Medical Management of Acute Radiation Syndrome (ARS)

Doran M. Christensen DO
Associate Director/Staff Physician
Radiation Emergency Assistance Center / Training Site
Oak Ridge Institute for Science and Education (ORISE)
U.S. Department of Energy (DOE)
24/7 Emergency Phone 865-576-1005

Terminal Objective

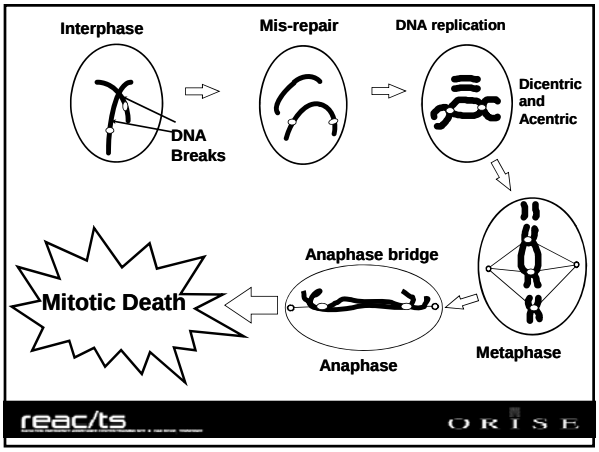
Understand the basics of medical management of ionizing radiation injuries and illnesses

Enabling Objectives

- Review the phases of the Acute Radiation Syndrome(s) = ARS
- Review clinical signs and symptoms of ARS
- Review early management of irradiated and/or contaminated patients
- Review clinical and biologic dosimetry as the basis for medical management
- Review principles of management of internal contamination

Mechanisms of Cell Death

- Reproductive or mitotic death



Mechanisms of Cell Death

- Reproductive or mitotic death
- Apoptosis or "programmed cell death" – normal physiological process also triggered by other stimuli

Factors that "Determine" Effects of Ionizing Radiation

- Total dose
- Dose rate
- Volume of tissue irradiated
- Type and quality of radiation
- Presence of trauma or burns
- Pre-existing conditions
- Individual susceptibility

reac/ts ORISE

Sensitivity of Cells to Ionizing Radiation

More Radiosensitive

In general,
- Undifferentiated
- Divide quickly
- High metabolic activity

Mature Lymphocytes
Spermatogonia
Blood Cell Precursors
Intestinal Crypt Cells
Epidermal Stem Cells
Endothelial Cells
Gastric Gland Cells
Osteoblasts
Chrondroblasts
Spermatocytes
Granulocytes
Osteocytes
Spermatozoa
Erythrocytes
Fibrocytes
Chondrocytes

Less Radiosensitive or "Radioresistant"

In general,
- Differentiated
- Slow or no division
- Slower metabolism

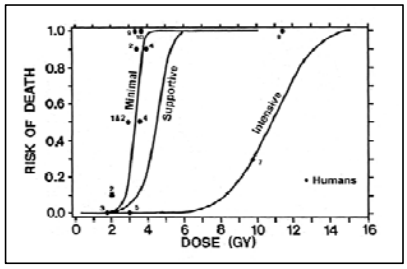
reac/ts ORISE

Animal Response to Radiation: Terminology

- $LD_{50/30}$ or $LD_{50/60}$ - dose necessary to cause 50% death in an irradiated population in 30 and 60 days respectively, without treatment
  - For radiation, acute whole body dose
  - $LD_{50/60}$ = 350 rad = 350 cGy = 3.5 Gy

reac/ts ORISE

As medical care becomes progressively more aggressive, the $LD_{50/60}$ can be pushed beyond 350-400 rad (3.5-4 Gy)



Eric J Hall, Radiobiology for the Radiologist
4th Edition, 1994

10

Terminology

- Deterministic effects
  - Early or late effects that have dose-effect relationship, *i.e.*, a threshold dose
  - Increase in effects with increasing dose – as the dose increases, the effect becomes worse

reac/ts ORISE

Terminology

- Stochastic effects
  - Long-term random or chance effects
  - No lower threshold dose for effects
  - As the doses increases, the number of "events" increases, *e.g.*, carcinogenesis or cancer formation

reac/ts ORISE

12

Medical Consequences

- Types of injuries
  - Whole or Total Body Irradiations (WBI or TBI)
  - Partial Body Irradiations (PBI)
  - Cutaneous Radiation Injury (CRS)
  - Local Radiation Injury (LRI)
- Acute *versus* chronic effects
- Early *versus* late effects

