Acute Radiation Syndrome (ARS)

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REAC/TS

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 acute radiation syndrome (ARS)

Enabling Objectives

- Review radiobiology
- Review the phases Acute Radiation Syndrome (ARS)
- Review clinical signs and symptoms of ARS
- Review management of ARS

Ionizing Radiation Can Cause

- Injuries/Illnesses
  - Whole or Total Body Irradiation (WBI or TBI)
  - Partial Body Irradiation (PBI)
  - Cutaneous Radiation Injury (CRS)
  - Local Radiation Injury (LRI)
- Acute *versus* chronic effects
- Early *versus* late effects

Radiation Does Not Cause

- Immediate burns, wounds or sudden incapacitation (except at very high & unsurvivable doses)
- Treat life and limb threatening conditions first then deal with radiological issues

Irradiation or contamination alone is not a medical emergency

Ionizing Radiation

Directly breaking bonds in cellular components

Indirectly acting on water molecules

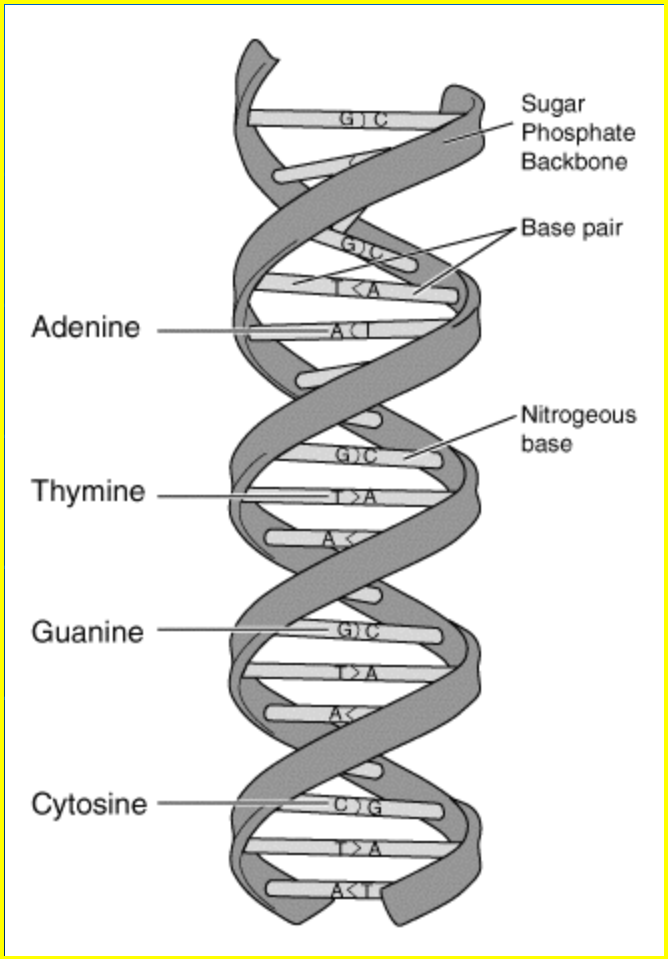
- Creates unstable, highly reactive radicals
- Causes oxidation of molecules by removing electrons or hydrogen atoms

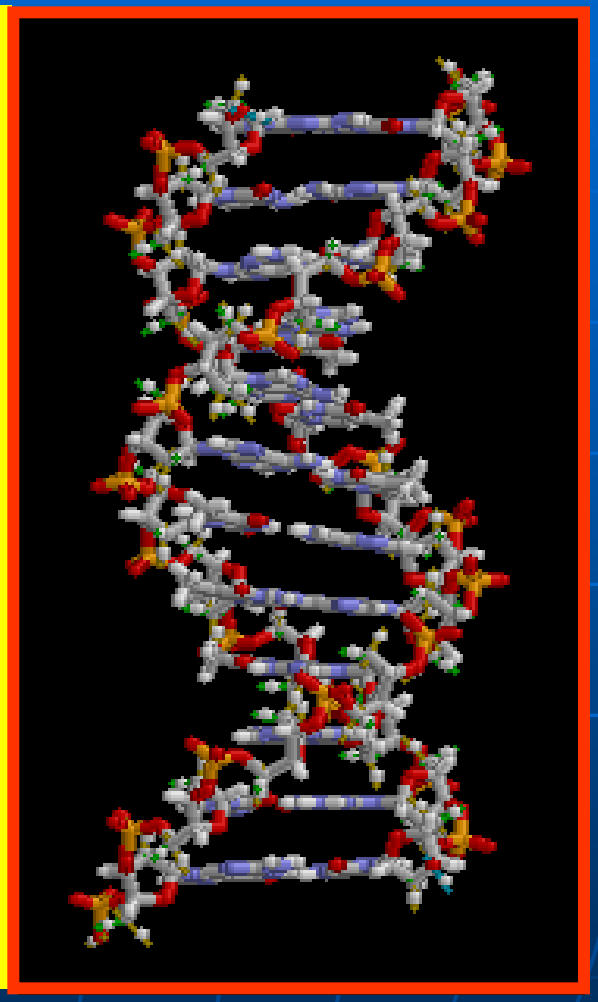
DNA Damage

May cause damage to DNA:

- **Single-stranded breaks** (SSB)
  - May be repaired, one strand acts as template for second
- **Double-stranded breaks** (DSB)
  - Often misrepaired
    - Mutations
    - Asymmetrical chromosome aberrations are lethal at mitosis

DNA

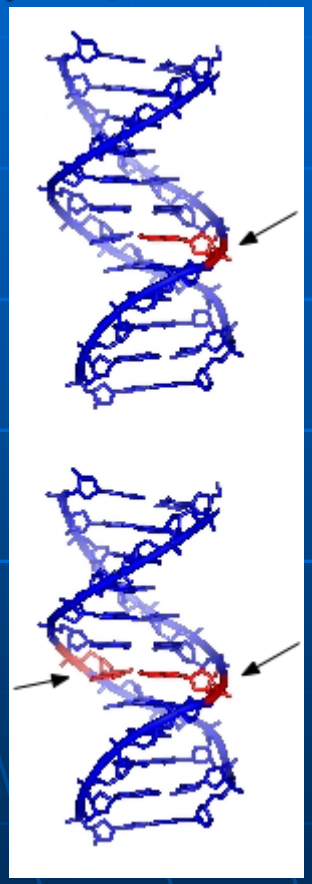

Sugar
Phosphate
Backbone
Base pair
Adenine
Nitrogeous
base
Thymine
Guanine
Cytosine



