Current and Future Capabilities in the Prevention, Assessment, and Treatment of Radiological Injuries

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Disclaimer

The US response to any large disaster is based on the National Response Plan. A large scale radiological incident is addressed in the radiological / nuclear annex of this plan.

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Outline

- Current Protocols of Treatment for Radiological Injuries
- Capabilities of Current Compounds Undergoing Therapeutic Trials
- Summary

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Current Protocols for Treatment of Radiological Injury

- Dosimetry (for assessing exposure)
  - Biodosimetry
  - Spin-resonance
  - Lymphocyte
- Irradiation Injury
  - Hematological
  - Skin
- Internal Contamination
- Combined Injury

Biological Dosimetric Assays

- Fluorescence *in situ* hybridization (FISH)
  - Assay useful for measuring chromosome exchanges resulting in unstable aberrations such as dicentrics, rings, acentric fragments and other asymmetrical rearrangements
- Measurement of radiation-induced apoptosis in human lymphocytes
- Counting the frequency or number of micronuclei in the cytoplasm of irradiated cells
- Electron spin resonance
  - Provides an estimate of neutron exposure
- Detection of free radical formation in tooth enamel
- Measurement of serum biochemical markers, such as:
  - amylase
  - IL-6
  - iron
  - cholesterol
  - apolipoprotein levels

