Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency

The RITN is a cooperative effort of the National Marrow Donor Program® (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT).

Tuesday, September 25, 2007
8:00 a.m. – 5:00 p.m.
(Registration/Breakfast begins at 7:30 a.m.)

Marriott Bethesda
5151 Pooks Hill Road, Bethesda, MD 20814
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Chair</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:30 - 8:00</td>
<td>Registration / Breakfast</td>
<td></td>
</tr>
</tbody>
</table>
| 8:00 - 8:15  | Opening Comments                                                                         | Dennis Confer, M.D. - National Marrow Donor Program  
Nelson Chao, M.D., M.B.A. - Duke University |
| 8:15 - 8:45  | Improving National Preparedness Using the Nuclear Scenario                               | Brooke Buddemeier, C.H.P. - Lawrence Livermore National Laboratory |
| 8:45 - 9:15  | Estimating Medical Requirements for a 10KT Nuclear Detonation                            | Carl Curling, Sc.D. - Institute for Defense Analysis |
| 9:15 - 9:45  | Bone Marrow Injuries after the Chernobyl Accident: Management, Outcome, and Lessons Learned | Alla Shapiro, M.D., Ph.D. - U.S. Food and Drug Administration |
| 9:45 - 10:15 | Mass Casualty Event Case Studies (Hurricane Katrina, Goianna)                            | David Rutstein, M.D., M.P.H. - U.S. Public Health Service (Lessons Learned from Hurricane Katrina)  
Nelson Valverde, M.D. - State University of Rio de Janeiro (The Golânia Accident: Past and Present) |
| 10:15 - 10:45| Discussion and Break                                                                      |                                |
| 10:45 - 11:15| Introduction to Radiation Biology                                                          | Michael Robbins, Ph.D. - Wake Forest University School of Medicine |
| 11:15 - 11:45| Cytogenetic Biodosimetry                                                                  | Albert Wiley, Jr., M.D., Ph.D. - REAC/TS & WHO Collaborating Center at Oak Ridge |
| 11:45 - 12:45| Discussion and Lunch                                                                      |                                |
| 12:45 - 1:05 | The Clinical Approach of METREPOL: A Challenge for Hematology to Provide Indicators of Effect and Repair Dictating Options for Therapy | Theodor Fliedner, M.D. - Ulm University |
| 1:05 - 1:25  | Acute Radiation Syndrome of the Skin: New Aspects in Pathophysiology and Treatments Following Radiation Exposure | Viktor Meineke, M.D. - Bundeswehr Institute of Radiobiology |
| 1:25 - 1:45  | Role of Gastrointestinal Injury in Acute Radiation Syndromes                              | Martin Hauer-Jensen, M.D., Ph.D., - University of Arkansas for Medical Sciences |
| 1:45 - 2:05  | Neurovascular/CNS Syndrome                                                                | Michael Robbins, Ph.D. - Wake Forest University School of Medicine |
| 2:05 - 2:25  | Multi-organ Failure                                                                       | Marc Benderitter, M.D. - Institut De Radioprotection et de Surete Nucleaire |
| 2:25 - 3:00  | Discussion and Break                                                                      |                                |
| 3:00 - 3:30  | National Response Process                                                                 | C. Norman Coleman, M.D. - National Institute of Health |
| 3:30 - 4:00  | RITN Overview                                                                             | Cullen Case, Jr. - National Marrow Donor Program |
| 4:00 - 4:30  | Novel Agents                                                                              | Nelson Chao, M.D., M.B.A. - Duke University |
| 4:30 - 5:00  | Discussion and Closing Comments                                                           | Dennis Confer, M.D. - National Marrow Donor Program |
Speaker Disclosure

To ensure balance, independence, objectivity and scientific rigor in all of its educational activities the organizers require all CME activity planners and faculty to disclose their relevant financial relationships to the audience. Any relationship that is disclosed has been resolved to ensure it is fair and balanced and free of commercial bias.

Speakers:

Brooke Buddemeier, CHP None

Carl Curling, Sc.D. None

Alla Shapiro, M.D. Invention Royalty: National Institutes of Health

David Rutstein, M.D. None


Michael Robbins, Ph.D. None

Albert Wiley, M.D., Ph.D. None

Viktor Meineke, M.D. None

Theodor Fiedner, M.D. None

Martin Hauer-Jensen, M.D. None

Marc Benderitter, M.D. None

C. Norman Coleman, M.D. None

Cullen Case, Jr. None

Planning Committee Members:

Richard Hatchett, M.D. None

Daniel Weisdorf, M.D. None

David Weinstock, M.D. None

Dennis L. Confer, M.D. None

Nelson J. Chao, M.D. None
Program Overview

Program Description:
This seminar will provide an overview of the impact and medical challenges that would arise after the detonation of a nuclear bomb within the United States borders. Presentations will include assessments of the current threat and will review possible scenarios. In-depth information on the medical complications of Acute Radiation Syndrome and its impact on target organs will also be discussed.

Educational Objectives:
1. Understand the current radiation/nuclear threat to the United States.
2. Describe the biological effects of ionizing radiation on multiple organs (skin, hematological, gastrointestinal, neurological and multi-organ failure).
3. Explain the basics of calculating radiation dose based on bio-dosimetry.
4. Describe current operational concepts from triage through delivery of care, including transfers to other treatment facilities.
5. Understand hospital management of severely injured patients exposed to radiation.

Target Audience:
Hematologist, oncologists, bone marrow transplant physicians, transplant center directors, hospital administrators, medical physics professionals, nuclear medicine practitioners, and selected staff of the Department of Defense, Health and Human Services, and other federal agencies as applicable.

Accreditation and Designation of Credit:
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Medical College of Wisconsin, and the National Marrow Donor Program® (NMDP). The Medical College of Wisconsin is accredited by the ACCME to provide continuing medical education for physicians.

The Medical College of Wisconsin designates this educational activity for a maximum of 6.0 AMA PRA Category 1 credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Disclosure Policy:
It is the policy of the Medical College of Wisconsin Office of Continuing Medical Education to ensure balance, independence, objectivity and scientific rigor in all of its sponsored educational activities. All faculty participating in sponsored programs are expected to disclose to the program audience any real or apparent conflict of interest related to the content of their presentation.
Improving National Preparedness Using the Nuclear Scenario

Brooke Buddemeier, CHP
Lawrence Livermore National Laboratory
Improving National Preparedness Using The Nuclear Scenario

“the United States must be prepared to respond to the use of WMD against our citizens, our military forces, and those of friends and allies. We will develop and maintain the capability to reduce to the extent possible the potentially horrific consequences of WMD attacks at home and abroad.”


Preparedness

Preparedness & Readiness; we all know what we mean when we say it, but how do you really evaluate it…

How prepared Is “Prepared Enough?”

How do prioritize your resources?
The Best Laid Plans…

Preparedness is more than just planning

National Planning Scenarios

“While much preparedness applies across the all-hazards spectrum, the National Strategy attaches special emphasis to preparing for catastrophic threats with “the greatest risk of mass casualties, massive property loss, and immense social disruption.” To address this requirement, a Federal interagency working group developed National Planning Scenarios to illustrate the potential scope, magnitude, and complexity of a plausible range of major events, including terrorist attacks, major disasters, and other emergencies.”

~Interim National Preparedness Goal (2005)
National Planning Scenario #1; Low Yield Nuclear Detonation

- Most **Prompt** Casualties are from blast and thermal injuries
- **Fallout** Casualties are from Radiation

**Promp**t Effects:
- Blast overpressure
- Lethal prompt (initial) radiation

**Fallout** Effects:
- Severe shockwave damage
- Severe thermal damage
- General radioactive fallout pattern

Ground Zero
**Blast Effects; Buildings & People**

- **Low Survival of Heavy Buildings within area**
  - Overpressure lung injury & fatalities from impact
  - >10 psi 678m

- **Low Survival of Light Buildings within area**
  - Eardrum ruptures and possible incapacitation
  - >5 psi 1 km ~250k people (day)

**Radiation and Thermal Effects**

**Unprotected Population (Clear Day)**

- **3° Burns LD-50**
  - 1.5 km ~360,000 people

- **300cGy LD-50**
  - 1.4 km 300,000 people
Improving National Preparedness Using Nuclear Scenario

Long Range Prompt Effects

- EMP: Service disruptions & Equipment Damage
- EMP: Temporary disruptions
- Missile Injury Threshold: 0.6psi 4.5km ~750k people
- Flash: Blindness 7km to 12 km

Combined Effects

<table>
<thead>
<tr>
<th>Typical Overpressure Damage</th>
<th>Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>psi</td>
<td>Damage</td>
</tr>
<tr>
<td>1</td>
<td>Windows shattered</td>
</tr>
<tr>
<td>2</td>
<td>Aluminum panels ripped off</td>
</tr>
<tr>
<td>3</td>
<td>Wall of 12-inch concrete shattered; parked aircraft destroyed</td>
</tr>
<tr>
<td>5</td>
<td>Brick houses destroyed; trucks overturned; telephone poles collapsed</td>
</tr>
<tr>
<td>15</td>
<td>Lung Damage</td>
</tr>
<tr>
<td>50</td>
<td>LD_{50}</td>
</tr>
</tbody>
</table>

Nighttime shot, the only light is from the blast

Thermal pulse ignites paint and wood

Pressure wave destroys house

1km from ~16kT yields (~ 6 psi)
Prompt Effects Summary

- Most prompt casualties (injuries + fatalities) are from **blast and thermal energy (not radiation)**

- **Literature and models predict:**
  - **100,000s casualties** can occur from the prompt effects in the first few minutes within a few miles of ground zero (GZ),
  - Overall number of casualties likely to be reduced by protection from the urban landscape and being within heavy buildings, however
  - Tertiary effects (building collapse, glass and debris missiles, and flash-blindness accidents) may increase number of casualties

- Those outdoors within a few miles can be temporarily blinded

- Dust and debris (initially **not** fallout) will cloud the air

FALLOUT

- The nuclear detonation creates a large cloud of radioactive dust & water vapor which fall back to earth contaminating horizontal surfaces

- Dangerous levels of fallout creates visible dust and debris, These particles give off **penetrating radiation** that can injure people (even indoors)

- **Fallout decays rapidly away with time**, and is most dangerous in the first few hours after the detonation
2 Hour Integrated Outdoor Exposure

Missile Injury Threshold
4.5km ~ 750,000 people in area

Fallout Acute Injury Threshold
25km long ~ 400,000 people

Prompt Exposure > 100 rem

Fallout Effects

- >300 cGy
  - 7.6km
  - 9.8 km²
- >200 cGy
  - 10.0km
  - 13.3 km²
- >100 cGy
  - 14.8km
  - 25.1 km²
- >50 cGy
  - 20.3km
  - 44.1 km²
- >25 cGy
  - 26.6km
  - 73.9 km²

- Most Potential acute Injuries confined to within 15km
- Prompt and fallout areas not congruent

Downwind Dose Rate @ 15 Minutes

Dose Rate

- 100 cGy/hr
  - Injury in 1 hour
- 10 cGy/hr
  - Injury in 10 hour
- 1 cGy/hr
  - Injury in 4 days
- .1 cGy/hr

1,500 cGy/hr
  - Injury in 3 minutes, LD-50 in 10 minutes
## Downwind Dose Rate @ 2 hours

<table>
<thead>
<tr>
<th>Dose Rate</th>
<th>Fallout Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 cGy/hr</td>
<td>Injury in 1 hour</td>
</tr>
<tr>
<td>10 cGy/hr</td>
<td>Injury in 10 hours</td>
</tr>
<tr>
<td>1 cGy/hr</td>
<td>Injury in 4 days</td>
</tr>
<tr>
<td>.1 cGy/hr</td>
<td></td>
</tr>
</tbody>
</table>

### 180 cGy/hr
- Injury in 30 minutes,
- LD-50 in 2 hours

## Downwind Dose Rate @ 48 hours

<table>
<thead>
<tr>
<th>Dose Rate</th>
<th>Fallout Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 cGy/hr</td>
<td>Injury in 10 hours</td>
</tr>
<tr>
<td>1 cGy/hr</td>
<td>Injury in 4 days</td>
</tr>
<tr>
<td>.1 cGy/hr</td>
<td></td>
</tr>
</tbody>
</table>

### 7 cGy/hr
- Injury in 14 hours
Improving National Preparedness Using Nuclear Scenario

2 Hour Integrated Outdoor Exposure

Flash Blindness
7km to 12 km

Missile Injury Threshold
4.5km ~ 750k people in area

2 Hour Integrated Outdoor Exposure

(cGy = rem)
Extent
Area

>1,000 cGy
2.5km
2.0 km2

>800 cGy
3.0km
2.6 km2

>600 cGy
4.3km
3.7 km2

>500 cGy
5.1km
4.7 km2

>400 cGy
6.3km
6.2 km2
**4 Day Integrated Outdoor Exposure**

- Large population and short arrival times make evacuation difficult
- Model uncertainties and “shadow evacuation” likely to greatly increase effected population

**Fallout Effects Summary**

- The fallout cloud will climb 8km (5 miles) high and will be carried by jet-stream winds
- 100,000s of acute casualties from radioactive fallout can occur within 15km (9 miles) downwind of the GZ
- The number of fallout casualties can be reduced by action (shelter / evacuation)
- Radiation levels decay rapidly with time
- In the first few days, the primary health hazard is external gamma radiation from fallout on horizontal surfaces. Breathing in fallout dust (internal contamination) is a minor concern.
- Radiation has a delayed effect. Although radiation sickness may occur within a few hours, victims of lethal radiation may not succumb for days or weeks.
Why Exercise the Impossible?

**National Priority:** Expand regional collaboration through mutual aid agreements and assistance compacts in order to meet the target levels of capability in the most effective and expedient manner.

- **Large Scale Incident Response Coordination**
  - Multi-Jurisdictional Response
  - Extensive and Diverse federal Involvement
- **Mass Casualty**
  - Potentially 100,000s with immediate and delayed medical needs
  - Large variety of injuries, trauma, burns, and radiation illness
- **Mass Evacuation and Mass Care**
  - Millions in (or near) fallout area
- **Mass Decontamination**

Unique Exercise Challenges

Critical life saving activity depends on actions taken in the first few minutes and hours of the event.