DNA Damage

Direct Action

(alpha, neutron)



Single DNA break

Double DNA break

High Linear Energy Transfer (LET)

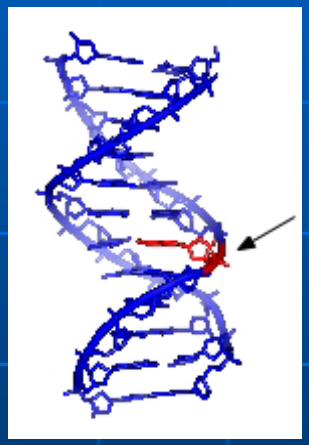
Indirect Action

(x-rays, gamma)

Accounts for about 2/3 of damage

Photon

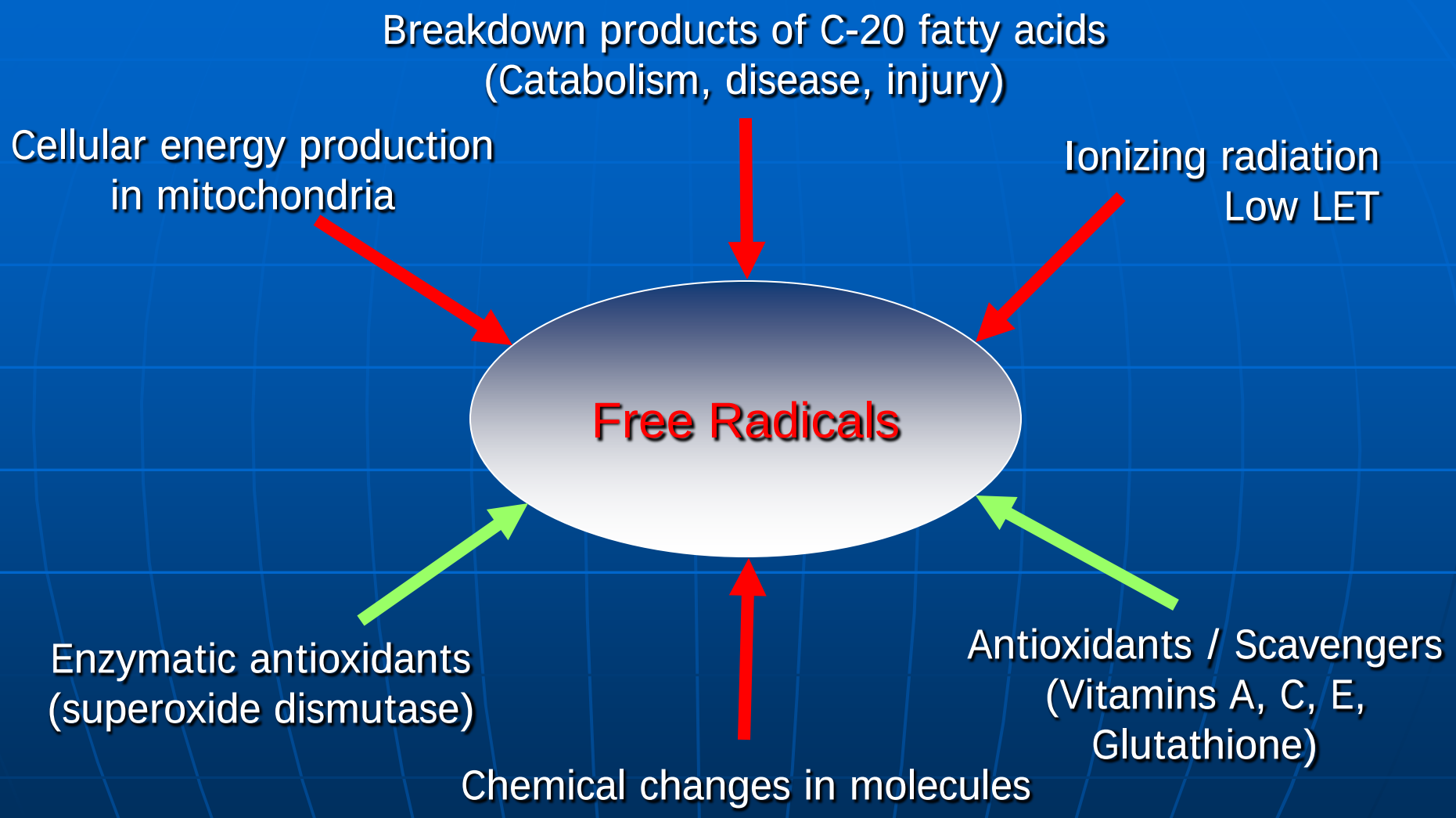
Free Radicals



Single DNA break

Low Linear Energy Transfer (LET)

