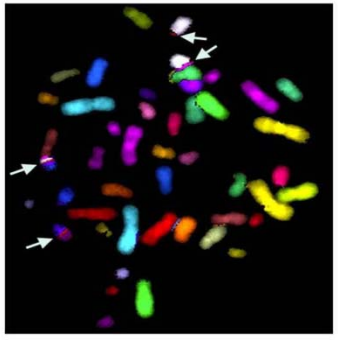
- Significant advances over last decade in characterizing DNA lesions, repair kinetics and pathways, and effects at chromosomal and cellular levels
- High-LET radiation and low-energy secondary electrons from photon radiation (~ 30 % of dose) can produce complex clustered double-strand break (DSB) damage – the least repairable type of damage that can lead to DNA losses and rearrangements
- Nonhomologous end joining (NHEJ) at site of DSB is a more important repair pathway than homologous recombination events
- Signaling factors such as ATM kinase play a key role in initiating DNA repair processes that depend on nucleases and other factors

Molecular Pathways of Low-Dose Radiation Damage and Repair to DNA and Chromosomes (con't)

- DSB introduce both S/G2 and G2/M cell-cycle checkpoints that provide time and signals for initiating repair pathways, but cells can have as many as 10 unrepaired DSB and enter mitosis (a possible mechanism for later expression of genetic damage in progeny cells)
- Low and high doses of radiation have similar effects on gene expression in mouse and human cells, and low doses ($\leq$ 100 mGy) have some notably different transcriptional effects than higher doses on genes involved in cell-cycle regulation, cell-cell interactions, oxidative stress responses, and protein and fatty acid metabolism
- Results of studies on mice irradiated *in vivo* have shown significant tissue-specific variations in effects on gene expression

Molecular Pathways of Low-Dose Radiation Damage and Repair to DNA and Chromosomes (con't)

- Visualization of chromatid and chromosome damage significantly enhanced by use of multi-color fluorescence in situ hybridization (mFISH) painting, use of γH2AX markers of DSB loci, and micronuclei assays
- Dicentrics, complex translocations, inversions and deletions all provide indications of radiation damage, but dicentrics remain the most common assay for low-dose effects



- Not only dicentrics and translocations are indicators of mutation and potential neoplastic transformation, but inversions and interstitial deletions on chromosomes can serve as markers

Factors Modifying Response to Low Radiation Doses – 1: Non-targeted Effects

Bystander Effects: **Adverse responses, including cytogenetic effects and cell death, in cells not directly "hit" by radiation**

-- Successfully demonstrated by α-particle microbeam experiments and other radiation modalities

-- Mechanism(s) for transmission of signals from hit cells to neighboring cells remain under study, but could include cell-to-cell transmission of molecular factors (*e.g.*, cytokines) via gap junctions or release of these factors into blood or tissue fluids

Genomic Instability: **Delayed genomic effects in progeny of "hit" cells, manifested by effects such as chromosome alterations, mutation, changes in gene expression, and cell death**

Factors Modifying Response to Low Radiation Doses – 1: Non-targeted Effects (con't)

***Radioadaptive Responses*: Small priming doses (≤ 50 mGy) lead to reduced adverse effects of larger challenge doses (*e.g.*, less cytogenetic damage, cell death, and carcinogenic risk)**

-- Upregulation of the *TP53* gene by low doses may be a "switch" increasing transcription of a broad array of other genes involved in protective responses to larger challenge doses

-- Low-dose radiation can produce adaptive responses that have been found in experimental systems to reduce the frequency of chromosomal alterations, cell mutation and neoplastic transformation to or below the spontaneous level

Factors Modifying Response to Low Radiation Doses – 1: Non-targeted Effects (con't)

***Integrated Tissue Responses*: Studies with epithelial tissue models *in vitro* have demonstrated that low radiation doses (≤ 100 mGy) can induce dysfunctional cell-cell and cell-extracellular matrix interactions that lead to heritable phenotypic changes characteristic of malignancy; the "trigger" is a radiation-induced elevation in transforming growth factor, which serves to sustain extracellularly-regulated activation of kinases at the integrated tissue level. These effects are well characterized by a "systems biology" modeling approach.**