- **Crisis Communication**
- **Time Critical Decision Making**
- **Resource Prioritization**
- **Coordinated Multiple State Response**
Exercise NPS#1 Because:

- Supports overall catastrophic event planning that improves *all-hazard* preparedness
- Breaks down jurisdictional/discipline barriers
- Prioritizes response elements
- Frankly, a little radiological response planning wouldn’t hurt
  - Many concepts apply universally to radiological incidents as well as terrorism
  - Many “Cold War” response paradigms no longer apply
  - Reduction of risk, to both public and responders, through better understanding of radiological issues
Estimating Medical Requirements for a 10KT Nuclear Detonation

Carl Curling, Sc.D.
Institute for Defense Analysis

Not available for Internet publication
Bone Marrow Injuries after the Chernobyl Accident: Management, Outcome, and Lessons Learned

Alla Shapiro, M.D., Ph.D.,
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Counter-Terrorism and Emergency Coordination (OCTEC)
Bone Marrow Injuries after the Chernobyl Accident: Management, Outcome, and Lessons Learned

National Marrow Donor Program

“Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency”

September 25, 2007

Alla Shapiro, M.D., PhD,
Medical Officer,
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Counter-Terrorism and Emergency Coordination (OCTEC)

Financial Disclosure - Invention Royalty:
National Institutes of Health

Presentation Outline

- Early Effects of High Radiation Doses in victims of the Chernobyl Accident
- Bone Marrow Syndrome and its Treatment
- Overview of Other Injuries and their Treatment
- Conclusions
Basic Information on the Radionuclide Releases and the Types of Exposure at Chernobyl

- 100% of gaseous fraction of the noble gases and nuclides may have escaped from the plant
- Cesium, Iodine and Tellurium isotopes accounted for up to 10-20% of the nuclides inventory
- Transuranic elements (Plutonium, Curium and Americium) were found only in the lungs
- Neutron irradiation was not significant
- ARS was caused by α- and gamma-irradiation of the whole body and by beta-irradiation of the skin surface


Sequence of the Initial Intervention (1)

<table>
<thead>
<tr>
<th>Time</th>
<th>Intervention</th>
<th>Treatment/Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min – 3-4 hours</td>
<td>Initial treatment on the site</td>
<td>evacuation from the site, antiemetics, sedative, cardiotonic</td>
</tr>
<tr>
<td>4 hours - 12 hours</td>
<td>Evaluation and treatment at the nuclear plant medical facility</td>
<td>discharged if condition is OK, remained hospitalized</td>
</tr>
<tr>
<td>12 hours - 36 hours</td>
<td>Specialized team arrived</td>
<td>Assessment, blood tests, administration of KI, priority for hospitalization established</td>
</tr>
</tbody>
</table>

Guskova et al. 1986. Acute radiation effects in exposed persons at the Chernobyl Atomic Power Station Accident. Medical Radiology, (477), pp.3-18
Sequence of the Initial Intervention (2)

- Within the first three days, 299 persons were sent to the specialized treatment center in Moscow and to hospitals in Kiev.

- Over the subsequent days hundreds of additional persons were admitted for examination.

- Criteria for hospitalization included for patients with the suspected ARS:
  - Presence, time of onset and intensity of nausea and vomiting
  - Primary erythema of the skin
  - Decrease of the lymphocyte count in the peripheral blood <1X10^9/L in first 24 hours after the exposure

Thousands of concerned citizens were admitted to the hospitals for examination and blood work.

Primary Diagnostic Criteria of ARS: Diagnostic Coefficient (DC)

<table>
<thead>
<tr>
<th>Time to the onset of vomiting</th>
<th>Hours</th>
<th>Diagnostic Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-0.4</td>
<td>+8</td>
</tr>
<tr>
<td></td>
<td>0.41-0.8</td>
<td>+4</td>
</tr>
<tr>
<td></td>
<td>0.81-1.2</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>1.21 – 1.6</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td>&gt;2.0</td>
<td>-10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymphocyte count</th>
<th>10^9x1-1</th>
<th>Diagnostic Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte count on Day 2</td>
<td>0-0.2</td>
<td>+6</td>
</tr>
<tr>
<td>Lymphocyte count on Day 2</td>
<td>0.61-0.8</td>
<td>-15</td>
</tr>
<tr>
<td>Lymphocyte count Days 4 – 7</td>
<td>0.01</td>
<td>+5</td>
</tr>
<tr>
<td>Lymphocyte count Days 4 – 7</td>
<td>&gt;0.15</td>
<td>-15</td>
</tr>
</tbody>
</table>

A sum of +10 is the basis for the prognosis of irreversible myelosuppression; a sum of -10 is a prognosis for NO irreversible myelosuppression.
The Bone Marrow Syndrome and its Treatment in Chernobyl Victims (1)

- **Antiseptic regimen**
  - Isolation
  - Air sterilization
  - Changes of underclothing for patients at least once/day
  - Maintaining the micro-organism population at less than 500/mm³ in the room air

- **Supportive therapy**
  - Antimicrobial decontamination of the intestine
  - Administration of systemic antibiotics
  - Acyclovir
  - Transfusions of blood cells (e.g. fresh donor platelets and RBC)


Bone Marrow Syndrome and its Treatment in Chernobyl Victims (2)

- HLA-matched unrelated bone marrow donors from large HLA-typed volunteer donor pools – 13 patients

- Fetal liver cells – 6 patients

- Bone marrow syndrome combined with other Injuries
  - Skin
  - GI
  - Oropharyngeal
  - Radiation pneumonitis
### Severity and Outcome of ARS in Chernobyl Victims

<table>
<thead>
<tr>
<th>ARS Grade</th>
<th>Dose (Gy)</th>
<th>Total</th>
<th>Alive</th>
<th>Died (day to death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.8 - 2.1</td>
<td>31</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>2.0 - 4.0</td>
<td>43</td>
<td>42</td>
<td>1 96</td>
</tr>
<tr>
<td>III</td>
<td>4.2 - 6.3</td>
<td>21</td>
<td>14</td>
<td>7 16 - 48</td>
</tr>
<tr>
<td>IV</td>
<td>6.0 - 16.0</td>
<td>20</td>
<td>1</td>
<td>19 14 - 91</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>115</td>
<td>88</td>
<td>27*</td>
</tr>
</tbody>
</table>

* In addition to the patients who died of ARS, one person died at the plant site, and another within the first 12 hours following the accident as a result of thermal burns.


### Causes of Death from Direct Radiation Effects in First 3 months

<table>
<thead>
<tr>
<th>Number of patients died (TOTAL = 27)</th>
<th>Days of death after the exposure</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>14 - 34</td>
<td>In 20/22 patients β-burns were the main cause of death</td>
</tr>
<tr>
<td>5</td>
<td>48 – 99*</td>
<td>Died after the bone marrow recovery stage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* Patient on Day #96 died from ischemic stroke</td>
</tr>
</tbody>
</table>

### Indications for an Allogeneic BMT or an Embryonic Live Cell Transplantation

- Whole body γ-irradiation dose **6.0 Gy -16.0 Gy**
- Irreversible degree of myelosuppression using a Diagnostic Coefficient (DC) 
  - plus additional criteria
  - Vomiting during the first **30 minutes**
  - Diarrhea during **1-2 hours** after the exposure
  - Swelling of the parotid glands during the first **24-36 hours**

Ref: UNSCEAR 1988 Report

### Outcome (Survival or Cause of Death) in Patients Receiving BMT

<table>
<thead>
<tr>
<th>Dose range (Gy)</th>
<th>Number of patients</th>
<th>Deaths*</th>
<th>Deaths**</th>
<th>Number of survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6.5</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>6.5 – 9.0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 9.0</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>13</strong></td>
<td><strong>7</strong></td>
<td><strong>4</strong></td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>

*Skin and GI injuries

**GVHD + infection

Problems that Complicated the Use of BMT for Chernobyl Victims

- Determination of the radiation dose
- Several kinds of irradiation (external $\gamma$- and $\beta$, and inhaled and ingested isotopes)
- Partial shielding of body parts by physical structures
- Rapid onset of lymphocytopenia made HLA typing difficult. Donor-recipient histocompatibility was not accurately determined
- Most individuals who received a sufficiently high dose of irradiation had thermal burns as well as injuries to the GI tract and other tissues

Non-bone Marrow Syndromes Caused by Radiation Exposure

<table>
<thead>
<tr>
<th>Acute Radiation Syndrome</th>
<th>Skin burns (%)</th>
<th>Oropharyngeal Syndrome (%)</th>
<th>Gastro-intestinal (%)</th>
<th>Radiation Pneumonitis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>115</td>
<td>56 (48.6)</td>
<td>80 (69.5)</td>
<td>17 (14.7)</td>
<td>7 (6.1)</td>
</tr>
</tbody>
</table>

Barabanova A., Vojnosanit Pregl. 2006 May;63(5):477-80
Ministry of Health, Clinical Department of the Institute of Biophysics, Moscow, Russia. abarananova@rambler.ru
### Varying Severity of Skin Damage in Patients with ARS

<table>
<thead>
<tr>
<th>Severity (Grade) of Acute Radiation Syndrome (ARS)</th>
<th>Number of Patients with ARS</th>
<th>Percentage of Skin Involvement in Patients with ARS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50% 10-50% 1-10% TOTAL</td>
</tr>
<tr>
<td>IV</td>
<td>20</td>
<td>9 10 1 20</td>
</tr>
<tr>
<td>III</td>
<td>21</td>
<td>3 15 3 21</td>
</tr>
<tr>
<td>II</td>
<td>43</td>
<td>1 9 2 12</td>
</tr>
<tr>
<td>I</td>
<td>31</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>115</td>
<td>13 35 8 56</td>
</tr>
</tbody>
</table>

Guskova et al, Acute radiation effects in exposed persons at the Chernobyl Atomic Power Station Accident, Soviet Radiology, 1986 (article in Russian)

### Treatment Experience of Skin Injuries in Chernobyl victims

- **Systemic treatment**
  
  Hemoperfusion, plasmapheresis, continuous heparinization and administration of freshly frozen plasma

- **Local treatment**
  
  Use of Combutec-2 for local treatment of skin injuries
  
  Aerosol Lioxanol
  
  Solution Balis-2

- **Pain management**
  
  was challenging and not effective due to an absence of the local anesthetics in the treatment arsenal

- **Necessity of surgical operations at an early stage**

Causes of Death Among ARS Survivors (1986 through 2006)

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Grade I ARS</th>
<th>Grade II ARS</th>
<th>Grade III ARS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncological and oncohematological pathology</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Internal organ systems and neurological diseases</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Traumas and accidents</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>6</strong></td>
<td><strong>7</strong></td>
<td><strong>5</strong></td>
<td><strong>18</strong></td>
</tr>
</tbody>
</table>

What was the Most Unexpected for us?

- Diversity of clinical manifestations of skin lesions
- Unaccustomed course of clinical phases of a radiation injury to skin
- Significant severity of injuries
- Serious influence of skin burns on the general state of a patient
- Need for surgical operations at an early stage
**Major Lessons of Chernobyl (1)**

- Communications: who/how to contact, how to verify and confirm information

- Confidentiality: different understanding of what was classified and what was not, limited information available for International professional community

- Public health implications of the radiological accident: International significance was not as well understood as for communicable diseases incidents

"An accident has occurred at Chernobyl nuclear power station. One of the atomic reactors has been damaged. Measures are being taken to eliminate the consequences of the accident. Aid is being given to the victims. A government commission has been set up."
Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency

Major Lessons of Chernobyl (2)

- Effective medical care is generally not possible for accident victims with high-dose TBI
- Most individuals will not receive a sufficiently high dose to make a bone marrow transplant necessary for hematological recovery
- Only a small number of patients will have bone marrow syndrome without other life-threatening non-bone marrow related complication
- Transplants should probably be considered for victims receiving more than 7 to 8 Gy of external radiation

Major Lessons of Chernobyl (3)

- Maximize education of health care providers
- Medical community must be provided with practical tools how to identify and assess radiation victims
- Conflicting information should be avoided
- Situation should be explained to population in plain language
Foremost Considerations

- Prevention of future accidents
- Precautions to minimize radiation injuries (protective measures for workers called in to control a nuclear accident, prospective HLA typing)
- Cryopreservation of autologous bone marrow may also be considered for selected individuals
- Biodosimetry and biomarkers should be used in determining the dose of the exposure
Lessons Learned from Hurricane Katrina

David Rutstein, M.D., M.P.H.
United States Public Health Service
Lessons Learned From Hurricane Katrina

David Rutstein, M.D., M.P.H.
CAPT & Chief Medical Officer, USPHS

Presented to the
Medical and Organizational Challenges
Resulting from a Radiological/Nuclear Emergency Seminar

25 September 2007

No financial relationships to disclose or honorariums received.
The Federal Response to Hurricane Katrina Lessons Learned

- 11 career Federal employees
- access to every official document and every situation report
- 530+ interviews
- released by the White House on February 23, 2006
- 17 critical challenge areas
- 125 recommendations for improving the Federal response to disasters

Critical Challenges

1. National Preparedness
2. Integrated Use of Military Capabilities
3. Communications
4. Logistics and Evacuation
5. Search and Rescue
6. Public Safety and Security
7. Public Health and Medical Support
8. Human Services
9. Mass Care and Housing
10. Public Communications
11. Critical Infrastructure and Impact Assessment
12. Environmental Hazards and Debris Removal
13. Foreign Assistance
14. Non-Governmental Aid
15. Training, Exercises, and Lessons Learned
16. Homeland Security Professional Development and Education
17. Citizen and Community Preparedness

Communications

• Communications infrastructure was destroyed
• 3 million customers lost telephone service.
• Up to 50% of broadcast communications were disrupted.
• Both responders and citizens lacked a reliable communications network.
• No national, State of region plans to incorporate available communications assets.
Logistics and Evacuations

• State and local officials worked with FEMA, DOD and DOT.
• Shelters (chosen or de-facto) were inadequate.
• Flooding continuously impeded efforts.
• Lack of communications infrastructure compounded the problem.
Search and Rescue

• Mostly from Federal agencies (USCG, FEMA, DOD).
• Lack of overarching plan led to coordination problems.
Rescue

Public Safety and Security

• Looting, violent crimes occurred, but were less prevalent than initially reported.
• Security problems obstructed the speed of the Federal response.
• Criminal justice system was crippled.
• Federal law enforcement officers were deployed, but lacked coordination and were impeded by State and local ordinances.
Human Services

- Needs of victims quickly exceeded State and local capacities.
- FEMA and the American Red Cross led the Federal effort to meet these needs.
- Lack of single point of contact where victims could register for all Federal services created inefficiencies that hampered delivery of assistance.
Mass Care and Housing

• Shelters were inadequate but still utilized.
• Interagency coordination was lacking, resulting in unused housing assets.
New Orleans Superdome

- 20,000 evacuees and 590 SNPs
- Swelled to 38,000 evacuees and 1700 SNPs in 12 hrs…
- 200 ambulances, 40 Blackhawks and 4 Chinooks

Public Communications

- Public affairs structures were non-existent or incapacitated.
- Contradictory messages to the public created confusion, eroded confidence.
- The media gathered and aired uncorroborated information which interfered with ongoing response efforts.
Health and Medical Challenges

• Identification, triage and treatment of acutely sick and injured patients.
• Management of chronic medical conditions in large numbers of evacuees with special health care needs.
• Assessment, communication and mitigation of public health risks.
• Mortuary support.
• Assistance to State and local officials to re-establish health care delivery systems and public health infrastructures.
Federal Health and Medical Support

- HHS and DOD collaborated with State and local health officials.
- NDMS teams collectively treated over 100,000 patients.
- Supplies from the Strategic National Stockpile.
- HHS deployed 24 public health teams.
- VA delivered care in their facilities.
- Command and control of these activities was poorly planned and executed.
**Health and Medical Inefficiencies**

- Command and control of these activities was poorly planned and executed.
- Inadequate evacuation of patients.
- Weak State and local infrastructures.
- Insufficient pre-storm communications to the public.
- Absence of uniform electronic health records.