Radiation Does Not Cause

- Immediate death
- Immediate burns or wounds
- Sudden incapacitation (except at very high & unsurvivable doses)

Deal with life and limb threatening conditions first then deal with radiological issues

Irradiation or contamination alone is not a medical emergency, or threat to responders, other persons or facilities

Low-dose Deterministic Effects

Dose	Effects
< 10 rads (cGy)	no detectable difference in exposed *versus* non-exposed patients
> 12 rads (cGy)	sperm count decreases to minimum by about day 45
20 rads (cGy) whole body	detectable increase in dicentric chromosome aberrations - no clinical signs or symptoms
75-100 rads (cGy) whole body	• detectable bone marrow depression • nausea/vomiting in a small percentage of the population

Acute Radiation Syndrome

- An acute illness, which follows a roughly predictable course over a period of time ranging from a few hours to several weeks after exposure to ionizing radiation.
- Characterized by the development of groups of signs and symptoms that are manifestations of damage to various tissues and organs by ionizing radiation.

reac/ts ORISE

Manifest Illness Phase

Symptoms and signs are related to the tissue damaged

- Hematopoietic
- Gastrointestinal
- Cutaneous
- Cerebrovascular/Central Nervous System ("Neurovascular")

reac/ts ORISE

Acute Radiation Syndromes

Subclinical	0 - ~100 rad (0- ~1 Gy)
Hematopoietic	~100 - 800 rad (~1-8 Gy)
Cutaneous / Local	> ~300 rad (> 3 Gy)
Gastrointestinal	> ~600 rad (> ~6 Gy)
Respiratory	> ~600 rad (> ~6 Gy)*
CV/CNS	> ~3000 rad (> ~30 Gy)

*Usually delayed 1-4 months

reac/ts ORISE

Clinical Course

Irradiation Occurs

Prodrome
0 - 48 hours

Latent
Hours – 21 days

Manifest Illness
Hours – 30 days

Death or Recovery
Hours - > 60 days

reac/ts ORISE

Clinical Course

Irradiation Occurs

Immediate effect of cell membrane damage

Prodrome
0 - 48 hours

Release of vasoactive and other amines that initiate an inflammatory response

- Anorexia
- Nausea
- Vomiting
- Lymphopenia

- Diarrhea
- Fever (low-grade)
- Granulocytosis

Mediated neurologically by the parasympathetic nervous system

reac/ts ORISE

Clinical Course

Irradiation Occurs

Prodrome
0 - 48 hours

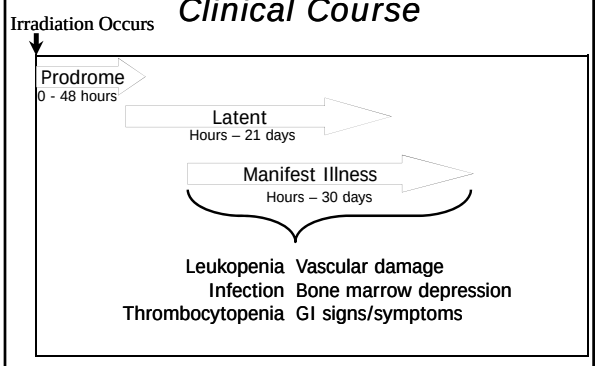
Only appears to be "latent"

Latent
Hours – 21 days

Prodromata absent or diminished

reac/ts ORISE

Clinical Course



reac/ts ORISE

Clinical Presentations

- Hematopoietic Syndrome:
  - Nausea/vomiting
  - Lymphocytopenia (lymphopenia)
  - Leukocytopenia (Leukopenia)
  - Pancytopenia
  - Immunodysfunction
  - Sepsis
  - Impaired wound healing
  - GI bleeding (20-30 days post-incident)

reac/ts ORISE 23

Clinical Presentations

- Gastrointestinal Syndrome
  - Nausea/vomiting
  - Diarrhea
  - Bloody diarrhea
  - Malabsorption
  - Ileus (obstruction)
  - Fluid and electrolyte imbalance
  - Hypovolemia
  - Acute renal failure
  - Cardiovascular failure (8-14 days post-incident)

reac/ts ORISE 24

Clinical Presentations

- Neurovascular Syndrome:
  - Confusion and disorientation
  - Hypotension
  - Cerebral edema
  - Ataxia
  - Convulsions/coma (1-2 days post-accident)
- IONIZING RADIATION DOES NOT CAUSE COGNITIVE OR NEUROLOGICAL SIGNS EXCEPT AT VERY HIGH DOSES!