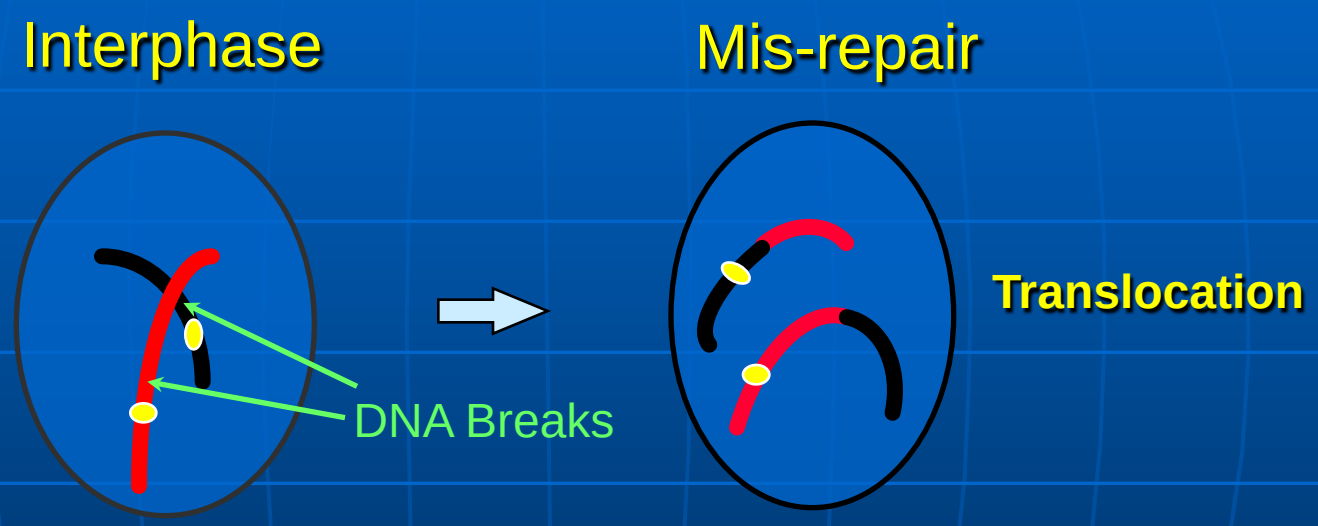
Free Radicals

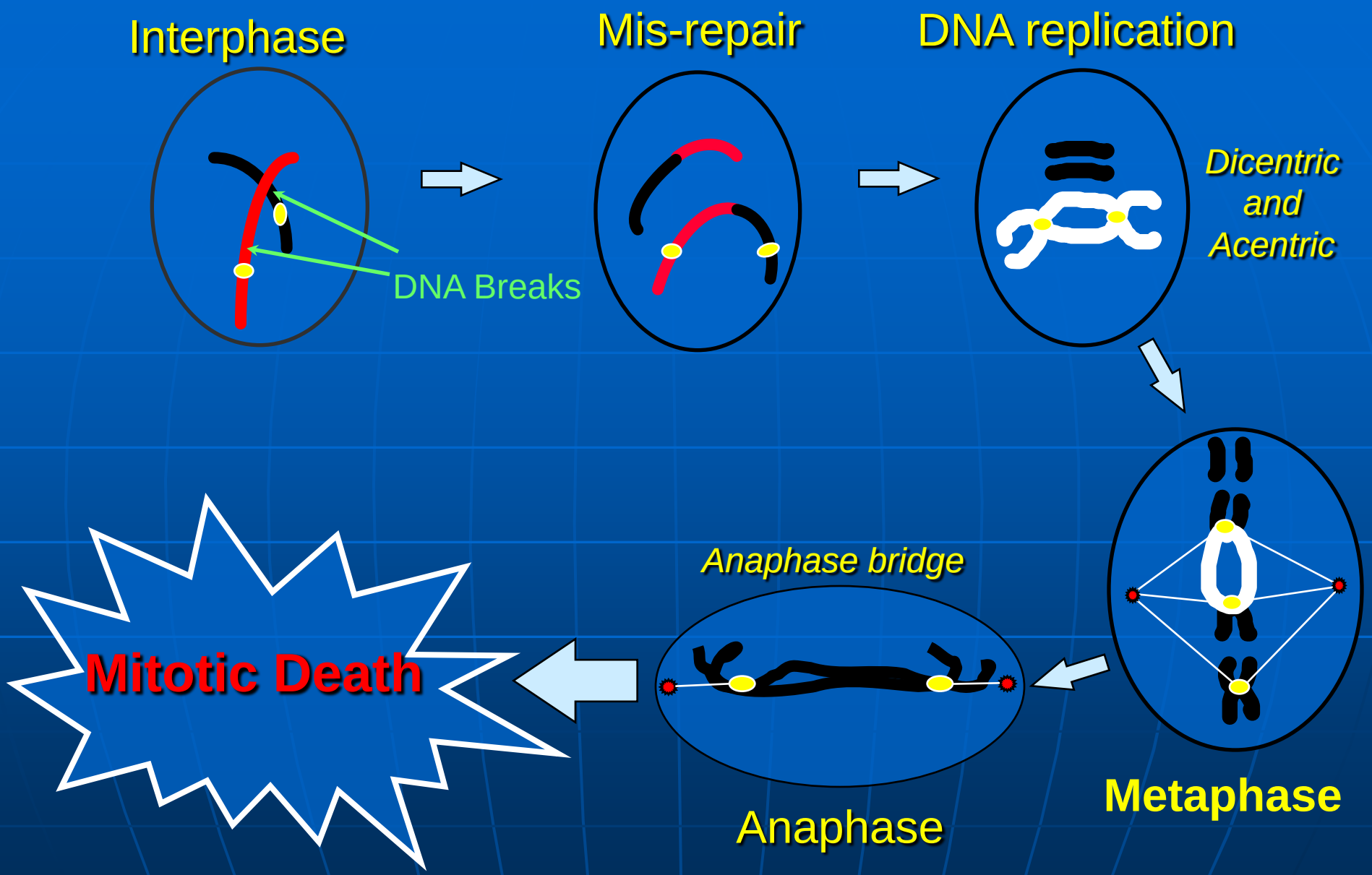


Damaged DNA Results

- Delayed division
- Inaccurate division
- Failure to divide

Damaged DNA




Interphase
DNA Breaks
Mis-repair
DNA replication
Dicentric and Acentric
Metaphase
Anaphase
Anaphase bridge
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

Cell Sensitivity

- Sensitivity is increased in
  - Cells in the stage of mitosis
  - Less differentiated cells
  - Cells that are more metabolically active

Sensitivity of Cells to Ionizing Radiation

More Radiosensitive

In general,

- Undifferentiated
- Divide quickly
- High metabolic activity

Mature Lymphocytes
Spermatogonia
Myeloblasts
Intestinal Crypt Cells
Epidermal Stem Cells
Endothelial Cells
Gastric Gland Cells
Osteoblasts
Chrondroblasts
Spermatocytes
Granulocytes
Osteocytes
Spermatozoa
Erythrocytes
Fibrocytes
Chondrocytes
Muscle Cells
Nerve Cells