*greater analysis and planning.....*

---

**Planning**

- Base Plan
- Appendixes
- ESF Annexes
- Support Annexes
- Incident Annexes

State and Local Response

- Extensive damage to facilities and equipment.
- Local responders were severely impacted.
- Complete devastation of communications infrastructure.

  *the result…*

- It was difficult or impossible to establish functioning incident command structures.
General Recommendation

- Responders to national emergencies will operate according to a single, comprehensive but flexible plan that is understood, practiced and continuously evaluated by all responding entities.
  - National Response Plan – NRP
  - National Incident Management System – NIMS
General Recommendation

• Effective disaster response efforts must include operable and interoperable communications capabilities.

General Recommendation

• Disasters will continue to cause a sudden increase in the size of vulnerable populations.
General Recommendation

• The military must be more effectively integrated into disaster responses.

General Recommendation

• The Nation as a must be better prepared for future disasters.
  – a National Preparedness System
  – a Culture of Preparedness
Public Health and Medical Support

• Responders must be from all levels of government as well as the private sector.
  – all types of health professionals
  – working collaboratively

Public Health and Medical Support

• Communication to the public is the single most important function to prevent and mitigate morbidity and mortality associated with disasters.
Public Health and Medical Support

• Local and State health departments must gain added disaster preparedness and response capabilities.

Public Health and Medical Support

• All medical responders must use an interoperable electronic health records system.
Lesson Learned for greater success…

• Competency determines responsibility.
• A strengthened public health and medical command drives successful efforts.
  – Communication of public health information and medical data is vital.
  – Local and State health departments must play a greater role.
  – Effective integration ofuniformed personnel and assets is essential.
• Collaboration occurs between people, not organizations.

Contact Info

David Rutstein, M.D., M.P.H.
CAPT & Chief Medical Officer, USPHS
Director, Office of Force Readiness and Deployment
Office of the Surgeon General
5600 Fishers Lane, Suite 18C-26
Rockville, MD 20857
Tel: 301.443.6588
david.rutstein@hhs.gov

Questions?
The Goiânia Accident: Past and Present

Nelson J. Valverde, M.D. – Laboratory of Radiological Sciences, State University of Rio de Janeiro, Brazil
The Goiânia accident: past and present

Valverde NJ – Laboratory of Radiological Sciences, State University of Rio de Janeiro, Brazil

Curado MP – Superintendence Leide das Neves Ferreira, State of Goiás Health Agency, Goiânia, Brazil

Financial Disclosure - Management Position:
Hygia Integral Occupational Health and Safety

The past

On September 13, 1987, two scavengers entered the abandoned premises of a radiotherapy clinic in Goiânia and removed the rotating assembly of a $^{137}$Cs radiotherapy device. At the house of one of them, they managed to break open the shutter of the collimator orifice and were exposed to radiation.
The past

Five days later, the violated equipment was sold to a junkyard. During the next days, fragments of Cs were given to many persons and pieces of the equipment were sold to two other junkyards. Some people put fragments of Cs in pockets or rubbed them on the skin.

The past

During the next days, people developed prodromal manifestations of ARS and local radiation injuries (CRS). Manifestations were not recognised by local physicians as radiation induced.
On September 28, 1987, MG suspected the manifestations people were presenting were caused by exposure to “the object”. She and another individual took it to the Sanitary Surveillance Secretary of Goiânia.

People were admitted to local hospitals, diagnosed as pemphigus, “allergic dermatitis” and food intoxication. Finally, on September 29, a local physicist identified the nature of the accident.
The past: immediate medical impact

- 20 persons hospitalised (ARS/CRS/external and internal contamination)
- 28 persons with CRS
- One amputation
- 4 deaths
- 112,800 persons screened at the Olympic Stadium for radiation contamination (~15% of the population)

The past: environmental impact - waste generation – 3,500 m³

- 1.347 boxes;
- 4.223 drums;
- 10 sea containers and
- 8 concrete drums.
The past: seven houses demolished

- Discrimination against victims, relatives, friends, neighbours ...
- Vehicles with Goiás plates not allowed in other states
- Prejudice against Goiás citizens in airports, interstate bus stations ...
- The Goiás representation was not allowed in a traditional beneficent Catholic fair in Rio
- Police force used during burials
- Goiás income lowered 30% after 4 months of the accident
The past: disturbances during burials

Definitive waste disposal site
## Regional Centre of Nuclear Sciences Abadia de Goiás

![Image of Regional Centre of Nuclear Sciences Abadia de Goiás](image)

## The present: follow-up by SULEIDE

<table>
<thead>
<tr>
<th>Group</th>
<th>Criteria</th>
<th>Persons</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ARS and or CRS and or cytogenetics dose $\geq 0.2$ Gy and or $^{137}$Cs burden $\geq 1/2$ALI</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td>II</td>
<td>Cytogenetics dose $\leq 0.2$ Gy and or $^{137}$Cs burden $\leq 1/2$ALI</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>Not included in the above criteria, but a “social” victim (eg: the person lost his/her house)</td>
<td>518</td>
<td>22</td>
</tr>
<tr>
<td>IV</td>
<td>Included by legal determination</td>
<td>417</td>
<td>7</td>
</tr>
</tbody>
</table>
The present: cancer deaths up to 2006

<table>
<thead>
<tr>
<th>Kind of cancer</th>
<th>Group</th>
<th>Gender</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>I</td>
<td>Male</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pharynx</td>
<td>III</td>
<td>Male</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>III</td>
<td>Female</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Uterus</td>
<td>III</td>
<td>Male</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tonsil</td>
<td>III</td>
<td>Female</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>III</td>
<td>Female</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>III</td>
<td>Male</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>III</td>
<td>Female</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Skin (melanoma)</td>
<td>III</td>
<td>Male</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sarcoma (maxilla)</td>
<td>III</td>
<td>Female</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

One GI patient died of cirrhosis and had esophagus and prostate cancer
A Group I patient was recently diagnosed as having MDS syndrome

The present: local radiation injuries

- sequels (amputations)
- recurrences
  - **three cases**
- one patient with necrosis of the femur
Past and present: influences for the psychological consequences

- The magnitude of the accident
- The myth of radiation as an evil force
- Severe medical manifestations and deaths
- The press and lack of information
- The low cultural and social background of victims and patients

Special consideration on the administration of PB

1. Cesium contamination was caused mainly by ingestion and penetration through local radiation injuries.

2. A total of 46 individuals received PB. Daily doses varied from 3 to 10 g d⁻¹.

3. PB was given 2 to 6 times per day. The minimum interval was 2 hours. Four patients received 20g during one day, but gastric complaints determined discontinuing this.

4. Drug administration started in day 19 PE, but even latter in some patients.
Side effects

- hypokalemia (possible – values 2.5 to 2.9 mEq L⁻¹) [The effect of PB in decorporating Cs>Rb>K>Na];
- intestinal constipation in 10 individuals;
- dyspepsia (6 mo latter, in 11 individual that had also other causes for the manifestation).

PB efficacy

1. The efficacy of PB to reducing Cs burden was followed by about 4,000 urine and faeces bio-assays.

2. The average reduction of $^{137}\text{Cs} \text{ biological } T_{\frac{1}{2}}$ with PB was the same either with a daily dose of 3, 6 or 10g:
   - In adults – 69%
   - In adolescents – 46%
   - In children – 43%
Influence of PB on the biological half-life of $^{137}$Cs in adults

(adapted from IAEA-TECDOC-1009 – *Dosimetric and medical aspects of the radiological accident in Goiânia in 1987 – Efficacy of Prussian Blue therapy for decorporation of cesium* – p.39)

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>3 g d$^{-1}$</th>
<th>6 g d$^{-1}$</th>
<th>10 g d$^{-1}$</th>
<th>after PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>x</td>
<td>20</td>
<td>33</td>
<td>58</td>
</tr>
<tr>
<td>b</td>
<td>21</td>
<td>17</td>
<td>x</td>
<td>75</td>
</tr>
<tr>
<td>c</td>
<td>26</td>
<td>63</td>
<td>x</td>
<td>106</td>
</tr>
<tr>
<td>d</td>
<td>17</td>
<td>39</td>
<td>x</td>
<td>80</td>
</tr>
<tr>
<td>e</td>
<td>21</td>
<td>15</td>
<td>x</td>
<td>75</td>
</tr>
<tr>
<td>Mean - +/- SD</td>
<td>25 +/- 9</td>
<td>25 +/- 15</td>
<td>26 +/- 6</td>
<td>x</td>
</tr>
</tbody>
</table>

PB clearly altered the feces to urine 1:4 caesium ratio of excretion

Feces to urine ratio for people subjected to PB treatment (from IAEA-TECDOC-1009 – *Dosimetric and medical aspects of the radiological accident in Goiânia in 1987 – Efficacy of Prussian Blue therapy for decorporation of cesium* – p.40)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Prussian Blue (g d$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>EDF</td>
<td>0.19</td>
</tr>
<tr>
<td>DAF</td>
<td>0.24</td>
</tr>
<tr>
<td>GGS</td>
<td>0.02</td>
</tr>
<tr>
<td>WMP</td>
<td>0.50</td>
</tr>
<tr>
<td>RAS</td>
<td>0.28</td>
</tr>
<tr>
<td>EAS</td>
<td>0.17</td>
</tr>
<tr>
<td>LOMS</td>
<td>2.82</td>
</tr>
<tr>
<td>DAF</td>
<td>2.50</td>
</tr>
<tr>
<td>KSS</td>
<td>2.16</td>
</tr>
<tr>
<td>ERF</td>
<td>1.44</td>
</tr>
</tbody>
</table>
PB clearly altered the feces to urine 1:4 caesium ratio of excretion: example of the effect of PB administration (from IAEA *The Radiological Accident in Goiânia* – p.53)

Activity in excreta – $10^4$ Bq

- Activity in urine
- Activity in feces

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Activity (Bq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>3.7</td>
</tr>
<tr>
<td>30</td>
<td>7.4</td>
</tr>
<tr>
<td>40</td>
<td>11.1</td>
</tr>
<tr>
<td>50</td>
<td>14.8</td>
</tr>
<tr>
<td>60</td>
<td>18.5</td>
</tr>
<tr>
<td>70</td>
<td>22.2</td>
</tr>
</tbody>
</table>

**A special case**

- Patient LNF, 6 yr-old
- Initial calculated Cs intake: 1,677 MBq (279.5 ALI)
- PB: 6g/d
- Blood activity on day 10: 52.92 MBq/L
- Blood activity on day 24: 18.14 MBq/L
- $^{137}\text{Cs } T_{ef}$ for a 6 yr-old girl:
  - 8.8 d for 44% of the burden
  - 32 d for 56% of the burden
Conclusions

- The Goiania accident was characterized by protracted exposures of individuals of the public to ionizing radiation.
- The violation of the cesium source happened on September 13, 1987 and the accident’s nature was only evident sixteen days later.
- This fact was mainly caused because local health personnel were not able to identify the clinical manifestations of the victims as radiation induced ones.

Conclusions

- A planted radiation source could also determine protracted exposures of individuals of the public.

- One lesson from Goiania is that health personnel must be aware of the clinical manifestations of whole body and local radiation exposures (“acute” radiation and cutaneous radiation syndromes).
Conclusions

- Besides conventional injuries, the detonation of a radiation dispersal device (RDD) could also cause both external irradiation and also contamination (like in Goiania). It is possible that the preferable radiation source in a “dirty bomb” would be a $^{137}\text{Cs}$ one, because its chemical properties (like in Goiania).

- Authorities in charge to responding to a radiation emergency must consider aspects like:
  - hospitals preparedness to cope with patients both with conventional trauma but also with radiation contamination;
  - the supply of specific drugs like Prussian Blue;
  - medical protocols for triage and treatment of victims with radiation injuries;
  - mass communication and the psychological consequences of a radiation emergency.

Conclusions

- It is likely that the detonation of a radiation dispersal device (RDD) would cause a disproportional fear of the “radiation risk” in the public in general (like in Goiania).