reac/ts ORISE

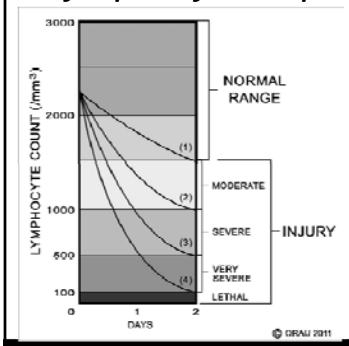
25

Hematopoietic Phase - Kinetics

- Peripheral lymphocytes are one of the more radiosensitive cells in the body
- Lymphocytes can be killed in interphase
- Careful observation of lymphocyte decrease with time after exposure provides an early estimate of dose <u>and</u> prognosis
- Granulocytes - less sensitive
- RBC and platelet reductions appear later

reac/ts ORISE

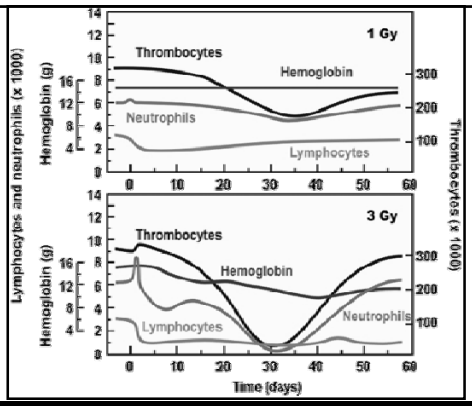
Lymphocyte Depletion Kinetics



•Curve 1 – 3.1 Gy
•Curve 2 – 4.4 Gy
•Curve 3 – 5.6 Gy
•Curve 4 – 7.1 Gy

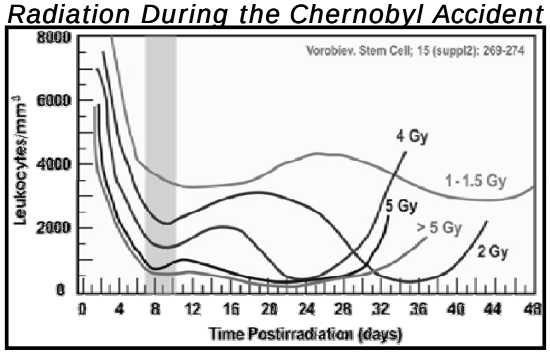
From Goans RE, Holloway EC, Berger ME and Ricks RC, "Early Dose Assessment Following Severe Radiation Accidents," *Health Physics* 72(4): 1997.