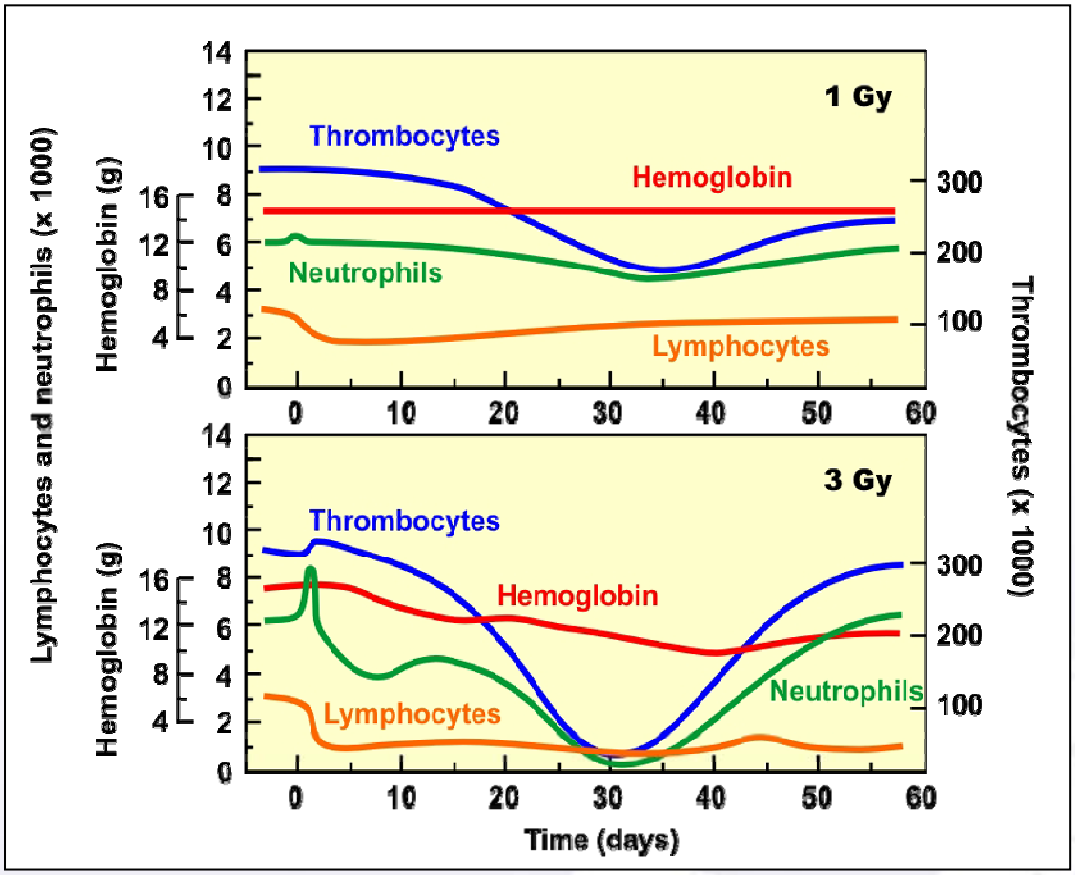
Rapid Dosimetry - Lymphocytes

- Utilizing an absolute lymphocyte count taken approximately 8-12 hours after an incident, an estimate for whole-body dose may be obtained from the table

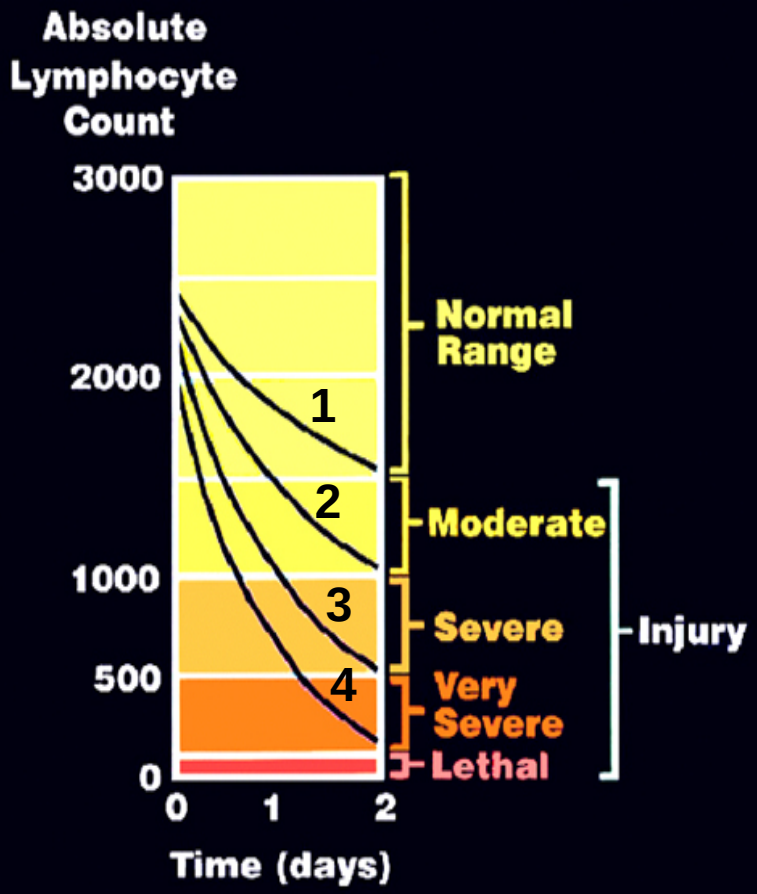
Dose Range	Absolute Lymphocyte Count 8-12 Hours Post Incident
< 1 Gy	Normal – 2500/mm^3
1-5 Gy	1700-2500
5-9 Gy	1200-1700
> 10 Gy	<1000

- A conservative rule of thumb is that a lymphocyte count < 1 x 10^3 μL^{-1} within 24-48 hours suggests that the patient has received at least a moderate (> 2 Gy) absorbed dose of radiation

Changes in Lymphocyte Counts and Degree of Irradiation Injury



Classic Andrews Lymphocyte Depletion Curves (1965)