Less Radiosensitive or "Radioresistant"

In general,

- Differentiated
- Slow or no division
- Slower metabolism

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
  - $LD_{50/60}$ = 400 rad = 400 cGy = 4 Gy

- Deterministic effects – early or late effects that have dose-effect relationship, *i.e.*, an increase in effects with increasing dose
- Stochastic effect - only the probability of an event increases with increasing dose

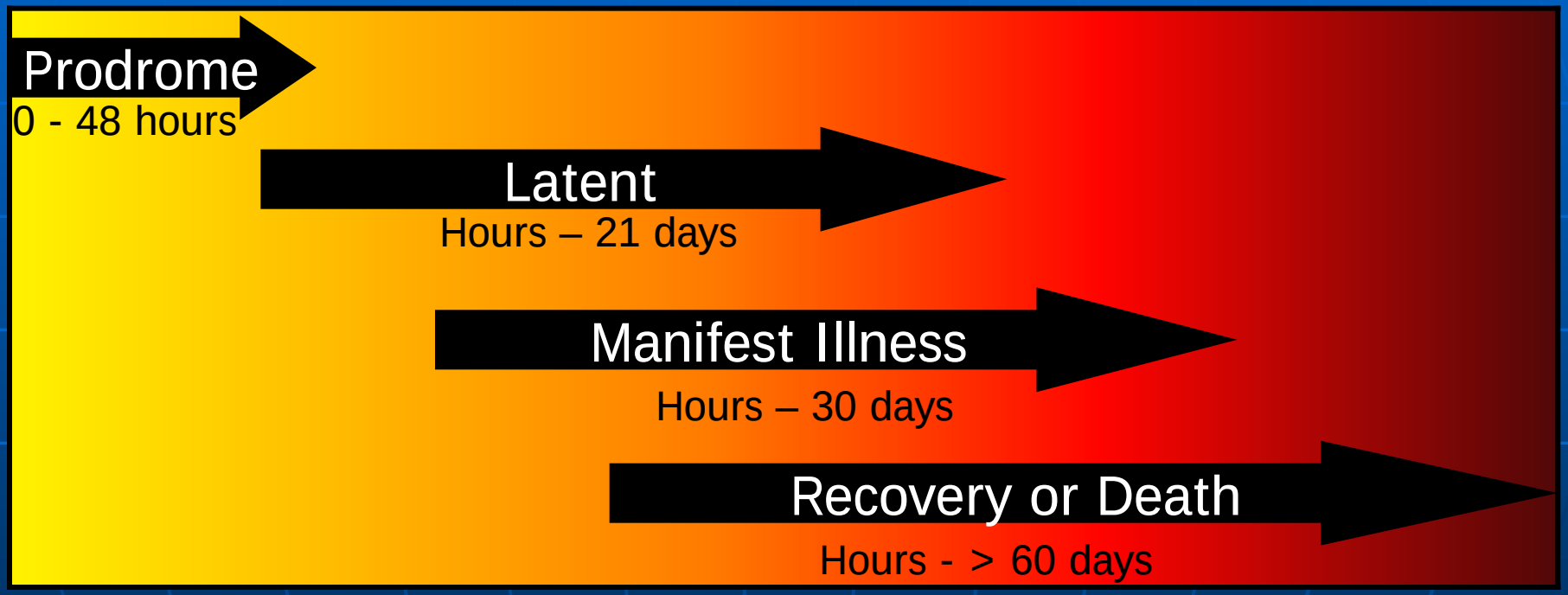
Acute Radiation Syndrome

- 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.

Clinical Course

Irradiation Occurs



Acute Radiation Syndromes

➢ Subclinical	0-1 Gy
➢ Hematopoietic	> 1 Gy
➢ Gastrointestinal	> 6 – 8 Gy
➢ Neurovascular	> 20Gy

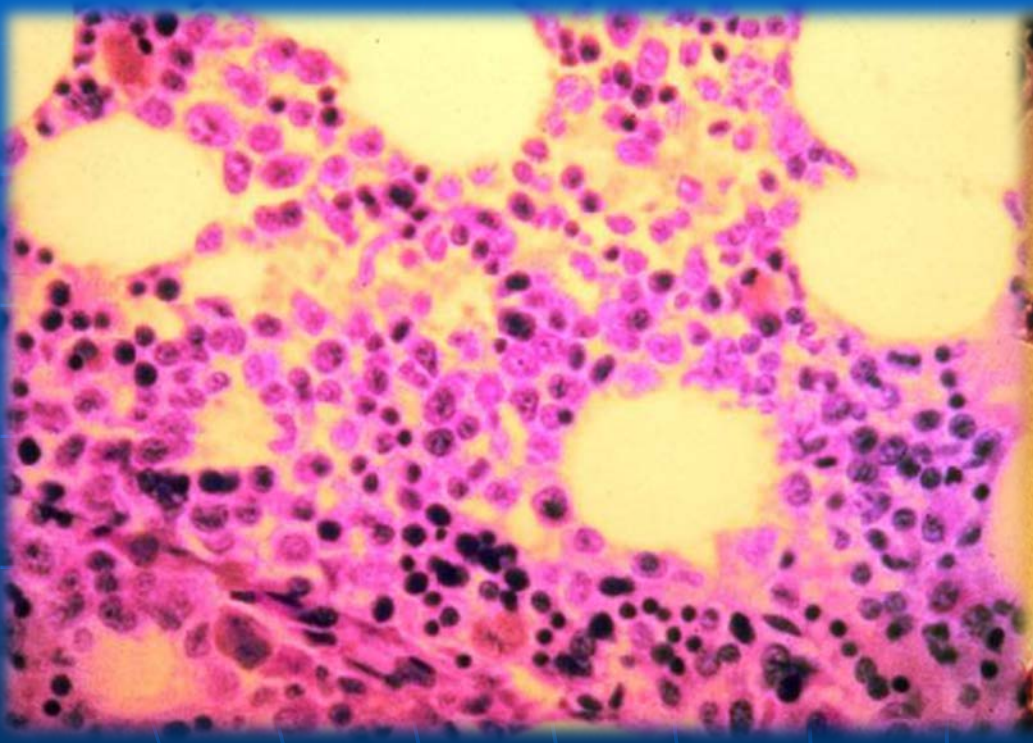
Subclinical (< 1 Gy)