Factors Modifying Response to Low Radiation Doses – 2: Individual Factors

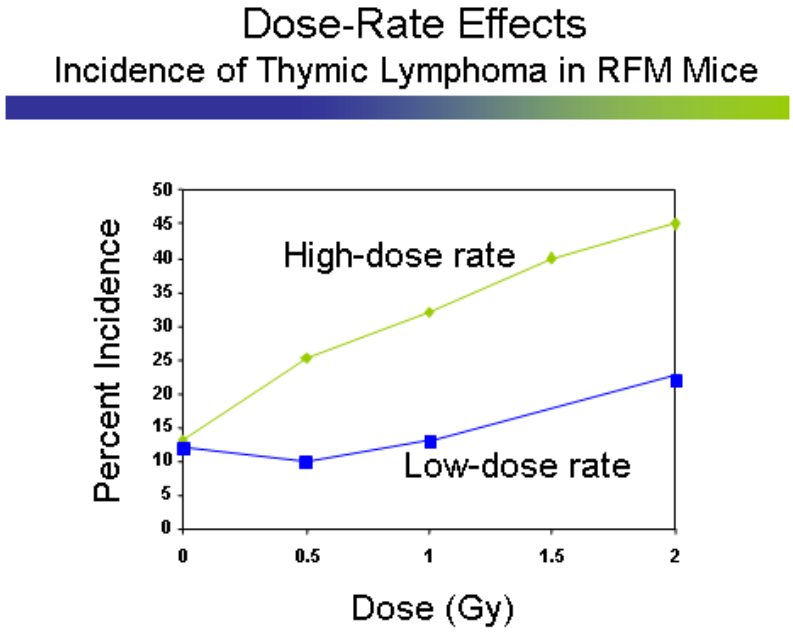
Genetic Susceptibility: **Although relatively small groups of people have well-documented diseases associated with susceptibility to radiation-induced cancer (*e.g.*, AT and Rb), it is expected that the fraction of humans with uncharacterized sensitivity to radiation may be much larger (perhaps 20% or more)**

-- Many laboratory animal-based studies have clearly demonstrated the effects of defined genetic mutations on susceptibility to radiation carcinogenesis

-- Some candidate genotypic markers of susceptibility have been identified in humans (*e.g.*, BRCA 1 and 2 genes in breast tissue), but progress is at an early stage

Factors Modifying Response to Low Radiation Doses – 3: RBE and Dose Rate

•***Relative Biological Effectiveness (RBE)*: Different tissue, cellular, and cytogenetic endpoints often exhibit significant variations in RBE estimates for high-LET radiations – a factor of importance in evaluating health risks for persons exposed to neutrons and charged-particle radiation**



•*Dose and Dose-Rate Effectiveness Factor (DDREF)*: Large variations observed for different biological endpoints, but DDREF estimates are generally consistent with the value of 2.0 proposed by ICRP and NCRP**

Importance of Gaining Increased Knowledge on Low-Dose Radiation Effects in Relation to Public Policy and Regulatory Decisions

Regulatory Agency Views: **Efforts to obtain an improved knowledge of low-dose radiation effects are considered an important activity with a potential impact on future guidelines for public and worker exposure limits and actions to counteract nuclear/radiological terrorism**

-- A major area of interest is the confirmation, or the development of a scientifically defensible alternative(s), to the LNT dose-response model as a basis for regulations

-- Research focused on characterizing the range of individual sensitivities to radiation health effects is considered to be an area of major importance

-- Changes in regulatory policies and guidance will not occur rapidly, but will be given a high priority if changes are warranted on the basis of well-documented scientific evidence and reliable predictive models of radiation health effects of low-dose radiation effects

Major Challenges in Understanding Low Dose Radiation Effects – Research Needs

- Expand systems biology approaches to defining dose-response properties at the organ, tissue and animal levels
- Pursue research on the impact on radiation damage of non-targeted effects, specific intercellular responses, tissue signaling and extracellular matrix effects
- Continue exploration of biomarkers of radiation sensitivity and health risk
- Pursue a better understanding of modifying factors that influence radiation response at a networked multicellular level (*e.g.*, RBE and DDREF)

Major Challenges in Understanding Low-Dose Radiation Effects – Epidemiology Studies

- Continue collecting data on Japanese A-bomb survivors, especially incidence and mortality information on solid tumors
- Continue large ongoing epidemiology studies on workers (*e.g.*, the 15-country occupational exposure studies)
- Further explore meta-analysis of large epidemiology studies and better understand the influence of confounding factors
- Initiate new epidemiology studies that include recording of predictive biomarkers to relate low-dose exposures with risk of disease causation (both cancer and non-cancer effects)

Concluding Remarks

Congratulations to AFRRI from NCRP on 50 years of outstanding achievements

We look forward to continuing and expanding our productive collaborations over the coming 50 years!

Please visit the NCRP website at http://NCRPonline.org and the publications website at http://NCRPpublications.org