reac/ts ORISE



reac/ts ORISE

White Blood Cells in Patients Exposed to Radiation During the Chernobyl Accident



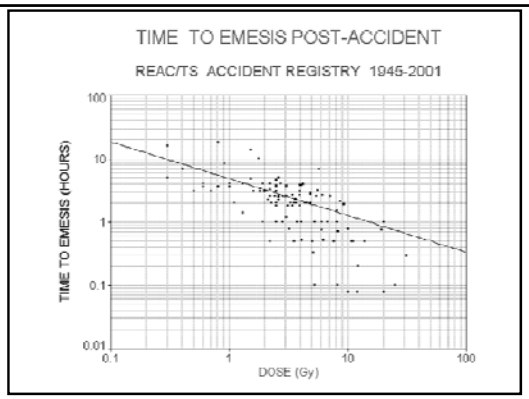
reac/ts ORISE

Biodosimetry Based on Acute Photon-Equivalent Exposures

Dose [Gy]	Onset of vomiting %	Onset of vomiting Time [hr]	Lymphocyte count ($x10^9$/liter) by day 0.5	1	2	4	6	8	Lymphocyte depletion rate Rate constant	Number of dicentrics Per 50 cells	Number of dicentrics Per 1000 cells
0	--	--	2.45*	2.45	2.45	2.45	2.45	2.45	--	0.05 – 0.1	1-2
1	19		2.30	2.15	1.90	1.48	1.15	0.89	0.126	4	88
2	35	4.63	2.19	1.90	1.49	0.88	0.54	0.33	0.252	12	234
3	54	2.62	2.03	1.58	1.15	0.54	0.25	0.12	0.378	22	439
4	72	1.74	1.90	1.49	0.89	0.33	0.12	.044	0.504	35	703
5	86	1.27	1.75	1.31	0.69	0.20	0.05	.020	00.63	51	1024
6	94	0.99	1.55	1.15	0.54	0.12	0.03	.006	0.756		
7	98	0.79	1.35	1.01	0.42	.072	.012	.002	0.881		
8	99	0.66	1.45	0.89	0.30	.044	.006	<.001	1.01		
9	100	0.56	1.35	0.75	0.25	.030	.003	<.001	1.13		
10	100	0.48	1.31	0.70	0.20	.020	.001	<.001	1.26		

* The normal range for lymphocytes in human blood is between 1.5 and 3.5 x 10^9 per liter.

Lymphocyte depletion rate is based on the model $L_t = 2.45 \times 10^9/\text{liter} \times e^{-k(Dt)}$ where L_t equals the lymphocyte count ($x10^9$/liter), 2.45×10^9/liter equals the a constant representing the consensus mean lymphocyte count in the general population, k equals the lymphocyte depletion rate constant for a specific acute photon dose, and t equals the time after exposure (days).



reac/ts ORISE

Biodosimetry Based on Acute Photon-Equivalent Exposures

Dose [Gy]	Onset of vomiting %	Onset of vomiting Time [hr]	Lymphocyte count (x10⁹/liter) by day 0.5	1	2	4	6	8	Lymphocyte depletion rate: Rate constant	Number of dicentrics: Per 50 cells	Number of dicentrics: Per 1000 cells
0	--	--	2.45*	2.45	2.45	2.45	2.45	2.45	--	0.05 – 0.1	1-2
1	19		2.36	2.19	1.90	1.49	1.15	0.89	0.126	4	88
2	35	4.63	2.16	1.90	1.49	0.86	0.54	0.33	0.252	12	234
3	54	2.62	2.03	1.69	1.15	0.54	0.25	0.12	0.378	22	439
4	72	1.74	1.90	1.49	0.89	0.33	0.12	.044	0.504	35	703
5	86	1.27	1.79	1.31	0.69	0.20	0.06	.020	00.63	51	1024
6	94	0.99	1.65	1.15	0.54	0.12	0.03	.006	0.756		
7	98	0.79	1.53	1.01	0.42	.072	.012	.002	0.881		
8	99	0.66	1.48	0.89	0.30	.044	.006	<.001	1.01		
9	100	0.56	1.39	0.79	0.25	.030	.003	<.001	1.13		
10	100	0.48	1.31	0.70	0.20	.020	.001	<.001	1.26		

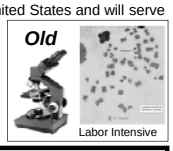
* The normal range for lymphocytes in human blood is between 1.4 and 3.5 x 10⁹ per liter.
Lymphocyte depletion rate is based on the model $L_t = 2.45 \times 10^9/\text{liter} \times e^{-kt}$ where L_t equals the lymphocyte count ($\times 10^9$/liter), 2.45×10^9/liter equals the a constant representing the consensus mean lymphocyte count in the general population, k equals the lymphocyte depletion rate constant for a specific acute photon dose, and t equals the time after exposure (days).

Cytogenetics Biodosimetry Laboratory (CBL)

Cytogenetics Biodosimetry is the "gold" standard for radiation dose assessments. The REAC/TS CBL will be the only civilian CBL in the United States and will serve as a national emergency response asset under DOE.

Cytogenetics Biodosimetry utilizes metaphase spreads of lymphocytes to search for targeted chromosome aberrations (dicentrics) specific to radiation exposures.

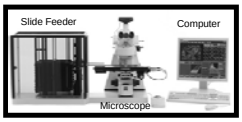
Old



Labor Intensive

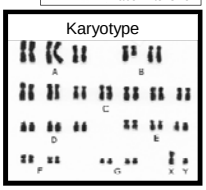
New

Automated slide handling and scanning. Computer karyotyping (identification/arranging) of the chromosomes and identification of aberrations.