- < 10 cGy (0.10 Gy) **no detectable difference** in exposed vs non-exposed patients
- > 12 cGy (0.12 Gy)sperm count decreases to minimum by about day 45
- 20 cGy (0.20 Gy) whole body detectable **increase in dicentric chromosome aberrations** - no signs or symptoms
- 75-100 cGy (0.75 – 1.0 Gy) whole body **detectable bone marrow suppression**
  - nausea/vomiting in approximately 10% population

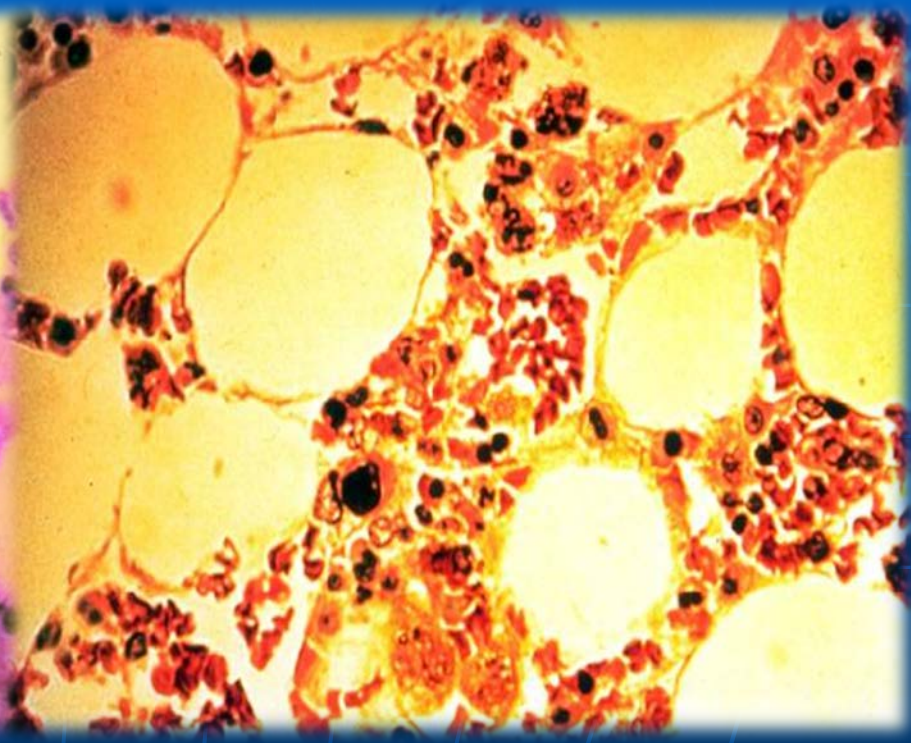
Hematopoietic Syndrome (> 1 Gy)

- Loss of lymphocytes and neutrophils
  - later RBCs and platelets
  - pancytopenia
  - possible hemorrhage
- Immune dysfunction
- Infections and sepsis
- Impaired wound healing