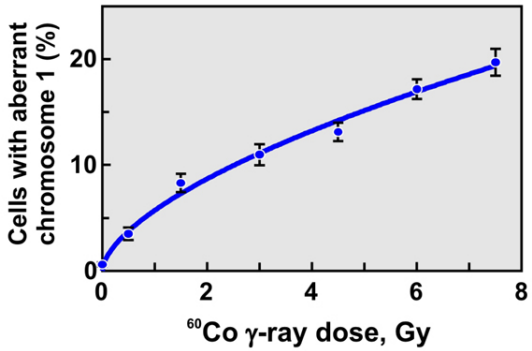


Curve 1: 3.1 Gy
Curve 2: 4.4 Gy
Curve 3: 5.6 Gy
Curve 4: 7.1 Gy

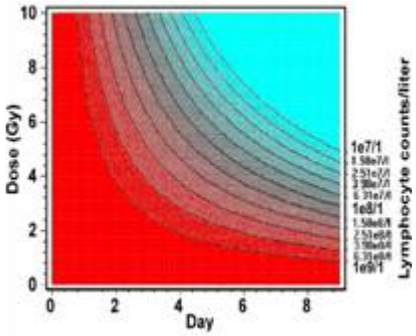
Biodosimetry

Multi-Assay Strategy Using High-Throughput Deployable Systems

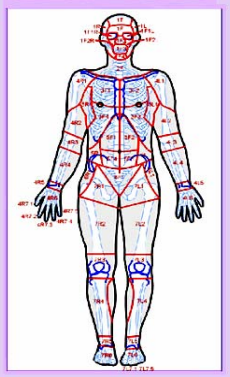
Chromosome Aberrations



Blood Cell Counts

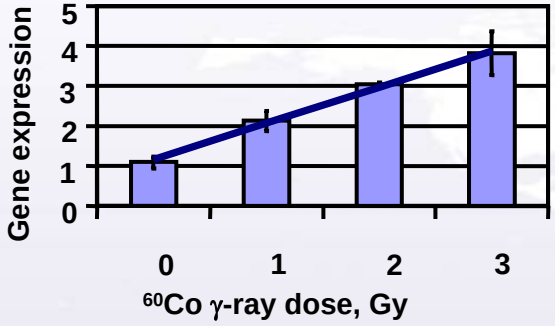


BAT Software Application

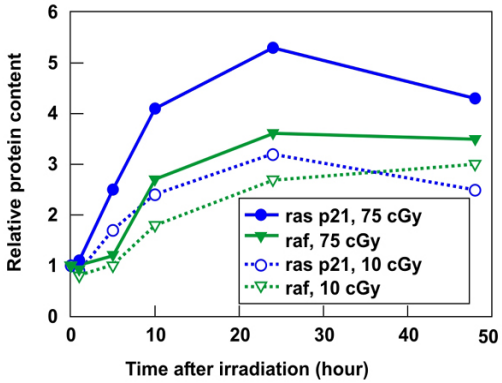


- Physical dosimetry
- Blood cell kinetics
- Prodromal symptoms
- Erythema
- Internal contamination
- Infection
- Lymphocyte cytogenetics

Nucleic Acid Biomarkers



Protein Biomarkers



Internal Contamination

Inhalation Pathway

- Most efficient route
- Inhale radiation-emitting particulate matter

  (We do not "inhale radiation")
- Particle size — key factor
- Secondary source for ingestion