- In this respect, authorities in charge to responding to a radiation attack must consider aspects like:
  - timely and adequate information;
  - reassuring;
  - psychosocial assistance.
Thank you!
Introduction to Radiation Biology

Mike Robbins, Ph.D.
Wake Forest University School of Medicine
Introduction to Radiation Biology

Mike Robbins, PhD
Radiation Biology Section
Department of Radiation Oncology
Wake Forest University School of Medicine

Radiation Can Dissipate Its Energy By Two Methods

- EXCITATION
- IONIZATION
Excitation

Amount of energy absorbed raises an electron in an atom/molecule to a higher energy level without ejection of the electron

- Occurs following exposure to non-ionizing radiation e.g., UV

Ionization

- Occurs when the absorbed radiation has enough energy to eject one or more orbital electrons from the atom/molecule

- Energy dissipated per ionizing event is ~ 33eV; only 4.9 eV required to break a C=C bond

- Radiation with such energy called ionizing radiation, e.g., α and β particles [particulate radiation], X and γ rays [electromagnetic radiation]
Particulate Radiation

α particle: positively charged particle emitted by radioactive materials. Consists of 2 protons + 2 neutrons, identical to a helium nucleus

- VERY ionizing; thousands of ionization events/cm of travel
- Internal hazard only: inhalation/ingestion/wound
- Easily stopped by sheet of paper

Polonium$^{210}$ emits α particles, penetrate ~ 60 mm in biological tissues
- Highly toxic if internalized, taken up by a broad spectrum of tissues

Alexander Litvinenko, 1963-2006
**Particulate Radiation**

β particle emitted from a nucleus during radioactive decay. Negatively charged β particle identical to electron; positively charged β particle called a positron

- ~7200x less massive than α
- Can present internal and external hazard to humans, particularly skin burns
- Stopped by Lucite shielding or thin metal sheet

**Types of Ionizing Radiation**

Gamma rays (γ): a quantum (packet) of electromagnetic energy, similar to x-ray (only difference is origin)

- Travel at speed of light
- VERY hazardous; require massive shielding for human protection
Electromagnetic Spectrum

Examples: X rays and γ rays

Can view as either a wave of electrical and mechanical energy or as photons (packets of energy)
Ionizing Radiation

- Irradiating biological material leads to a random distribution of energy in tissues and cells

- With ionizing radiation photons contain sufficient energy to break chemical bonds leading to biological effects

DNA Damage is a Critical Event in Radiation-induced Cell death

- Microirradiation studies indicate that to kill cells by irradiation the cytoplasm requires much greater doses than the nucleus; >250 Gy compared with ~2 Gy

- Isotopes such as $^3$H and $^{125}$I that emit short range $\beta$ particles, when incorporated intercellular DNA, efficiently produce radiation cell kill and DNA damage

- The incidence of chromosomal aberrations following irradiation is closely linked to cell kill

- Thymidine analogues such as IUdr and BrUdr when specifically incorporated into DNA modify radiosensitivity. Substituted deoxyuridines, which are not incorporated into DNA, have little affect on cellular radiosensitivity
Ionization and Radical Formation

Ionization of water leads to generation of an ion pair

\[ \text{H}_2\text{O} + \text{radiation} \rightarrow \text{H}_2\text{O}^+ + e^- \]

\(\text{H}_2\text{O}^+\) is an ion radical: ion is an atom/molecule that is electrically charged since it has lost an electron

Free radical is an atom/molecule that possesses one or more unpaired electrons; highly reactive

\[ e^- + \text{H}_2\text{O} \rightarrow e^-_{\text{aq}} \]

A hydrogen free radical can also be produced, together with some hydrogen peroxide:

\[ e^-_{\text{aq}} + \text{H}^+ \rightarrow \text{H}^\bullet \]

\[ \text{HO}^\bullet + \text{HO}^\bullet \rightarrow \text{H}_2\text{O}_2 \]
Ionization and Radical Formation

Radiolysis of water:

\[ \text{H}_2\text{O} + \text{radiation} \rightarrow e^-_{\text{aq}} + \text{HO}^\bullet + \text{H}^\bullet + \text{H}_2\text{O}_2 \]

G values: 2.63 2.72 0.55 0.68

G value: measured yield of molecules produced by absorption of 100 eV X rays. For low LET, highest yields are \( e^-_{\text{aq}} \) and \( \text{HO}^\bullet \).

Direct and Indirect Effects of Radiation

Direct effect: target molecule itself reacts directly with radiation

\[ \text{RH} \rightarrow \text{RH}^+ \]

\[ \text{RH}^+ \rightarrow \text{R}^\bullet + \text{H}^+ \]
Direct and Indirect Effects of Radiation

Indirect effect: ionizing radiation generates free radicals from the radiolysis of water

These can indirectly form radicals with the target molecule

\[ \text{RH} + \text{HO}^* \rightarrow \text{R}^* + \text{H}_2\text{O} \]

\[ \text{RH} + \text{H}^+ \rightarrow \text{R}^* + \text{H}_2 \]

“Fixation” of Biological Injury

In the presence of oxygen, an organic peroxy radical is formed. This cannot easily be repaired, and so acts to “fix” the biological injury

\[ \text{R}^* + \text{O}_2 \rightarrow \text{ROO}^* \]
Absorption of radiation 

Ionization/Excitation 

Chemical lesion 

Enzymatic repair or fixation of damage 

Biological Effects 

X rays 

$10^{-5}$ seconds 

$10^{-5}$ seconds 

Hours 

Days to months to years 

Radiation Cell Killing 

- For cells proliferating \textit{in vitro}, define cell death as loss of \textit{reproductive ability} 

- Refers to cell losing its ability to exhibit unlimited cell division 

- Clonogenic cell: cell that has reproductive ability, can divide indefinitely to produce a large colony or clone
Radiation Cell Killing

- In vivo, predominant form of cell death following irradiation occurs at mitosis, requires a dose of ~ 2 Gy
- Irradiating non-dividing or rarely dividing cells with very high doses, ~ 100 Gy can cause loss of cell function and death, i.e., Interphase Death
- Apoptosis or programmed cell death: involves programmed sequence of events controlled by specific genes. Can occur at low doses of radiation

Construction of an in vitro cell survival curve

Hall, Radiobiology for the Radiologist
Cell Survival Curve

To construct a cell survival curve use a range of doses and determine the surviving fraction, SF, after each dose.

\[ SF \text{ after dose } D = \frac{\text{mean number of colonies after dose } D/\text{dish}}{\text{mean number of cells plated/dish}} \times PE \]

Number of cells seeded per dish needs to be adjusted so that a countable number of colonies is obtained.

Mammalian Cell Survival Curves
Dose-Rate Effect

- For X- or γ rays, dose rate is one of the most important factors that determine the biologic effect of a given dose.

- As dose rate is lowered and exposure time increased, biologic effect is in general reduced.

- Seen over a dose range of 1 Gy/min to 0.3 Gy/h; with decreasing dose-rate see loss of shoulder.

Dose-Rate Effect
Dose-Rate Effect

Linear Energy Transfer (LET)

- LET is the energy transferred per unit length of track
- Unit is the kiloelectron volt per micrometer (keV/μm) of unit density material
- LET is an average value that can be calculated in different ways
Linear Energy Transfer (LET)

- Track average: obtained by dividing the track into equal lengths, calculating the energy deposited in each length, and finding the mean.

- Energy average: obtained by dividing the track into equal energy increments and averaging the lengths of track over which these energy increments are deposited.

For X rays or monoenergetic charged particles, the two methods give similar results.

However, very different for 14-MeV neutrons; track average is ~12 keV/μm, energy average LET is ~ 75 keV/μm.

Biological properties of neutrons tend to correlate best with the energy average.
Relative Biological Effectiveness

- The amount of radiation dose is expressed in terms of absorbed energy; dose in Gy is a measure of energy absorbed/unit mass of tissue.

- However, equal doses of different types of radiation DO NOT produce equal biological effects.

- Key to the difference lies in the pattern of energy deposition at the microscopic level.

Relative Biological Effectiveness

- To compare the biological effect of different types of radiation use x-rays as the standard.

- RBE is formally defined as follows:

\[
\text{RBE} = \frac{\text{dose of x-rays to produce a given effect}}{\text{dose of test radiation to produce a given effect}}
\]
Relative Biological Effectiveness

- RBE is not a single value
- Depends on the level of biological damage (and thus the dose) chosen
- In general, RBE ↑ as dose ↓ until limiting value reached
Relative Biological Effectiveness

As LET increases, radiation produces more cell kill per Gy.

As LET increases, survival curves become steeper and the shoulder becomes progressively smaller.
RBE as a function of LET

- If plot RBE as a function of LET, RBE increases slowly at first, then more rapidly as LET > 10 keV/μm.
- RBE then increases rapidly to a peak value of ~ 100 keV/μm, after which RBE decreases rapidly.
- The LET at which RBE peaks is essentially the same for a wide variety of mammalian cells.

Optimal LET

Why is radiation with an LET of 100 keV/μm optimal?

- At this density of ionization, average separation density between ionizing events roughly coincides with diameter of DNA double helix, i.e., 2nm (20Å).
- Radiation of this density has the greatest probability of causing a double-strand break by the passage of a single charged particle; double-strand breaks are the basis for most biologic effects.
Optimal LET

- LET radiation > 100 keV/µm results in wasted energy or overkill
- Very high LET radiation is inefficient since it deposits more energy than needed in critical sites
- These cells are overkilled and Gy there is less likelihood that other cells will be killed, leading to a reduced biological effect

Factors that determine RBE

- Radiation quality (LET)
- Radiation dose
- Dose rate
- Biologic system or endpoint
At low LET, corresponding to x-rays or γ rays, OER is 2.5-3.
As LET increases, OER decreases slowly until the LET > ~60 keV/μm. OER then falls rapidly, reaching unity when LET around 200 keV/μm.
Cytogenetic Biodosimetry

Albert L. Wiley, Jr., MD, Ph.D.
WHO Collaborating Center at Oak Ridge
and Radiation Emergency Assistance
Center/Training Site (REAC/TS)
Cytogenetic Biodosimetry

Albert L. Wiley, Jr., M.D., Ph.D., USNR(RET)
Director, WHO Collaborating Ctr. at Oak Ridge and Radiation Emergency Assistance Center / Training Site (REAC/TS)

The REAC/TS Cytogenetic Biodosimetry Lab (CBL) is funded by NNSA (DOE)

Why use peripheral blood lymphocytes as biological dosimeters?

- High degree of radiosensitivity,
- Circulation throughout all organs,
- Accessibility by routine venipuncture,
- Ease of in vitro culture.

What is Cytogenetic Biodosimetry?

A type of Cytogenetic Biodosimetry utilizes metaphase spreads of peripheral blood lymphocytes to search for radiation specific chromosome aberrations which are counted to determine a dose estimate.
Dicentric Chromosome Analysis is a type of Cytogenetic Biodosimetry which is the “Gold” Standard for clinical radiation biodosimetry assessments.

The REAC/TS Cytogenetic Biodosimetry Lab (CBL) serves as a national emergency response asset under DOE/NNSA.
Cytogenetic Biodosimetry takes advantage of the human body's generalized response to radiation exposure; and it can be used to supplement physical dosimetry, or to substitute for physical dosimeters when they are not present, such as when there is a need to evaluate the general public's exposures. Peripheral lymphocytes can essentially act as dosimeters.

To Assist Triage in Multi-Casualty Incidents

By Categorizing radiation dose levels into dose ranges, i.e.,:

- <1 Gy, 2-4 Gy, and >4 Gy
  - 1 Gy, 8-12 dicentrics/100 metaphase cells.
  - 4 Gy, 100 dicentrics/100 metaphase cells.

A useful scoring strategy for rapid triage may be the analyzing of 25-50 cells per person which would permit assignment of each casualty into a dose range category, thereby assisting the subsequent medical management.
**Accidental dosimetry**

**PHYSICAL DOSIMETRY**
- DOSE RECONSTRUCTION, Personal Dosimeters

**BIOLOGICAL DOSIMETRY**
- CYTOGENETIC DOSIMETRY
  - Dicentrics, FISH, PCC, MNA

**CLINICAL DOSIMETRY**
- NAUSEA, VOMITING, BLOOD CELLS
- COUNTS, SKIN REACTIONS...

**OTHER BIOINDICATORS**

---

**Biophysical background to chromosome damage**

High LET

Low LET
DNA damage

Classification of chromosomal aberrations

Symmetrical Breaks (STABLE)  Asymmetrical Breaks (UNSTABLE)

Inversion  Intrachange  Centric Ring

Interchange  Translocation  Dicentric
Biological dose assessment using standard dicentric analysis

- Introduced by M. Bender in 1964
- Isolated lymphocytes stimulated by phytohaemagglutinin (PHA) into mitosis
- Arrest of metaphase using colchicine
- Scoring of dicentric chromosome aberrations in metaphase spreads

Typical Dose Response Relationships for Induction of Chromosome Aberrations

Low Linear Energy Transfer (LET)

Dicentric Analysis

Quadratic (linear-quadratic)

\[ Y = \alpha D + \beta D^2 \]

High Linear Energy Transfer (LET)

Linear

\[ Y = \alpha D \]
Dose estimation of acute vs chronic exposure

\[
\begin{align*}
\text{Gamma rays, } X\text{-rays acute exposure (Low LET)} & : Y = c + \alpha D \\
\text{Gamma rays, } X\text{-rays chronic exposure (Low LET)} & : Y = c + \alpha D + \beta D^2 \\
\text{\(\alpha\) particles, Fast neutrons (High LET)} & : Y = c + \alpha D
\end{align*}
\]

What is the process for Cytogenetic Biodosimetry?

- Obtain a blood sample
- Culture the lymphocytes (~2 days) to obtain first division metaphases
- Stain and prepare the slides
- Score the cells - cells on the slide are scored for dicentrics (aberrations)
- Estimate dose – The number of dicentrics is then compared to a source specific calibration curve
The Automated Cytogenetic Workstation has automated slide handling and scanning. Computer karyotyping (identification/arranging) of the chromosomes and identification of aberrations, unlike the old system where the cytogeneticist had to find and score each cell by hand.