Hematopoietic Syndrome



Normal bone marrow cells

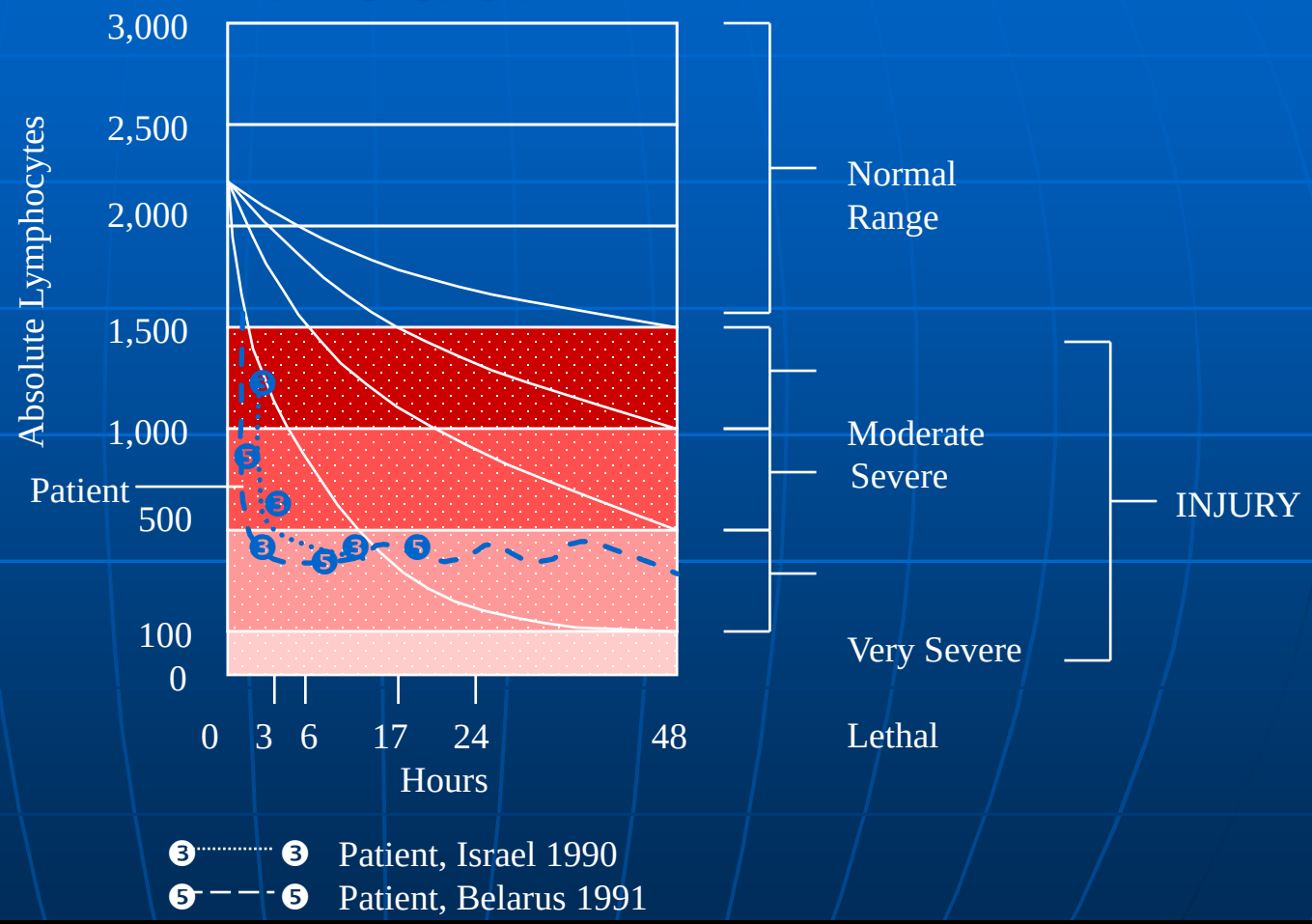


Irradiated Bone Marrow Cells

Hematopoietic Phase - Kinetics

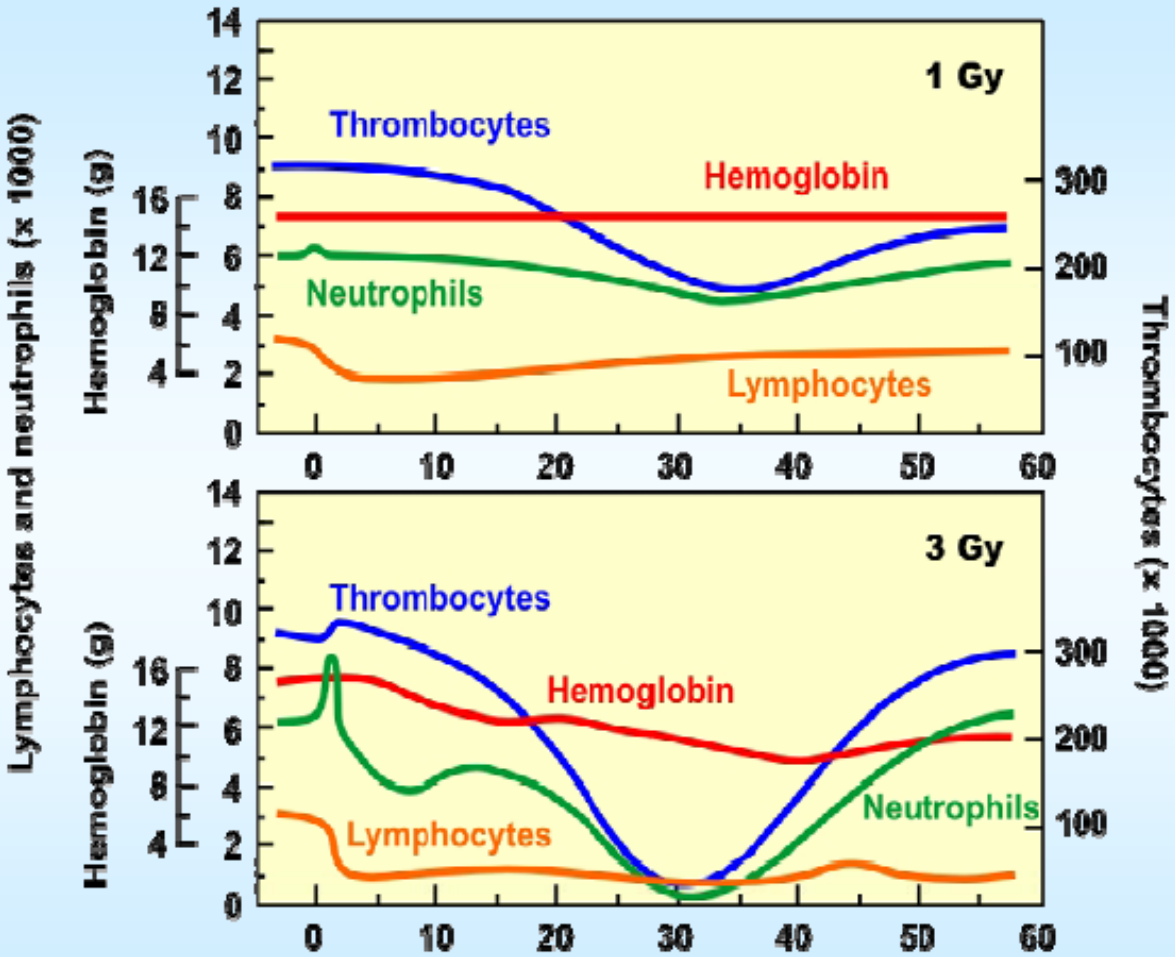
- Peripheral lymphocytes are one of the more radiosensitive cells in the body
- Lymphocytes can be killed in interphase
- Careful observation of lymphocyte decrease with time after exposure provides an early **estimate of dose <u>and</u> prognosis**
- Granulocytes - less sensitive
- RBC and platelet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

Comparison of Lymphocyte Counts with Values Predicted by Andrews' Model



From Andrews GA, Auxier, Jr., Lushbaugh, CC. *The importance of dosimetry to the medical management of persons accidentally exposed to high levels of radiation.* In: Personnel Dosimetry for Radiation Accidents. Vienna: International Atomic Energy Agency, 1965.