Internal Contamination Routes of: Intake / Absorption / Uptake

Intake → Absorption

Nose

Mouth

Lung

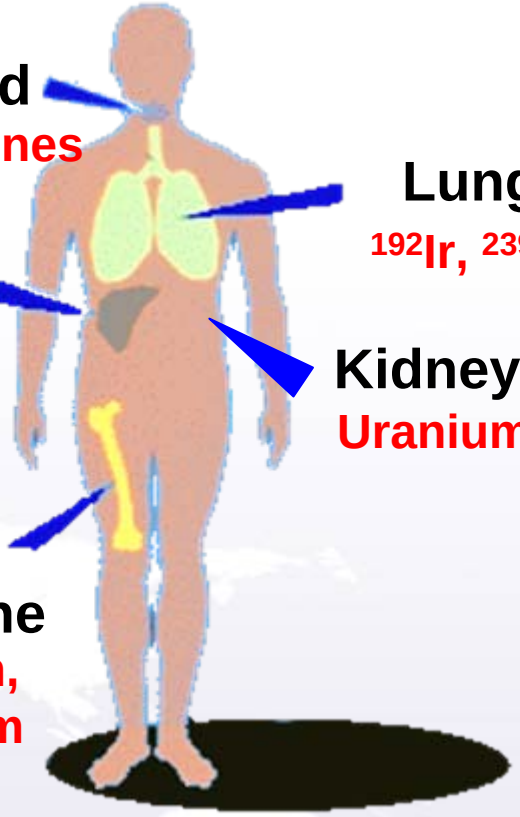
Intact Skin

Gut

Injection

Wound

Uptake → Deposition



Thyroid

Radioiodines

Lung

^{192}Ir, ^{239}Pu

Liver

Kidney

Uranium

Bone

^{226}Ra, ^{90}Sr, ^{241}Am, ^{238},^{239}Pu, Uranium

Whole Body: ^{24}Na, ^{137}Cs, ^{3}H, ^{60}Co

Detonation Potential Casualties

	1-KT	10-KT
Prompt fatalities:	> 7K	> 13K
Expectant (> 8.3 Sv):	~ 18K	~ 114K
Intensive care (IC) ward (5.3 – 8.3):	**~ 19K**	**~ 90K**
IC/minimum care ward (3 – 5.0):	**~ 33K**	**~ 141K**
Minimum care ward (1.5 - 3):	**~ 66K**	**~ 150K**
Outpatient (0.7 -1.50):	~ 83K	~ 159K
Health monitoring (0.25 -0.7):	~ 106K	~ 128K
Worried well (< 0.25):	> 150K	> 212K

Detonation Combined Injury

Type of injury		Distribution
Single injuries (30%~40%)		
	Irradiation*	15~20%
	Burns	15~20%
	Wounds	≤ 5%
Combined injuries (65%~70%)		
	Burns + irradiation	40%
	Burns + wounds + irradiation	20%
	Wounds + irradiation	5%
	Wounds + burns	5%
* Including fallout		

Therapeutics: Antimicrobial Agents

- Infection is the main medical complication and primary cause of mortality following exposure to ionizing radiation.
- Antimicrobial defenses are weakened because the skin and gastrointestinal tract are compromised and the immune response to pathogens is reduced.
- The microbial flora in the gut is disrupted, local toxins are released, and pathogens can cross from the intestine to other tissues, leading to systemic infection that can result in shock and death.

Therapeutics: Cytokines and Growth Factors

- There are several therapeutics available which are US-FDA approved for cancer chemotherapy. An indication for radiation injury does not yet exist although most of the necessary animal studies already are complete.
  - G-CSF (filgrastim, Neupogen®)
  - Pegylated G-CSF (pegfilgrastim, Neulasta®)
  - GM-CSF (sargramostim, Leukine®)
  - IL-11 (oprelvekin, Neumega®)

- G-CSF and IL-11 need to be administered by daily injection for an extended period of time.
- IL-11 has serious toxicity.

National Institutes of Health Research Program and the Strategic National Stockpile

- The U.S. Strategic National Stockpile (SNS) is a repository of licensed vaccines, antibiotics, antitoxins, chemical antidotes, and other essential materials needed for emergency deployment as a medical response on a national scale.

- The SNS includes a limited number of medications specific for radiation exposure, such as:
  - KI, Ca- and Zn-DTPA, Prussian blue
  - Cytokines for emergency use under an Investigational New Drug (IND) application

- NIH facilitates and accelerates product development research conducted by academia, industry, and federal laboratories:
  - Animal efficacy and toxicity studies, including studies of large animal models
  - Preclinical pharmacokinetics and pharmacodynamics
  - Development of new product formulations, radioprotectant drugs and post-exposure mitigation/treatment regimens
  - Development of new animal models to provide mechanistic, safety, and efficacy data to support FDA approval of new products for human use

Summary of Currently Available Radiation Countermeasures

- Cytokines
  - Shorten absolute period of neutropenia
  - G-CSF (filgrastim, Neupogen®)
  - pegG-CSF (pegfilgrastim, Neulasta®)
  - GM-CSF (sargramostim, Leukine®)
- Antimicrobials and supportive therapy
  - Required use with anti-neutropenic cytokines
  - After onset of infection, anemia, etc.
- Blocking agents
  - Potassium iodide – suitable for youth within 5 -13 km of a radioiodine gas release
- Chelators
  - DTPA – heavy transuranic metals
- Ion-exchange resins
  - Prussian blue – cesium & thallium

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Animal Studies

There is a need to understand the mechanisms of radiation induced injury in the body and how it affects the organs.