MN and nucleoplasmic bridges in binucleated cells (Giemsa stained)
Acute Whole Body Exposure
penetrating Low-LET Radiation

All cells in body at equal and random risk for exposure

Cytogenetic Dosimetry
Accurate estimates of equivalent whole body dose of ~ 10-20 cGy

El Salvador Co\textsuperscript{60} Accident

- 18,000 Ci source (stacked wafers)
- Medical Sterilization Unit (blood storage products, tubes, etc)
- Three workers exposed to unshielded source
Cytogenetic Dose Estimates for three men exposed to $^{60}$Co gamma radiation in the El Salvador Accident

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cells</th>
<th>Dicent</th>
<th>Dicent per cell</th>
<th>Dose (Gy)*</th>
<th>95% CI</th>
<th>Fraction**</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A)</td>
<td>35</td>
<td>131</td>
<td>3.74</td>
<td>8.2</td>
<td>7.4 - 9.0</td>
<td>99%</td>
</tr>
<tr>
<td>(B)</td>
<td>350</td>
<td>308</td>
<td>0.87</td>
<td>4.4</td>
<td>4.2 - 4.7</td>
<td>91%</td>
</tr>
<tr>
<td>(C)</td>
<td>500</td>
<td>266</td>
<td>0.53</td>
<td>3.2</td>
<td>3.0 - 3.5</td>
<td>92%</td>
</tr>
</tbody>
</table>

- Estimated dose to exposed fraction of lymphocytes
- Estimated fraction of lymphocytes exposed
Acute Partial Body Exposure
penetrating Low-LET Radiation

Cytogenetic Dosimetry
I  May not detect evidence of exposure
II >1/3 to 1/2 body exposed, easily detected
Fractionated / Protracted Whole Body Exposure
penetrating Low-LET Radiation

Source

All cells in body at equal and random risk for exposure

Cytogenetic Dosimetry
Dose rate effectiveness factor may be considered
Biological Dose Estimate may not predict clinical findings
Summary

Cytogenetic biodosimetry may be a useful form of clinical dosimetry for assessing actual and possible radiation exposures:

- **Sensitivity** – a relatively low threshold for large volume exposures to photons and some particles (like neutrons). Some sensitivity to partial body exposures.
- **Highly Specific** for chromosome damage by radiation.
- **Timely** – although analysis requires 4 to 5 days, it may still be useful for detection/triage/treatment for doses > ~0.25 Gy – and for re-assuring people who are concerned about possible radiation exposures.
- **International acceptance** – International Standards Organization (ISO) certification and standardization protocols.
The Clinical Approach of METREPOL: A Challenge for Hematology to Provide Indicators of Effect and Repair Dictating Options for Therapy

Prof. Dr. Theodor M. Fliedner
Radiation Medicine Research Group and WHO Liaison Institute for Radiation Accident Management
Faculty of Medicine, University of Ulm
The Clinical Approach of METREPOL: A Challenge for Hematology to Provide Indicators of Effect and Repair Dictating Options for Therapy

Prof. Dr. Theodor M. Fliedner
Radiation Medicine Research Group and
WHO Liaison Institute for Radiation Accident Management
Faculty of Medicine, University of Ulm, Germany

A Contribution to the RITN Seminar on Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency
Washington, DC, September 25, 2007
Executive Summary:

“... a new strategic approach for the diagnosis of the ARS is proposed: the Response Category (RC) concept. It focuses on the integrative quantification of the impairment of the organism by ionizing radiation and does not rely at all on physical or biological estimates of the radiation dose. ...”
ARS: A complex reality requiring a new appraisal of well-known observations

The Ulm Database SEARCH (System for Evaluation and Archiving of Radiation Accidents based on Case Histories) contains 824 case reports of 81 radiation accidents reported from 19 countries that occurred between 1945 and 2001. The systematic analysis of 110 severe cases was used to assess the significance of multiorgan involvement and results in a new description of the ARS:

"The ARS evolves in a regular fashion as a function of time after a short-term total body radiation exposure resulting in an involvement of all cells, cell and organ systems in relation to their turnover kinetics, their functional properties and potentials as well as their systemic interaction. If the compensatory potentials are exhausted, multi-organ involvement results in a multi-organ failure."

It is the purpose of the initial “clinical triage” to determine whether an autologous hemopoietic recovery is potentially possible or not. If yes, then it is sufficient to "bridge" the 1-2 weeks of granulocytopenia and thrombocytopenia by antibiotics or platelet transfusion. If not, a stem cell transplantation is the only way to restore hemopoiesis and to have any chance to treat the impairments of other organ systems later.
24 „Indicators of Effect“ used to characterize the Acute Radiation Syndrome as a function of time

Patient ID 999
Begin of exposure 01.01.2000 10:00
Examiner N.N.

<table>
<thead>
<tr>
<th>Symptom A</th>
<th>Symptom Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of severity</td>
<td>Degree of severity</td>
</tr>
<tr>
<td>Maximum</td>
<td>Grading</td>
</tr>
</tbody>
</table>

- Symptom A: 2
- Symptom Z: 1
- Maximum: 2
- Grading: N

- Symptom A: 2
- Symptom Z: 1
- Maximum: 2
- Grading: H

- Symptom A: 2
- Symptom Z: 1
- Maximum: 2
- Grading: C

- Symptom A: 1
- Symptom Z: 1
- Maximum: 1
- Grading: G

Terminology of the RC concept: from the organ-specific grading to the grading code and the corresponding RC at different times during ARS

Spreadsheets used for documentation of clinical signs and symptoms after a radiation accident. The prodromal symptom with the highest degree of severity determines the initial RC. A repeated complete system review provides information that may change the initial RC as a function of time (see example given for the first hours). Arrows indicate that this sheet is to be extended according to the Addendum/Compendium.

The METREPOL approach to assess the severity of effect to the hemopoietic system is aimed at the probability of a reversible or irreversible damage to the stem cell pool

<table>
<thead>
<tr>
<th>RC 4 (Grade H4)</th>
<th>RC 3 (Grade H3)</th>
<th>RC 2 (Grade H2)</th>
<th>RC 1 (Grade H1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous recovery</td>
<td>Stimulation (growth factor therapy)</td>
<td>Supportive care; Substitution (blood component therapy)</td>
<td>General support of recovery processes; usually no specific therapy</td>
</tr>
<tr>
<td>Stem cell transplantation</td>
<td>Internal haematological-oncological institutes with reverse isolation; Intensive care unit; Consultations of all medical specialties</td>
<td>Medical wards with haematological-oncological, neurological and dermatological consultation services</td>
<td>Outpatient care or general medical wards</td>
</tr>
</tbody>
</table>

Complexity of clinical care

Response Category | Therapeutic interventions | Institutional requirements

- Specialised hospital with experience in all areas of intensive care medicine, particularly allogeneic SCT
- Internal haematological-oncological institutes with reverse isolation; Intensive care unit; Consultations of all medical specialties
- Medical wards with haematological-oncological, neurological and dermatological consultation services
- Outpatient care or general medical wards
Blood cell changes in 17 patients characteristic for Grade H4 (essentially irreversible damage of stem cell pool)

Results from 17 patients from several radiation accidents

Comment: In 17 patients, a rather uniform blood cell response is seen. However, “the dose” (median) was 11 Gy with a wide spectrum from 8 Gy to 20 Gy.
Results for 21 patients of the Chernobyl workforce

Lymphocyte changes after accidental radiation exposure in relation to calculated doses

Comment:
The "median dose" in these patients showing a uniform blood cell response pattern was 3.9 Gy with a considerable spread between 2-7 Gy.
What is the scientific evidence for the recommendations underlying the METREPOL approach?

- Biomathematical models that were developed for the three cell renewal systems are able to simulate the pattern of cell changes and relate them to the vital conditions of the stem cell pool.

Clinical Course Patient A

**Blood cell response pattern**
- **G**: Initial granulocytosis, decline day 5-6
- **T**: Linear sharp decrease, nadir day 5-7
- **L**: Sharp decline, nadir day 2

**Therapy**
- PBSCT day 6 - 7
- Recovery starting day 16-17
- Type: mixed chimerism
- Death: day 83 after exposure
Blood cell response in 3 radiation accident victims after bone marrow stem cell transplantation

Lymphocyte responses in 3 radiation accident patients receiving B.M. stem stalls

Comment: In the cases observed with stem cell transplantation engraftment, the cells were given after 3 and 4 days respectively and resulted in a recovery of granulocytes and platelets about 10-12 days later. All of them would have been graded as H4.
What are consequences, options and open questions to treat patients assigned to grade H4?

- Selection of medical center (sufficient competence in HSCT, number of patients acceptable)
- Careful assessment of health impairments in the light of multi-organ involvement (what are the chances for recovery from ARS, if one could restore hematopoiesis quickly?)
- Selection of donors and type of cells (blood, BM, cord blood?) (which database can be used: international cooperation badly needed).
- Time of transplantation
- Bridging the gap with risk of infection and bleeding (antibiotics, platelet support) before onset of regeneration of blood cell system
- Gnotobiotic therapy? (The role of selective or complete bacterial decontamination)

What are consequences, options and open questions to treat patients assigned to grade H3, H2 and H1?

- Selection of medical center (competence in the treatment of cancer patients requiring severe chemo-/radiotherapy resulting in temporary pancytopenia)
- Assessment of the multi-organ oriented health impairment status (severity of injury to system other than hemopoiesis? Which service should take the lead in treating the patient)
- Bridging the period of granulocytopenia and thrombopenia (about 2 weeks) and treat or prevent infection and bleedings (antibiotics, platelet support)
- If patients are assigned to grade H3: What is the role of the administration of cytokines, if a spontaneous recovery of granulocytes and platelets can be expected at around days 35-40?
What are the organizational challenges “to be prepared” (I)

- In Europe, the EBMT network comprising medical centers with competence in stem cell transplantation is prepared to help the establishment of an “intelligent research and treatment network” that can be called upon to take care of radiation accident victims.
- EBMT is in preparation to offer “short advanced training courses” for medical specialists (medical doctors, nurses) to add “radiation medicine competence” to their knowledge.
- The content of these courses should be agreed upon on the international (European as well as Transatlantic) level to make sure that excellent care is provided worldwide from accredited hospitals.

What are the organizational challenges “to be prepared” (II)

- In case of nuclear emergencies (that can occur anywhere anytime) a pool of mobile laboratory containers should be available to be placed on demand into the immediate vicinity of the medical centers that have agreed to take patients. This laboratory should have all the hard- and software to help the medical centers to fulfill their task (nuclear emergency medical “rescue” team).
- International agreements should be conducted to allow “cross border” cooperation about the commitment to carry the cost of medical help and intervention.
Summary

1. The attempts on both sides of the Atlantic to be prepared for large-scale unclear emergencies appear to be important and timely. It is recommended to try to obtain an international consensus about means and ways to recognize and classify the responses of the organism regarding exposure to ionizing radiation. The METREPOL-concept should be considered as a valid approach to manage radiation accident victims from the viewpoint of practical medicine and used as the core of "advanced training courses" for clinicians, such as are being planned by the EMBT.

2. It appears essential from the viewpoint of hematology to determine the Response Category for radiation accident victims and the grade of injury as a basis for planning the therapy. The initial pattern of blood cell changes of granulocyte, lymphocytes and platelets is of decisive prognostic value as to whether one is dealing with a reversible or irreversible damage of the stem cell and precursor compartments. A stem cell transplantation is the only way to restore hemopoiesis (even if temporarily) if the indicators of effect suggest irreversible damage.

Summary (to be continued)

3. The autologous regeneration potential of the hemopoietic system is enormous due to the pathophysiological proportion of the system (such as role of circulating stem cells).

4. The multi-organ involvement seen in ARS patients requires a multi-organ approach to the clinical problem as described in the METREPOL concept and should pave the way for a computerized expert guidance system for a disease entity that is extremely rare but may result in a catastrophic situation if the numbers of victims exceed the potentials of the health care system.
What are the blood cell concentration patterns for granulocytes, platelets and lymphocytes in patients accidentally exposed to ionizing radiation? In particular, which pattern predicts hemopoietic failure (irreversible damage of the stem cell pool (damage grade H4))? 

- The pattern “stem cell pool irreversibly damaged”
  - **Granulocytes:**
    initial granulocytosis (days 1-3, values: up to 25,000/mm³),
    progressive decline with a $T/2$ of about 7 hours at days 4-5,
    severe granulocytopenia at days 5-6
  - **Platelets:**
    Progressive decline within the first 5-10 days, nadir of $<20,000$/mm³ within 5-8 days
  - **Lymphocytes:**
    Progressive decline within 24-48 hours, values below 100/mm³
What are the blood cell concentration patterns for granulocytes, platelets and lymphocytes in patients accidentally exposed to ionizing radiation? In particular, which initial pattern predicts hemopoietic injury of the stem cell pool able to recover autochthonously? (No stem cell support needed, but symptomatic therapy) (Grade H3, H2, H1)

Granulocytes:
Initial granulocytosis can be observed within days 1-3 with a subsequent decrease until day 5. An abortive rise can also be seen starting at around day 5, keeping the cell count at an average of $1 \times 10^9/l$ for about 5-8 days. Hereafter, the cell counts drop to levels below $0.5 \times 10^9/l$ around days 10-15. This low level is maintained for about 20 days (nadir, degree 3). Signs of increasing cell counts become obvious around days 30-35. The pattern of recovery varies: it may be slow or rapid leading to an overshoot.

Platelets:
Cell counts remain above the lower border of the normal range ($150 \times 10^9/l$) down to $100 \times 10^9/l$ until days 5-10. The nadir is reached at about day 16-18 at a level of $(0-50) \times 10^9/l$. The nadir lasts for about 12-15 days (nadir, degree 3). The recovery pattern varies from slow to overshooting and mostly shows an undulating pattern but does not begin before days 35-40.

Lymphocytes:
Cell counts drop almost linearly within the first 48 hours after exposure and remain between $0.25 \times 10^9/l$ and $1.0 \times 10^9/l$ (degree 3).

What does METREPOL stand for, why its importance for a Seminar on Nuclear Threats or – Emergencies?

- A consortium of experts from Europe with some support by experts from other parts of the world were charged by the European Commission to develop “Medical Treatment Protocols for Radiation Accident Victims as a Basis for a Computerized Guidance System”.
- The result was a “Manual on the Acute Radiation Syndrome” describing a new form of Medical Management of Radiation Accidents (British Institute of Radiology, London 2001).
- The EBMT (consisting of >472 hospitals of 34 countries in Europe which are competent to be charged with the care of ARS patients) through its Nuclear Emergency Subcommittee felt the need to provide assistance for governmental responsibilities, such as an infrastructure to deal with victims.
What's new? What are the lessons learned from previous nuclear emergency events?

- A new strategic approach is suggested for the medical management of the ARS: the Response Category Concept (RC) based on a professional assessment of the health impairment (grading) status of the four most relevant organ systems (NVS, H, C, Gi).
- This approach is advocated in order to base any therapy on the recognition of the quality and quantity of the "multi-organ involvement", which characterizes the ARS and not "a dose".
- A total of 24 "indicators of effect" (see Natl. Res. Council (NRC), USA) is used to assess the quality and quantity of the ARS as a function of time after radiation exposure.
- In particular, the hematological "indicators of effect" allow one to decide whether a stem cell transplantation is needed (irreversible stem cell damage) or whether the period of hemopoietic failure can be "bridged" by symptomatic therapy (reversible stem cell damage).