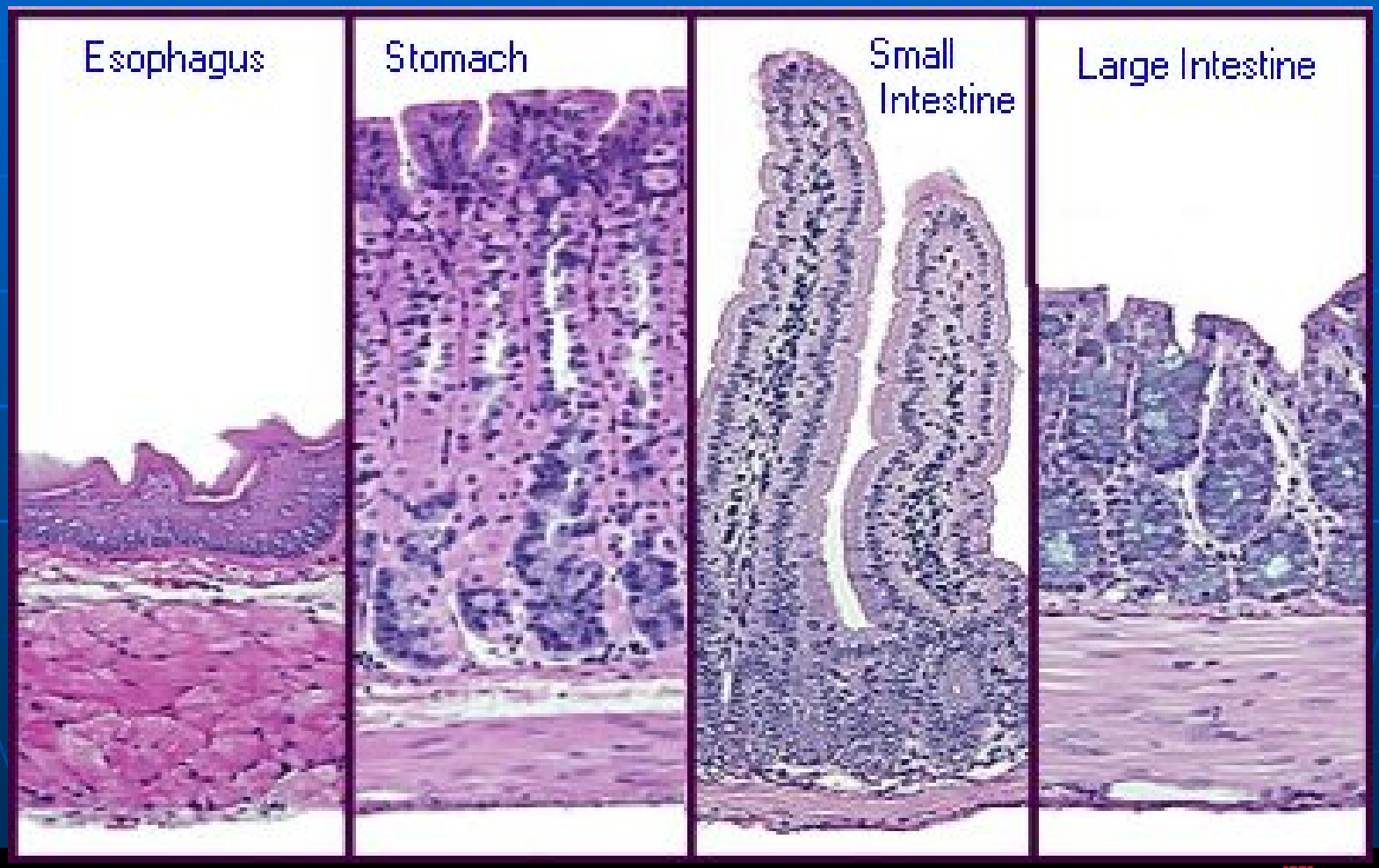
Hematological response to 1-3 Gy, whole body exposure to ionizing radiation



Gastrointestinal Syndrome (>6-8 Gy)

- Nausea, vomiting, diarrhea, bloody diarrhea and dehydration
- Malabsorption
- GI bleed
- Ileus
- Acute renal failure
- Cardiovascular failure (at 8-14 days)

Histology of the Digestive System



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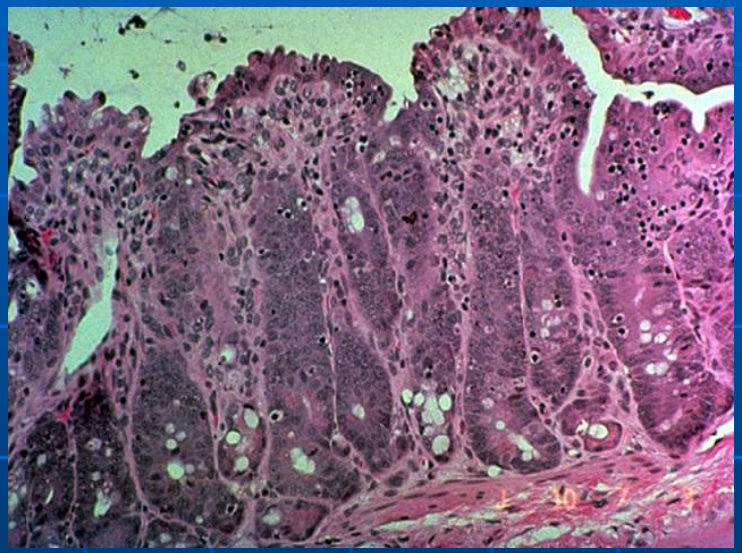

Irradiated GI Mucosa

Pathophysiology of the GI Syndrome

- Depletion of the epithelial cells lining lumen of gastrointestinal tract
- Intestinal bacteria gain free access to body
- Hemorrhage through denuded areas
- Loss of absorptive capacity

Neurovascular Syndrome (> 20 Gy)

- Nausea and vomiting within minutes
- Confusion and disorientation
- Severe hypotension
- Cerebral edema
- Ataxia
- Seizures
- Coma
- Fatal within 24 – 48 hours

Diagnosis of ARS

- Incident history – need health physics support for dose initial dose estimates
- History – onset and severity signs/symptoms
- Physical examination – including skin changes, document pertinent negatives