- **Cytokines**
  - Colony Stimulating Factors (CSFs) are not currently approved for treatment of radiation-induced neutropenia
  - Efficacy data from animal models would be sufficient to allow US-FDA approval under the “animal rule”
  - Safety data from humans would still be required
- **Keratinocyte growth factor (KGF)**
  - The cytoprotective properties of KGF have been amply demonstrated in multiple preclinical animal models of chemical and radiotherapy-related injuries
  - Significant survival benefit was noted in a small animal experimental model
  - Shows promise for treatment of the gastrointestinal syndrome that follows radiation exposure as well as for prevention of some of the late sequelae

Clinical Trials

- Genistein
  - Demonstrated minimal toxicity in Phase 1 clinical trials in both single and multiple dose forms
- Pentoxifylline (800 mg/d) and Vitamin E (1,000 IU/d) combined therapy
  - Treatment applied for at least 6 months
  - Radiotherapy for head and neck or breast cancer and had developed resulted in clinical regression and functional improvement
  - Combination given systemically can also be considered in the treatment of severe skin injury, including the cutaneous radiation syndrome seen in some Chernobyl accident victims
- 5-Androstenediol, a non-androgenic steroid
  - Ameliorates radiation effects on the immune system
  - Enhances survival after lethal doses of radiation in primates
  - Undergoing Phase 1 safety testing

Radioprotectants

- **Amifostine**
  - Demonstrated effectiveness as a radioprotectant in animal studies
  - FDA-approved for specific consequences of radiation therapy, but it has significant side effects and a limited window of effectiveness
- **Genistein**
  - A soy isoflavone being studied for usefulness as a radioprotectant
- **Vitamin E**
  - Being studied for usefulness as a radioprotectant

Diagnostics

Items/devices which may be stockpiled in the event of a large scale radiological or nuclear incident:

- Physical Dosimetry and Radioactivity Monitors
  - May include personal and/or portable colorimetric radiation detection devices
- Blood Cell Counts and Cytogenetic Biodosimeters
  - For example, blood sample collection kit

- Bioassays for Internal Contamination
  - For example, skin and/or wound swabs
- Deployable Hematology Laboratory Systems

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Knowledge Gaps

- Rapid diagnostic tools for mass casualties
  - Need for rapid identification to aid triage
  - Lymphocyte depletion
  - Cytogenetic studies
- Optimal antibiotic, diagnostic, and treatment tools
  - Radioprotectants
  - Bowel protectants
  - Radio-mitigants
- Research on timing of surgery
  - Prior study indicated timing important
- Support for hematologic, gastrointestinal systems and cutaneous systems
- Radiation's interaction with Toxic Industrial Chemicals and Toxic Industrial Materials

Conclusions

- **The supportive care of patients with radiation injury is complex!**
- **Antibiotics, transfusions, and Colony Stimulating Factors may improve survival:**
  - **If extramedullary injury is survivable**
  - **If viable stem cells exist**
  - **If adequate medical support can be made available**

QUESTIONS?

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References

- Department of Homeland Security Working Group on Radiological Dispersal Device (RDD) Preparedness Medical Preparedness and Response Sub-Group 1 May 2003
- National Institutes of Health, NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats June 2005
- Office of Science and Technology Policy Homeland Security Council, RADIOLOGICAL / NUCLEAR THREAT COUNTERMEASURES WORKING GROUP FINAL REPORT 16 October 2003
- Office of the Surgeon General Department of the Army, United States of America, Textbook of Military Medicine 1989