What are the assumptions regarding the hospitalization of patients in a mass accident scenario?

- In order to spare the competent hospitals from being overwhelmed with patients that require only ambulant care (minimal or non-radiological health impairments), there must be an "open field triage" to select these patients that require hospitalization immediately on the basis of quality of health judgement.
- A 5-digit code is suggested:
  1st digit: person involved yes/no
  2nd digit: type of radiation exposure
  3rd digit: additional trauma yes/no
  4th digit: TBI or PBI
  5th digit: immediate hospitalization yes/no
- No patient should enter the door of a hospital with evidence of any significant radioactive contamination. Further, the hospitals to accept patients should be accredited for the management suggested by the triage code.
What is the scientific evidence for the recommendations underlying the METREPOL approach?

- The University of Ulm group was able to establish a System for Evaluation and Archiving of Radiation Accidents based on Case Histories ("SEARCH") containing the clinical sequence of signs and symptoms of different organ systems as a function of time after ionizing radiation exposure.
- The blood cell forming tissues are affected: the clinical picture is the consequence of radiation induced damage at the level of stem cells distributed throughout the entire bone marrow sites.
- In particular: the assessment of the granulocyte-, platelet- und lymphocyte concentration pattern during the first 5-6 days allows one to predict whether the stem cell damage will turn out to be reversible or irreversible.

Typical blood cell response patterns after whole body penetrating exposure to ionizing radiation.

- H4 = most severe injury resulting in an essentially bone marrow failure which can be overcome only by stem cell transplantation.
- H3 = severe injury to bone marrow resulting in a transient system failure treatable by bridging the time of pancytopenia in the blood which is predictable from early blood cell change patterns. Code numbers: patients from radiation accidents.
What about H3/H2 and H1 patients?

- All patients assigned to one of the grades H3/H2/H1 should be taken to a medical facility accredited to handle patients with a severe (but transient) hematopoietic failure (as is often the case in the care of tumor patients receiving chemotherapy).

- In these patients, it should be considered whether other than the hematological system are severely affected (for instance, H3 or H2 in combination with C4 (severe and extensive effect in the skin)).

- In any event, the time period of pancytopenia (about 2 weeks from days 15-35) should be covered by platelet transfusion, antibiotics as well as growth factors (to shorten the time of cytopenia).

- Reverse isolation must be considered to avoid the development of bacterial and fungal infection.

---

is one able to understand the blood cell changes seen after irradiation related to the extent and type of stem cell damage?

**Model of Granulocytosis**

- **F** = mature circulating granulocytes  
  $t_{1/2} = 7$ hrs

- **R** = Mobilizable reserve of granulocytes responsible for initial granulocytosis

- **M** = Post-mitotic maturing pool of granulocytes (metamyelocytes, band forms)  
  $t = 4$ days

- **P** = Proliferation pool from myeloblast to small myelocytes  
  $t = 6$ days

- CBL/CBM = Progenitor cells, intact or injured

**Attention:** The possible "overshoot" of granulocytes seen between 40-60 days after exposure are a consequence of the feed-back regulation mechanisms of the system.

For the megakaryocyte/Platelet system as well as for the lymphocyte system appropriate biomathematical models were developed and are in use.
A: 4 patients with “irreversible damage of the stem cell pool: stem cell pool eradicated completely. The “system” runs out of cells.

B: 4 patients with “reversible damage of the stem cell pool: “the abortive rise phase” is compatible with the notion of an “injured” stem cell compartment.

C: Calculated values for different stem cell fractions.

**Table 1. Fractions of remaining, injured, and destroyed stem cells.**

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Remaining intact fraction (%)</th>
<th>Remaining injured fraction (%)</th>
<th>Destroyed fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>0.96</td>
<td>0.4</td>
<td>0.84</td>
</tr>
<tr>
<td>02</td>
<td>0.93</td>
<td>0.3</td>
<td>0.74</td>
</tr>
<tr>
<td>03</td>
<td>0.9884</td>
<td>0.2</td>
<td>0.72</td>
</tr>
<tr>
<td>04</td>
<td>0.9455</td>
<td>0.17</td>
<td>0.90</td>
</tr>
<tr>
<td>05</td>
<td>0.9849</td>
<td>0.19</td>
<td>0.90</td>
</tr>
<tr>
<td>06</td>
<td>0.99</td>
<td>0.1</td>
<td>0.90</td>
</tr>
<tr>
<td>07</td>
<td>1.0</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>08</td>
<td>0.9956</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>09</td>
<td>0.9956</td>
<td>0.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Interim Conclusions (I)**

- The hematological indicators of effect and repair are the early patterns of concentration changes of granulocytes, platelets, and lymphocytes.

- The “irreversible” stem cell pool damage as well as the simultaneous destruction of the precursor compartments of granulocytes and platelets results in a disappearance pattern characteristic for the normal fate of the cells released into blood.

- The “reversible” stem cell pool damage associated with some radiation-induced injury of the precursor compartments expresses itself through the slower decrease of granulocytes in the blood between days 4 and 7 (which means some normal proliferation and maturation - somewhere) and the “abortive rise”, which can be explained only by the “injured cell hypothesis” (injured stem cells with a reduced number of cell replications). The duration of an abortive recovery phase appears to be a consequence of the ratio of the intact vs. injured stem cells.
Interim Conclusions (II)

- The platelet disappearance pattern of an "reversible" stem cell pool damage is characterized by a continuation of some platelet production in the megakaryocyte compartment, resulting in a "shoulder" of the blood platelet concentration pattern before the nadir is reached after 25-30 days after exposure, followed by a progressive recovery.

- Lymphocyte recovery is slow but steady and cannot be used as a predictor of hematological recovery.

Engraftment of WBC in Patient A
Acute Radiation Syndrome of the Skin: New Aspects in Pathophysiology and Treatments Following Radiation Exposure

Prof. Dr. Viktor Meineke
Bundeswehr Institute of Radiobiology
Acute Radiation Syndrome of the Skin: New aspects in pathophysiology and treatments following radiation exposure

Prof. Dr. Viktor Meineke
Bundeswehr Institute of Radiobiology affiliated to the University of Ulm

Structure

- History and definitions of the cutaneous radiation syndrome (CRS)
- CRS in clinic and mass casualty management
- CRS on the molecular level
- CRS as one of the main factors in radiation-induced multi-organ failure
- Combined injuries and CRS
- Triage and therapeutic options to cope with CRS related health effects
History of the cutaneous radiation reaction

March 1896:
First publication on side effects after X-ray (localized hair loss, dermatitis)

Definitions to be taken into account!

- Acute Radiation Syndrome
- Chronic Radiation Syndrome (determinants are time and dose)
- Localized Radiation Injuries
- Whole body exposures (determinants are affected body surface and affected organs)
Survival curves for clonogenic assays of normal tissue cells

Surviving Fraction

Dose [Gy]

Human A-T Cells
Bone Marrow Colony Forming Units
Mammary Cells
Testis Stem Cells
Thyroid
Jejunal Crypt Cells

A-T: Ataxia telangiectasia (Chromosomal Damage Syndrome)

Early Radiation Induced Skin Lesions
Late Radiation Induced Skin Lesions

- fibrosis
- ulcers
- contracture
- epilation
- teleangiectasia
- keratosis
- haemangioma
- destruction of sweat glands
- carcinogenesis (squamous cell carcinomas, sarcoma)

CRS in clinic and mass casualty management
Time Course of Radiation Reaction

- **prodromal phase** (early erythema) 1.3 h after total body irradiation with 300 cGy
- **phase of manifestation** (acute radiodermatitis e.g. erythema, vesiculation, epitheliolysis, erosion) 1-4 weeks after skin irradiation with
  - 300 cGy - 3,000 cGy. Ulceration, necrosis
  - >3,000 cGy skin irradiation
- **chronic phase**

→ Cutaneous radiation syndrome

CRS as an essential clinical sign for unknown radiation exposure
Radiation accident Georgia 1997 / 2003


Dermatologic complications may be the limiting factor in treatment and prognosis of radiation victims
Acute radiation-induced skin lesions are emergencies

Triage and therapeutic options
Severity of skin lesions and affected body surface related to survival of the acute phase

![Graph showing BS vs. degree (mean)](image)

- Death in acute phase
- Survivors

Early development of skin lesions as a sign for poor prognosis

![Bar graph showing time to first development of skin lesions](image)

Dörr et al., submitted
Analysis of survival (Kaplan–Meier): hematopoetic H3-4 and cutaneous system: 65% of RC H 3 and BS <50% patients survive!

CRS on the molecular level

- Adhesion molecules
- Cytokines
- Mast cell mediators
Ionizing radiation up-regulates expression of ICAM-1 and TNF-α in skin cells

TNF-α amplifies the radiation effect on ICAM-1 expression in HaCaT cells


Experimental Hematology 33 (2007) 96-104

Radiation-induced alterations in cytokine production by skin cells

Kerstin Müller and Viktor Meinske
Bundeswehr Institute of Radiobiology, Munich, Germany

Ionizing radiation exposure of skin results in a cutaneous radiation reaction comprising all pathophysiological reactions and clinical symptoms in irradiated skin. Biological responses of skin occur in a characteristic temporal pattern and mainly depend on radiation quality, dose rate, total dose, and cellular conditions. Immediately after irradiation, production of cytokines by skin cells is initiated and continues as a cascade during all stages of the cutaneous radiation syndrome leading to progressive late syndromes, the predominant of which is fibrosis. Cytokines are important signaling molecules mediating communicative interactions both locally between different cell types within dermal tissues and distantly between organs. Although during recent years much progress has been made in dissecting the complex cytokine network, the role of cytokines in the pathophysiology of the cutaneous radiation reaction is only beginning to be elucidated. Previous studies indicate that the major cytokines in the response of skin cells to ionizing radiation include IL-1, interferon-α, IL-6, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, and the chemokines IL-8 and eotaxin. In this paper, existing data on the radiation-induced modulation of cytokine expression by skin cells are reviewed. © 2007 International Society for Experimental Hematology. Published by Elsevier Inc.
Mast cell number in skin is increased after exposure to ionizing radiation

human skin

\[ \downarrow \text{IR} \]

cutaneous radiation reaction

\[ \downarrow \text{acute effects} \]
- erythema
- swelling
- desquamation
- ulceration

\[ \downarrow \text{long-term effects} \]
- fibrosis
- telangiectasia
- necrosis
- dermal atrophy
- skin cancer

Ionizing radiation causes degranulation of mast cells \textit{ex vivo}

Control

5 Gy

Human mastocytoma

Serotonin release from mast cells *in vitro*

Serotonin release from HMC-1 after ionising radiation

Fibroblasts as a target of serotonin
CRS as one of the main factors in radiation-induced multi-organ failure

Morbidity and mortality relating to organ involvement and -failure within acute radiation syndrome at grading RC 4 (death within < 60 days, n = 45)

<table>
<thead>
<tr>
<th>survival-time [days]</th>
<th>n (total)</th>
<th>hemopoetic-system</th>
<th>skin</th>
<th>GIT</th>
<th>CNS</th>
<th>kidney</th>
<th>liver</th>
<th>respiratory-system</th>
<th>cardiovasc.-system</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>11-20</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>11</td>
<td>7</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>21-30</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>31-40</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Σ</td>
<td>45</td>
<td>45</td>
<td>43</td>
<td>45</td>
<td>45</td>
<td>32</td>
<td>25</td>
<td>32</td>
<td>20</td>
</tr>
</tbody>
</table>

Fliedner, Dör and Meineke (2005) Multi-organ involvement as a pathogenetic principle of the radiation syndromes: a study involving 110 case histories documented in SEARCH and classified as the bases of haematopoietic indicators of effect. British Journal of Radiology, Suppl 27
CRS is a determining factor in mass casualty management

**Table 1. The role of the skin in radiation-induced multi-organ failure**

<table>
<thead>
<tr>
<th>Diagnostic parameter</th>
<th>Critical organ</th>
<th>Possible trigger factor (e.g. immune reactions)</th>
<th>Determines the “point of no return”?</th>
<th>Treatment of skin complications may help to prevent multi-organ failure</th>
</tr>
</thead>
</table>


IN-DEPTH REVIEW

**Medical management of radiation injuries: current approaches**

**M. E. Berger, D. M. Christensen, P. C. Lowry, O. W. Jones and A. L. Wiley**

**Abstract**
The current approach to medical management of irradiated patients begins with early diagnosis of radiation injury. Medical assessment of radiation dose is based on event history, symptomatology and laboratory results, with emphasis on time to emesis and lymphocyte depletion kinetics. Dose assessment provides a basis for early use of hematopoietic growth factors that can shorten the period of neutropenia for patients with acute radiation syndrome. Assessments of hematopoietic, gastrointestinal and cutaneous syndromes have improved in recent years, but treatment options remain limited. Selected examples of current developments are presented.