Diagnosis of ARS

- CBC with differential every 6 hours
- Absolute Lymphocyte Count (ALC)
- Usual medical and trauma labs
- Serum amylase, C reactive protein
- Blood and tissue typing later but HLA typing early
- Urinalysis and urine for radiobioassay
- Begin 24-hour collection of urine and feces for radiobioassays
- Cytogenetic dosimetry/chromosome aberration analysis
- Imaging as indicated

Biodosimetry Based on Acute Photon-Equivalent Exposures

Dose [Gy]	Onset of vomiting		Lymphocyte count ($x10^9$/liter) by day						Lymphocyte depletion rate	Number of dicentrics	
	%	Time [hr]	0.5	1	2	4	6	8	Rate constant	Per 50 cells	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	2.16	1.90	1.48	1.15	0.89	0.126	4	88
2	35	4.63	2.16	1.90	1.48	0.89	0.54	0.33	0.252	12	234
3	54	2.62	2.03	1.68	1.15	0.54	0.25	0.12	0.378	22	439
4	72	1.74	1.90	1.48	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	1.68	1.15	0.54	0.12	0.03	.006	0.756		
7	98	0.79	1.58	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 10^9 per liter.**

Lymphocyte depletion rate is based on the model $L_t = 2.45 \times 10^9/\text{liter} \times e^{-k(D)t}$ where L_t equals the lymphocyte count ($x10^9$/liter), 2.45 x 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).

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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.

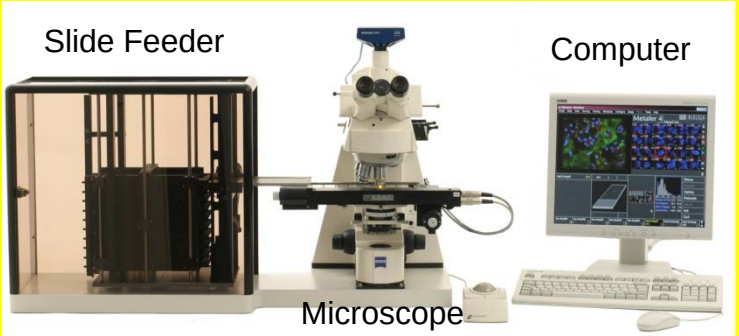
Cytogenetics Biodosimetry utilizes metaphase spreads of lymphocytes to search for targeted chromosome aberrations (dicentrics) specific to radiation exposures.

Old

Labor Intensive

New

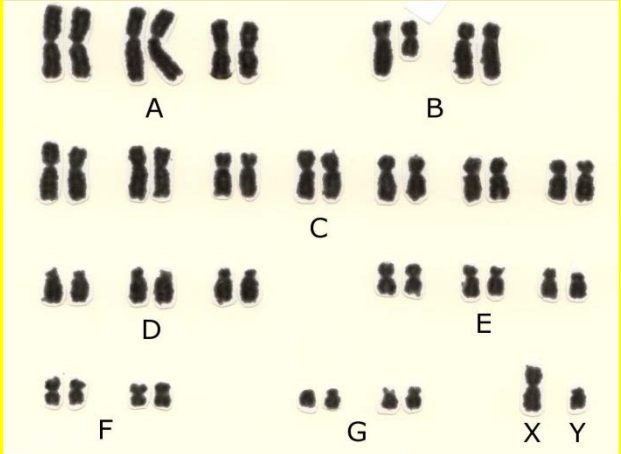
Automated slide handling and scanning. Computer karyotyping (identification/arranging) of the chromosomes and identification of aberrations.



Automated Cytogenetics Workstation

Output

Karyotype



Management Issues

- STABILIZE PATIENT FIRST
- Decontaminate, if necessary, after stabilization
- Treat other systemic symptoms & conditions
- Vomiting / emesis – use 5HT3 blockers
  - Granisetron (Kytril®)
  - Ondanestron (Zofran®)

Management Issues

Primary goal is reduction in severity and duration of leukopenia to avoid infection

- Keep absolute neutrophil count (ANC) > 100/mm^3
- ANC = WBCs X % neutrophils
- ANC = WBCs X (% bands + % segmented neutrophils)

Managment Issues

- "Neutropenic precautions"
- Early cytokine/colony stimulating factor therapy
- Antibiotic, anti-viral, anti-fungal prophylaxis and treatment
  - Don't forget Pneumocystis jiroveci, CMV, HSV
  - Gut decontamination

Management Issues

- Consider colony stimulating factors – as soon as possible when dose assessment >~2 Gy
- Granulocyte – Colony Stimulating Factor (G-CSF)
- Granulocyte – Monocyte Colony Stimulating Factor (GM – CSF)

Colony Stimulating Factors

- G-CSF Filgrastim (Neupogen®)
  - 2.5-5.0 µg/kg/day (100-200 µg/m^2/day)
- GM-CSF Sargramostim (Leukine®)
  - 5.0-10.0 µg/kg/day (200-400 µg/m^2/day)

Isolation Issues

- Treat ARS patients with estimated whole body irradiation >2 Gy in laminar flow / HEPA isolation rooms
- All personnel need to follow:
  - Strict hand washing / scrub before and after patient care
  - Gowns, caps, gloves, masks, shoe covers? – follow your facility's protocol

Infection Prevention Measures

- **Suppression of micro-organisms**
- **Physiological interventions**
  - Maintenance of gastric acidity
  - Avoidance of antacids and H_2 blockers
  - Sucralfate for stress ulcer prophylaxis to reduce gastric colonization and pneumonia
  - Early nutrition
- **Patient personal hygiene**
  - Chlorhexidine for skin disinfection, shampoo; **oral hygiene**

Consultations

- Hematology/Oncology
- Infectious Disease
- Surgery – Burn, Plastic, Vascular, Oncology
- Radiation Oncology, Nuclear Medicine, Toxicology
- Mental Health, Social Workers, Pastoral Care
- Interpreters, Cultural Awareness

Summary and Questions?

- Phases: Subclinical, hematopoietic, gastrointestinal, and neuroovascular
- Diagnosis: H & P, lab, radiobioassay, cytogenetics
- Treatment: Prophylaxis / treatment infection, cytokine therapy, neutropenia precautions
- Consults