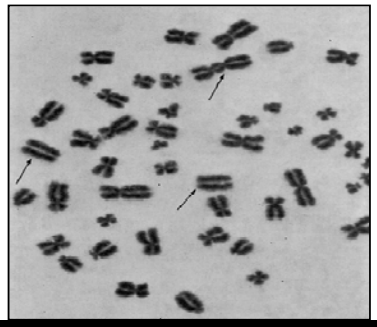
Automated Cytogenetics Workstation

Output



reac/ts ORISE

ABERRANT CHROMOSOMES: DICENTRIC AND ACENTRIC



reac/ts ORISE

Biodosimetry Based on Acute Photon-Equivalent Exposures

Dose [Gy]	Onset of vomiting %	Onset of vomiting Time [hr]	Lymphocyte count (x10⁹/liter) by day 0.5	1	2	4	6	8	Lymphocyte depletion rate: Rate constant	Number of dicentrics: Per 50 cells	Number of dicentrics: Per 1000 cells
0	--	--	2.45*	2.45	2.45	2.45	2.45	2.45	--	0.05 – 0.1	1-2
1	19		2.36	2.18	1.90	1.49	1.15	0.89	0.126	4	88
2	35	4.63	2.16	1.90	1.49	0.86	0.54	0.33	0.252	12	234
3	54	2.62	2.03	1.69	1.15	0.54	0.25	0.12	0.378	22	439
4	72	1.74	1.90	1.49	0.89	0.33	0.12	.044	0.504	35	703
5	86	1.27	1.79	1.31	0.69	0.20	0.06	.020	00.63	51	1024
6	94	0.99	1.65	1.15	0.54	0.12	0.03	.006	0.756		
7	98	0.79	1.53	1.01	0.42	.072	.012	.002	0.881		
8	99	0.66	1.48	0.89	0.33	.044	.006	<.001	1.01		
9	100	0.56	1.39	0.79	0.25	.030	.003	<.001	1.13		
10	100	0.48	1.31	0.70	0.20	.020	.001	<.001	1.26		

* The normal range for lymphocytes in human blood is between 1.4 and 3.5 x 10⁹ per liter.
Lymphocyte depletion rate is based on the model $L_t = 2.45 \times 10^9/\text{liter} \times e^{-kt(t)}$ where L_t equals the lymphocyte count ($\times 10^9$/liter), 2.45×10^9/liter equals the a constant representing the consensus mean lymphocyte count in the general population, k equals the lymphocyte depletion rate constant for a specific acute photon dose, and t equals the time after exposure (days).

Documentation in the ED

- History of exposure/accident scenario – need expert health physics support for dose reconstruction and initial dose estimates
- Symptoms/signs – time of onset and severity
- Physical examination – complete including skin changes, document pertinent negatives
- Document vital signs frequently – include temperature and weight

reac/ts ORISE

Documentation in the ED

- History of exposure/accident scenario – need expert health physics support for dose reconstruction and initial dose estimates
- Symptoms/signs - time of onset and severity
- Physical examination – complete including skin changes, document pertinent negatives
- Document vital signs frequently - include temperature and weight

reac/ts ORISE

Management Issues

- MANAGE UNSTABLE MEDICAL/SURGICAL CONDITIONS FIRST!
- Decontaminate if necessary after stabilization
- Treat other systemic symptoms & conditions
- Psychosocial support/pastoral care

reac/ts ORISE

Diagnosis of ARS

- CBC with differential every 8 hours
- Absolute Lymphocyte Count (ALC)
- Routine medical and trauma labs
- Serum amylase
- Blood and tissue typing – don't need early
- Routine UA
- Urine for radioassay
- Begin 24-hour collection of urine and feces for radiobioassays
- Cytogenetic dosimetry/chromosome aberration analysis

reac/ts ORISE

Management Issues

- Reverse isolation/strict sterile techniques
- Bacterial, viral and fungal infection prophylaxis – later infection control
- Surgical intervention – first 36 hours!
- Consider stimulation of hematopoietic system – cytokines or colony stimulating factors – as soon as possible when dose assessment >~2 Gy
- Transfusions – platelets, RBCs - later

reac/ts ORISE

Help!

- REAC/TS - call early!
- Hematology/Oncology Consultation
- Infectious Disease Consultation
- Surgery Consultation – Burn, Plastic, Vascular, Trauma
- Radiation Oncology, Nuclear Medicine, Toxicology
- Psychology, Psychiatry, Social Workers, Pastoral Care
- Interpreters, Cultural Awareness

reac/ts ORISE

QUESTIONS?

reac/ts

reac/ts ORISE