**Key words**
Combined injury; gastrointestinal syndrome; hematopoietic syndrome; internal contamination; local radiation injury; radiation injury; radiation medicine.
Dermatological treatment options for radiation injury

- steroids
- gamma interferon
- pentoxifylline
- alpha-tocopherol
- mesenchymal stem cells
- antioxidants, e.g. superoxide dismutase
- panthenol
- disinfectant solutions

There is a clear lack of common treatment protocols for acute radiation injury of the skin and there are no evidenced based approaches yet
Possible new pharmacological approaches to serotonergic effects

• Blocking identified 5HT-Receptors
• Reducing 5HT-synthesis in mast cells
• Investigation of specific trigger mechanisms of ionising radiation that cause mast cell degranulation
• Stabilising mast cells from degranulation

Combined injuries and CRS
Summary and Conclusions

- CRS is an important aspect in triage after accidental radiation exposure
- CRS is one of the determining factors in radiation-induced multi-organ involvement and failure and plays a special role in combined injuries
- Cytokines and mast cells products are promising targets to understand radiation effects
- There are no evidenced-based treatment options to cope with radiation-induced skin damage yet
- A deeper insight into the pathophysiology of radiation damage is needed to develop further treatment options
Bundeswehr Institute of Radiobiology
affiliated to the University of Ulm

Prof. Dr. V. Meineke

email: ViktorMeineke@bundeswehr.org
Role of Gastrointestinal Role of Gastrointestinal Injury in Acute Radiation Syndromes

Martin Hauer-Jensen, MD, PhD
University of Arkansas for Medical Sciences

Not available for Internet publication
Neurovascular/CNS Syndrome

Mike Robbins, PhD
Radiation Biology Section
Department of Radiation Oncology
Wake Forest University School of Medicine

Total body dose of approx. 100 Gy $\gamma$ rays will cause death in a few hours

N.B. All organs severely damaged and would cause death if the person survived long enough

- Cerebrovascular damage occurs rapidly, causing death within 24-48h. See severe nausea and vomiting within minutes, followed by disorientation, respiratory distress, diarrhea, seizures, coma, and death

- Pathogenesis thought to be massive edema leading to severe brain dysfunction
Neurovascular/CNS Syndrome

- 1964: 38 year-old-man working in a $^{235}$U recovery plant was involved in nuclear accident; received total dose of ~88 Gy (22 Gy neutrons, 66 Gy $\gamma$ rays)
- Recalled seeing a flash, hurled backwards but did not lose consciousness. Ran from scene of accident to another building 200 yards away
- Complained of abdominal cramps and headaches, vomited, was incontinent with bloody diarrheal stools. Next day patient comfortable but restless

On second day condition deteriorated

- Victim became restless, fatigued, apprehensive, short of breath, greatly impaired vision, hypotensive
- Six hours before death became disoriented, blood pressure could not be maintained
- Died 49 h after accident
In Utero Irradiation

Predominant effects of radiation in utero:

- Small head size (microcephaly) and mental retardation
- Reduction in head diameter seen in 62/1473 individuals irradiated between weeks 3-25
- Correlation seen between reduction and dose above 0.2 Gy

Effect of Dose and Pregnancy Trimester on Incidence of Microcephaly

*[Image of graph showing the effect of dose and trimester on the incidence of microcephaly]*

Mental Retardation

Of 1565 children, 30 showed clinically severe mental retardation, defined as

“Unable to perform simple calculations, to make simple conversation, to care for him/herself; and if he or she was completely unmanageable or has been institutionalized”

- Severe mental retardation was not observed to be induced by radiation before 8 weeks after 25 weeks post conception
- Most sensitive period was between 8-15 weeks; for exposure during weeks 16-25, the risk lowered 4-fold

Effect of Dose and Postovulatory Age on Incidence of Severe Mental Retardation

[Graph showing the effect of dose and postovulatory age on the incidence of severe mental retardation.]

Mental Retardation: Mechanism

- Human brain begins to develop during the first 6 weeks of development. The hemispheres then continue to grow and differentiate during fetal life and infancy.

- Period between weeks 8-15 corresponds to neuroblast proliferation:
  - Radiosensitive
  - Have limited capacity for proliferation; can only make up the loss of a few cells

Mental Retardation: Mechanism

Cell Migration

- Irradiation interferes with migration of cells destined to become neurons - during weeks 8-15 cortical neurons migrate from ventricles to cortex.

- In rats irradiated @ day 16 of gestation, doses as low as 15 cGy can inhibit neuronal migration, together with a reduction in the expression of the neural cell adhesion molecule N-CAM.
**Mental Retardation**

- Lack of mental retardation when irradiation occurs before 8 weeks of gestation due to neurons being not yet sensitive to radiation
- However, the glial cells, which provide support, are radiosensitive and thus see only a reduction in head size

**Radiation-induced Late Effects**

**Classic Dogma:**

- Radiation leads to chronic and progressive loss of function
- Radiation-induced late normal tissue injury solely due to reduction in clonogenic cell survival
- Radiation-induced injury is chronic, progressive and untreatable
Radiation-induced Late Effects

New paradigm:
- Late normal tissue injury involves complex dynamic interactions between multiple cell types
- Cells are *active participants* in an orchestrated response, not merely *passive bystanders*
- Organ response to injury is *limited, independent* of the initial insult and *treatable*

Radiation-induced Brain Injury

<table>
<thead>
<tr>
<th>days</th>
<th>weeks</th>
<th>months</th>
<th>years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE</td>
<td>EARLY DELAYED</td>
<td>LATE</td>
<td></td>
</tr>
</tbody>
</table>

- Edema
- Headache
- Somnolence
- Neuro. worsening
- Transient demyelination
- Somnolence
- Attention deficits
- Short-term memory loss
- Vascular abnormalities
- Demyelination
- White matter necrosis
- Cognitive impairment
- Dementia
- Death
Fractionated WBI is Associated with no Gross Histological Changes in the Rat Brain

Atwood et al Radiat Res, 2007 in press

Fractionated WBI Leads to Cognitive Impairment: Object Recognition (A) and Morris Water Maze (B)

Model of Radiation-induced Brain Injury

- Radiation
- Oxidative Stress & Inflammation
- Altered Glial/Neuronal Function/Phenotype
- Neurobiological & Vascular Changes
- Cognitive Impairment

Increased Proliferation and Oxidative Stress Follow the Rapid Depletion of Neural Precursors in the Irradiated Hippocampus

![Graph showing Ki67 positive cells and MDA (mM/mg protein) levels over days and weeks after radiation exposure.]

Limoli et al, PNAS 2004, 101:16052-7
Persistent Generation of ROS in Primary Rat Neural Precursor Cells after Irradiation


Lipoic Acid Attenuates ROS Levels

Irradiating the Mouse Brain Leads to Chronic Microglial Activation

Radiation-induced Microglial Activation Correlates with Decreased Number of Newborn Neurons in the Hippocampus

Monje ML et al Nat Med 8:955-962, 2002

White bar= Non-irradiated Black bar= Irradiated NeuN= Mature neuron Tuj-1= Immature neuron
Radiation-induced Microglial Activation is Alleviated by the Anti-inflammatory Drug Indomethacin

2 months post-irradiation.

IR = Radiation alone (10Gy)
IR+IND = Irradiation plus Indomethacin (2.5mg/kg)


The Renin-Angiotensin System

RAS Blockers and Treatment of Radiation Late Effects

- Agents directed at inhibiting activity of the RAS have proven effective in treatment of experimental radiation-induced injury in the kidney, lung and heart.

- Therapeutic efficacy of Ang II blockers reflects inhibition of Ang II locally generated within these organs. Each of these organs possesses a functioning, organ-based RAS.

Ramipril Reduces the Severity of Radiation-induced Optic Neuropathy

Table 1: Sequential change of VEP (ms) after radiation

<table>
<thead>
<tr>
<th>Time after radiation</th>
<th>Radiation alone</th>
<th>Radiation + ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (no radiation)</td>
<td>96.2 ± 7.9</td>
<td>96.2 ± 7.9</td>
</tr>
<tr>
<td>3 months</td>
<td>91.1 ± 14.2*</td>
<td>75.3 ± 9.9*</td>
</tr>
<tr>
<td>5 months</td>
<td>173 ± 9.9*</td>
<td>105.7 ± 9.3*</td>
</tr>
<tr>
<td>6 months</td>
<td>108.1 ± 9.7</td>
<td>105.7 ± 9.5</td>
</tr>
</tbody>
</table>

* P < 0.05

Table 2: Effect of ramipril dose on the magnitude of radiation-induced optic neuropathy

<table>
<thead>
<tr>
<th>Ramipril dose</th>
<th>Gross abnormality</th>
<th>Severe necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mg</td>
<td>25% (2/8)</td>
<td>43% (3/7)</td>
</tr>
<tr>
<td>1.0 mg</td>
<td>55% (5/9)</td>
<td>75% (6/8)</td>
</tr>
<tr>
<td>0.5 mg</td>
<td>62% (5/8)</td>
<td>100% (8/8)*</td>
</tr>
</tbody>
</table>

* P < 0.05

Ranipril started at 2 weeks after radiation
Severe necrosis was microscopically defined as area of necrosis >50% of the optic nerve/brachium in the whole mount specimen.
Daily Administration of the AT₁RA L158,809 ameliorates Radiation-induced Cognitive Impairment

**Summary**

Brain irradiation can lead to:

- A rapid reduction in neurogenesis
- Cognitive impairment months to years PI, in the absence of gross histologic changes
- Chronic oxidative stress and microglial activation
Summary and Future Directions

- Experimental interventional approaches that target chronic oxidative stress appear to prevent or reduce the severity of radiation-induced cognitive impairment.

- However, specific pathogenic mechanisms involved remain unclear.

- Need to consider affect of age on radiation response of the brain. Children and females are particularly sensitive to radiation-induced cognitive impairment. Elderly may also be more sensitive than young adults.
National Response Process

C. Norman Coleman, M.D.
Office of Preparedness and Emergency Operations

Not available for Internet publication
RITN Overview

Cullen Case, Jr.
National Marrow Donor Program
Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency

RITN Overview

Agenda

- Who is RITN?
- What Needs Does RITN Fill?
- What is RITN Doing to Prepare?
- What Can RITN Offer?
- Key Partners in the Development of RITN
- Concerns
- List of RITN Centers
Charter

The **Radiation Injury Treatment Network SM (RITN)** provides comprehensive evaluation and treatment for victims of radiation exposure or other marrow toxic injuries. RITN develops treatment guidelines, educates health care professionals, works to expand the network, and coordinates situation response. RITN is a cooperative effort of the National Marrow Donor Program (NMDP) and The American Society for Blood and Marrow Transplantation (ASBMT).

RITN Development Timeline

- **1986** - Initiation of NMDP - Navy relationship
- ‘86-’01 - Response network realized as an unfulfilled need
- **2001** - NMDP begins organizing concept of core network
- **2003** - NMDP transplant center physicians discuss options
- **2004** - ASBMT joins initiative
- **2005** - ASBMT increases emphasis
  - NMDP solicits HSCT physician support
- **2006** - NMDP initiates agreements with 13 transplant centers
  - RITN steering committee finalizes materials
- **2007** - Expansion of RITN to include donor centers and cord blood banks (52 total centers)

Tomorrow…
Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency

Organization of RITN

RITN Oversight and Management

Executive Committee Co-Chaired by NMDP & ASBMT

Steering Committee

NMDP
ASBMT

RITN Primary TC Medical Directors

External Advisors (civilian and government)

RITN Network Composition

9 NMDP Donor Centers

36 NMDP Transplant Centers

7 NMDP & NCBI Cord Blood Banks

13 RITN Primary Transplant Centers

23 RITN Secondary Transplant Centers

RITN Distribution Across USA

Primary Transplant Centers
Donor Centers
Cord Blood Banks
Secondary Transplant Centers
Possible Events Involving RITN

- Focus of preparations: Any incident resulting in mass casualties with a marrow toxic injury
- Examples of possible events:
  - Radiological
    - Improvised Nuclear Device (IND)
    - Military grade nuclear weapon
    - Radiological exposure device (open source)
    - Radiological Dispersal Device (RDD) a.k.a. dirty bomb
      - Less likely to overwhelm existing response resources
  - Chemical
    - Lewisite (a.k.a. Mustard gas)
  - Unknown

What Needs Does RITN Fill?

- Provide ready facilities with practicing specialists for intensive supportive care and treatment
  - Infrastructure and process for transplant if needed
- Increases transplant community awareness about potential need of their services in time of crisis
- Involves transplant community in emergency preparedness
What is RITN Doing to Prepare?

- Standard Operating Procedures
- Basic radiation training completed by staff
  - Grand rounds presentation in development
  - Additional training resources provided on RITN Web site
- Conduct an annual tabletop exercise
- Emergency communications tests
  - GETS cards and satellite telephones
- Coordinating with government (DHHS-ASPR)

What Can RITN Offer?

- Provide expert knowledge based on significant practical experience in treating patients with compromised immune-systems
- Treatment facilities for victims
- Regional dispersion other transplant physicians can talk to a peer in RITN
- Available through RITN Website: www.nmdp.org/ritn
  - RITN Acute Radiation Syndrome treatment guidelines
  - RITN center standard operating procedure templates
  - Donor selection criteria
  - NMDP data collection protocol
  - Training resources
  - Pertinent publications
Key Partners in the Development of RITN

- American Society for Blood and Marrow Transplantation (ASBMT)
- Department of Defense - Office of Naval Research (ONR)
- Health Resources and Services Administration (HRSA)
- Center for International Blood and Marrow Transplant Research (CIBMTR)
- Radiation Emergency Assistance Center/Training Site (NNSA, DOE)
- Dept. Health & Human Services - Asst. Secretary of Preparedness and Response (DHHS-ASPR)
- Leading hematopoietic stem cell transplantation physicians

Concerns

- Funding to cover cost of treatment
- Catastrophic event may overwhelm national capabilities
  - 10KT device → 30,000+ victims for treatment??
- Complacency in absence of an actual event
- International coordination
# Radiation Injury Treatment Network

## Participating Centers

<table>
<thead>
<tr>
<th>Primary Transplant Centers</th>
<th>Secondary Transplant Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA-City of Hope National Medical Center</td>
<td>AL - University of Alabama at Birmingham</td>
</tr>
<tr>
<td>CA-Stanford Hospital and Clinics</td>
<td>AZ - University Medical Center</td>
</tr>
<tr>
<td>CO-Presbyterian/St. Lukes Medical Center</td>
<td>CA - UCSF Medical Center</td>
</tr>
<tr>
<td>MA-Dana Farber/Partners Cancer Care</td>
<td>FL - H. Lee Moffitt Cancer Center</td>
</tr>
<tr>
<td>MN-University of Minnesota BMT Program</td>
<td>FL - Shands Hospital at the University of Florida</td>
</tr>
<tr>
<td>MO-Barnes-Jewish Hospital at Washington</td>
<td>GA - Emory University Hospital</td>
</tr>
<tr>
<td>NC-Duke University Medical Center</td>
<td>GA - Northside Hospital</td>
</tr>
<tr>
<td>NY-Memorial Sloan-Kettering Cancer Center</td>
<td>IA - University of Iowa Hospitals and Clinics</td>
</tr>
<tr>
<td>OH-Cincinnati Children's Hospital Medical Center</td>
<td>IN - St. Francis Hospital and Health Centers</td>
</tr>
<tr>
<td>PA-University of Pennsylvania Medical Center</td>
<td>MS - University of Mississippi Medical Center</td>
</tr>
<tr>
<td>TX-M.D. Anderson Cancer Center</td>
<td>NC - UNC Hospitals</td>
</tr>
<tr>
<td>TX-Texas Children's Hospital</td>
<td>NC - Wake Forest Univ Baptist Medical Center</td>
</tr>
<tr>
<td>WA-Seattle Cancer Care Alliance</td>
<td>NH - Dartmouth-Hitchcock Medical Center</td>
</tr>
</tbody>
</table>

### Donor Centers

<table>
<thead>
<tr>
<th>Donor Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA-City of Hope National Medical Center</td>
</tr>
<tr>
<td>CO-Colorado Marrow Donor Program</td>
</tr>
<tr>
<td>MD-C.W. Bill Young Marrow Donor Center</td>
</tr>
<tr>
<td>MI-NMDP operated center</td>
</tr>
<tr>
<td>NJ-The HLA Registry</td>
</tr>
<tr>
<td>WA-Puget Sound Blood Center</td>
</tr>
<tr>
<td>TN - NMDP operated center</td>
</tr>
<tr>
<td>IA-Iowa Marrow Donor Program</td>
</tr>
<tr>
<td>TX-Baylor University Medical Center</td>
</tr>
<tr>
<td>MI-NMDP operated center</td>
</tr>
<tr>
<td>NJ-The HLA Registry</td>
</tr>
<tr>
<td>WA-Puget Sound Blood Center</td>
</tr>
<tr>
<td>TN - NMDP operated center</td>
</tr>
<tr>
<td>IA-Iowa Marrow Donor Program</td>
</tr>
<tr>
<td>TX-Baylor University Medical Center</td>
</tr>
</tbody>
</table>

### Cord Blood Banks

<table>
<thead>
<tr>
<th>Cord Blood Banks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA - StemCyte International Cord Blood Center</td>
</tr>
<tr>
<td>IL - ITxM Cord Blood Services</td>
</tr>
<tr>
<td>MO – St. Louis Cord Blood Bank</td>
</tr>
<tr>
<td>NC - Carolinas Cord Blood Bank</td>
</tr>
<tr>
<td>WA - Puget Sound Blood Center</td>
</tr>
<tr>
<td>CO- University of Colorado</td>
</tr>
<tr>
<td>TX - MD Anderson</td>
</tr>
</tbody>
</table>

As of 25 OCT 07
Novel Agents

Nelson Chao, MD
Duke University
DEVELOPMENT OF RADIATION INJURY:

1. Definitions and Units
2. Development of Radiation Injury
3. Physics
4. Chemistry
5. DNA Damage and Repair
6. Cell Death Mechanisms
7. Modeling
• **Ionizing Radiation**
  - Type of radiation that produces the ejection of an orbital electron from an atom or molecule and results in the formation of an ion pair.
Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency

September 2007

Development of Radiation Injury

- Initial Physical Interaction: Excitation, Ionization
- Physiochemical: Free Radical Formation
- Chemical Damage: Radical Attack
- Biomolecular Damage: DNA, Proteins, etc.
- Early Biological Effects: Toxicity, Mutation
- Late Biological Effects: Cancer, Genetic Effects

DOE Low Dose Radiation Research Program

Classic Paradigm of Radiation Injury

- Ionizing Radiation
- DNA Damage
- Cell Death/Repair
- Early Effects of Radiation Sickness
- Late Effects of Radiation Damage
- Developmental Effects (fetal)
- Genetic Effects (high dose; low dose?)

Cancer

< 1 second — min - hours — days — weeks — months — years — generations
Radiation Effects on DNA

- Chromosome Breaks are DNA Double-Strand Breaks
- >90% of Low LET-Induced Breaks are Rejoined
- Restitution: No Repair; Mis repair
- Misrepair
  - Only broken ends (telomeres?)
  - symmetric/asymmetric
  - interchromosome/intrachromosome
  - Time/dose dependent

![Graph showing the relationship between absorbed dose (Gy) and aberrations per cell for human lymphocytes exposed to Co gamma rays. The graph depicts a quadratic relationship with the equation y = αD + βD^2.](image)
Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency

September 2007

### Multiple Lethal Events

- **Mutation**
  - Mitosis Independent
  - Mitosis Dependent
  - Active Process
  - Passive Event
  - Some Cells
  - All Cells

### Mitotic Events

- DNA Degradation
- Nuclear Condensation
- Apoptotic Bodies
- Cell Membrane Alterations
- Phagocytosis
- Giant Cells
- Micronuclei
- Abortive Colonies
- Inflammatory Response

### Time Frame

- Minutes to Hours
- 3-5 Divisions

### Lethal Events

- Mutation
- Irreversible
- Reversible
- Multiple Lethal Events

### Why Is It Difficult to Find Mitigators?

- **Multiple Pathways**
- **Multiple Targets**
- **Multiple Modifiers of Response**
  - Repair
    - Induced
    - Cell Cycle
  - Signal Transduction
    - Mitotic Death/Apoptosis
    - Cell Cycle Arrest
Best Practice

• First do no harm...
• Antibiotics/antivirals/antifungals
• Control of GI symptoms
• Mitigation of hematopoietic impact
• Mitigation of skin toxicity
Devising Treatment Strategies: Example of Intestinal Radiation Toxicity

<table>
<thead>
<tr>
<th>Pathophysiologic Process</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROS-induced injury</td>
<td>ROS scavengers, antioxidants, cytoprotective agents</td>
</tr>
<tr>
<td>Entercyte depletion</td>
<td>Nutrients, GI peptides, epithelial growth factors</td>
</tr>
<tr>
<td>Mucosal barrier breakdown</td>
<td>Modulators of intraluminal factors</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Immunomodulators, cytokines, endothelial-oriented interventions</td>
</tr>
<tr>
<td>Secretory diarrhea</td>
<td>Antidiarrheal interventions</td>
</tr>
<tr>
<td>Bacterial translocation</td>
<td>Antibiotics, probiotics</td>
</tr>
<tr>
<td>Adverse tissue remodeling</td>
<td>Antifibrotic strategies</td>
</tr>
</tbody>
</table>

CMCR Network
Agent Development Status

[Image of CMCR Network diagram]
### Radiation Countermeasure Mission Space

- **ARS**
  - Hematopoietic ARS:
    - Neutropenia
    - Thrombocytopenia
    - Anemia
    - Lymphopenia
  - GI ARS
  - CNS Injury
  - Lung Injury
  - Kidney Injury
- **Cutaneous Radiation Syndrome**
- **Combined Injury**

- **Radionuclide Threats**
  - Co-60
  - Cs-137
  - Sr-90
  - I-131
  - Ir-192
  - Po-210
  - Ur-235
  - Pu-239
  - Am-241

- **Carcinogenesis**
- **Cataractogenesis**

### Hematopoietic Syndrome

- **Neutropenia**
  - Neupogen/Neulasta Licensed
  - Leukine Licensed
  - Human Growth Hormone Licensed
  - Endothelial Cell Transplantation Preclinical
  - Myeloid Progenitor Cell Transplantation Preclinical

- **Thrombocytopenia**
  - AM6 531 Phase III Clinical Trial
  - Eltrombopag Phase II Clinical Trial
  - AKR 501 Phase II Clinical Trial
  - Peg-TPOmp Phase III Clinical Trial
  - TPIAO Licensed in China
Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency

Kuderer, et al. JCO 2007

Neupogen

Kuderer, et al. JCO 2007

Neupogen

Early Mortality

<table>
<thead>
<tr>
<th>Type</th>
<th>Citation</th>
<th>Treated Rate</th>
<th>Control Rate</th>
<th>BRR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>Cronfeld</td>
<td>0.001</td>
<td>0.097</td>
<td>0.363</td>
<td>0.311 to 0.419</td>
<td>.563</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Pedweigl</td>
<td>0.514</td>
<td>0.163</td>
<td>3.174</td>
<td>3.426 to 4.875</td>
<td>.544</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Trillet-Laper</td>
<td>0.015</td>
<td>0.047</td>
<td>0.326</td>
<td>0.226 to 0.473</td>
<td>.283</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Zaccari</td>
<td>0.019</td>
<td>0.000</td>
<td>1.016</td>
<td>0.919 to 1.124</td>
<td>.929</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Fussa</td>
<td>0.034</td>
<td>0.016</td>
<td>0.303</td>
<td>0.284 to 0.324</td>
<td>.910</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Goubel</td>
<td>0.054</td>
<td>0.094</td>
<td>0.190</td>
<td>0.200 to 1.270</td>
<td>.556</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Oly-CHOP</td>
<td>0.032</td>
<td>0.048</td>
<td>0.866</td>
<td>0.624 to 1.172</td>
<td>.266</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Tierney-Boeke</td>
<td>0.007</td>
<td>0.196</td>
<td>0.007</td>
<td>0.222 to 1.712</td>
<td>.651</td>
</tr>
<tr>
<td>Combined Filgrastim</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
<td>0.498 to 0.887</td>
<td>.019</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Churial</td>
<td>0.000</td>
<td>0.002</td>
<td>1.171</td>
<td>0.924 to 1.461</td>
<td>.250</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Bui</td>
<td>0.000</td>
<td>0.020</td>
<td>1.171</td>
<td>0.924 to 1.461</td>
<td>.250</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Gersleben</td>
<td>0.037</td>
<td>0.028</td>
<td>0.976</td>
<td>0.703 to 1.419</td>
<td>.875</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Guttermeier</td>
<td>0.036</td>
<td>0.040</td>
<td>1.171</td>
<td>0.924 to 1.461</td>
<td>.250</td>
</tr>
<tr>
<td>Combined Lenograstim</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
<td>0.498 to 0.887</td>
<td>.019</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Vogel</td>
<td>0.011</td>
<td>0.030</td>
<td>0.976</td>
<td>0.703 to 1.419</td>
<td>.875</td>
</tr>
<tr>
<td>Combined Pegfilgrastim</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
<td>0.498 to 0.887</td>
<td>.019</td>
</tr>
<tr>
<td>All G-CSF</td>
<td></td>
<td></td>
<td></td>
<td>0.059</td>
<td>0.433 to 0.830</td>
<td>.002</td>
</tr>
</tbody>
</table>
Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency

September 2007

Human Growth Hormone

![Graph showing the effect of Human Growth Hormone on probability of survival and white cells and platelets post irradiation.]

- **Probability of survival**
  - Saline control (n=28)
  - Growth hormone (n=28)
  - P<0.0001

- **White cells (µl blood)**
  - Saline control
  - Growth hormone
  - * * *

- **Platelets (x10³/µl blood)**
  - Saline control
  - Growth hormone
  - * * *
Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency

September 2007

TPO Survival Benefit

![Graph showing survival benefit over days after irradiation (0 Gy)]

- Placebo (n=54)
- Placebo (n=19)
- 0.3 ug TPO x 7d (2h; n=30)
- 0.3 ug TPO (2h; n=10)


TPO Receptor-activating Peptides

- **AMG 531 (Amgen)**
  - TPO receptor-activating peptide
  - Attached to IgG Fc
  - In phase III clinical trials
- **Peg-TPOmp (J&J)**
  - Pegylated TPO receptor-activating peptide
  - In phase III clinical trials
- **TPIAO (3SBio)**
  - Full-length recombinant human TPO
  - Licensed for use in China
Oral TPO-receptor Agonists

- **AKR 501 (AkaRx)**
  - Full agonist of TPO receptor
  - Efficacy with single dose
  - In phase II clinical trials
- **Eltrombopag (GSK)**
  - Partial agonist of TPO receptor
  - Requires repeated dosing for efficacy
  - In phase II clinical trials

Novel Cell Therapy Approaches

- **Myeloid Progenitor Cells** Preclinical
- **Mesenchymal Stem Cells** Phase III Clinical Trial
- **Endothelial Cells** Preclinical
**Mesenchymal Stem Cells (MSCs)**

- **“Magic” Stem Cells**
  - Home to injured tissue (whether radiation, trauma, or burn-induced, with engraftment shown in BM, intestines, kidney, lung, liver, thymus, skin)
  - Have immunomodulatory properties, reducing inflammation
  - Promote tissue regeneration
  - Secrete hematopoietic cytokines, facilitating hematopoietic reconstitution

- **Demonstrated efficacy in combined injury**
  - Accelerated healing of full-thickness round incisional wound + 20 Gy local irradiation
  - Facilitate wound healing in general

**MSCs - Radiation Skin Injury**

<table>
<thead>
<tr>
<th>Control</th>
<th>Treated</th>
</tr>
</thead>
</table>

- 30 Gy limb irradiation
- MSCs infused 24 hours post-irradiation

*Human MSC-injected NOD/scid mice*

**MSCs - Thermal Injury**

32 days after 30% BSA third-degree burns

3 days after topical application of allo MSCs

Skin grafting performed 33 days after injury with additional application of allo MSCs

24 hours after skin graft: pain relief

7-8 days after skin graft: blood chemistries begin to normalize

10 days after skin graft: 99% take observed

28 days after skin graft: patient discharged

30 days after skin graft: patient returns to work


---

**Endothelial Cell Transplantation**

![Graph]

1050 cGY

Control (n=11)

MBEC transplanted (n=7)

P=0.04
**Endothelial Cell Transplantation**

![Graph A]

![Graph B]

**Gastrointestinal Syndrome**

- Protectan (CLBL 502) Preclinical
- R-spondin 1 Preclinical
R-spondin 1 - Intestinal Mitogen


R-spondin 1 Antiinflammatory Effects

Cutaneous Radiation Syndrome

- Ulceration/Necrosis
  - Curcumin Phase I/II Clinical Trial
  - Esulentoside A (EsA) Preclinical
  - Celecoxib Licensed
  - Mesenchymal Stem Cells Phase III Clinical Trial
- Fibrosis
  - Pentoxifylline (+ Vitamin E) Licensed
  - MnSOD Phase I/II Clinical Trial

Curcumin

Radiation-induced Lung Injury

- **Pneumonitis**
  - KGF (palifermin) Licensed
  - Pentoxifylline Licensed
  - AEOL 10150 Phase Ib Clinical Trial
  - MnSOD Gene Therapy Preclinical

- **Fibrosis**
  - KGF (palifermin) Licensed
  - Pirfenidone Phase III Clinical Trial
  - AEOL 10150 Phase Ib Clinical Trial
  - Imatinib Licensed

---

**KGF (palifermin)**

Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency


One Organism Has Figured It Out

- Deinococcus Radiodurans
  - Isolated from samples of canned meat thought to be sterilized by radiation as well as radioactive waste pools
  - Ancient, 2 mill years old
  - Non-pathogenic
  - Survives 1.5 x 10^6 rads
  - Grows in 6000 rads/hr conditions
  - Rapid and proper correction of double stranded DNA breaks