

# **Current Thinking on the Early Effects from Uniform and Non-Uniform Radiation**

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# Casualties from radiation: 1896-2011

	# deaths	# injuries
Medical errors/overexposures	71	388
Reactor accidents**	62	495
Criticality accidents	21	56
Industrial accidents	17	181
Nuclear weapon-related	65,000*	111,000*
Intentional exposures	7	95
Theft/loss of source	42	142
Ingestion	10	74

\* Radiation alone

\*\* Includes Chernobyl (additional [thyroid] injuries due to fallout; ~ 10 deaths) and Fukushima (2 injuries)

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# What happens after WBI?

What is the most fundamental event following irradiation?

**CELL DEATH**

Which cells are most susceptible?

**DIVIDING CELLS**

Which dividing cells are most radiosensitive?

**STEM / PRECURSOR CELLS**

# Tolerance Doses (TD<sub>5/5</sub> - TD<sub>50/5</sub>)

## Single Dose (Gy)

Ovary	2 - 6	VCT	10 - 20
Bone marrow	2 - 10	Liver	15 - 20
Eye (lens)	2 - 10	Skin	15 - 20
Testes	2 - 10	Spinal cord	15 - 20
Lymphoid	2 - 20	Peripheral nerve	15 - 20
Gastrointestinal	5 - 10	Brain	15 - 25
Mucosa	5 - 20	Heart	18 - 20
Lung	7 - 10	Bone and cartilage	>30
Colorectal	10 - 20	Muscle	>70
Kidney	10 - 20		
Microvascular (endothelial cells) / epithelial cells			

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<b>Bone marrow</b>	<b>2 - 10</b>	<b>Hematopoietic (2-10 Gy; LD<sub>50/60</sub> 4-6 Gy)</b>	
Eye (lens)	2 - 10		
Testes	2 - 10	Peripheral nerve	15 - 20
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**Gastrointestinal (>6 Gy; LD<sub>50/7</sub> 10-12 Gy)**

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Mucosa	5 - 20	H	10 - 20
Lung	7 - 10	B	10 - 20
Colorectal	10 - 20	M	10 - 20
Kidney	10 - 20		

**CNS**

**(>15 Gy)**

Microvasculature (endothelial cells) / epithelial cells



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**CNS/cardiovasc.  
(>15 Gy)**

**Microvasculature (endothelial cells) / epithelial cells**

# Acute Radiation Syndromes (ARS)

- Hematopoietic
- Gastrointestinal
- Cardiovascular/CNS

Does tolerance (radiosensitivity) and cell death in critical tissues explain syndromes?

# Hematopoietic Syndrome

**Critical cells:** Stem/precursor cells

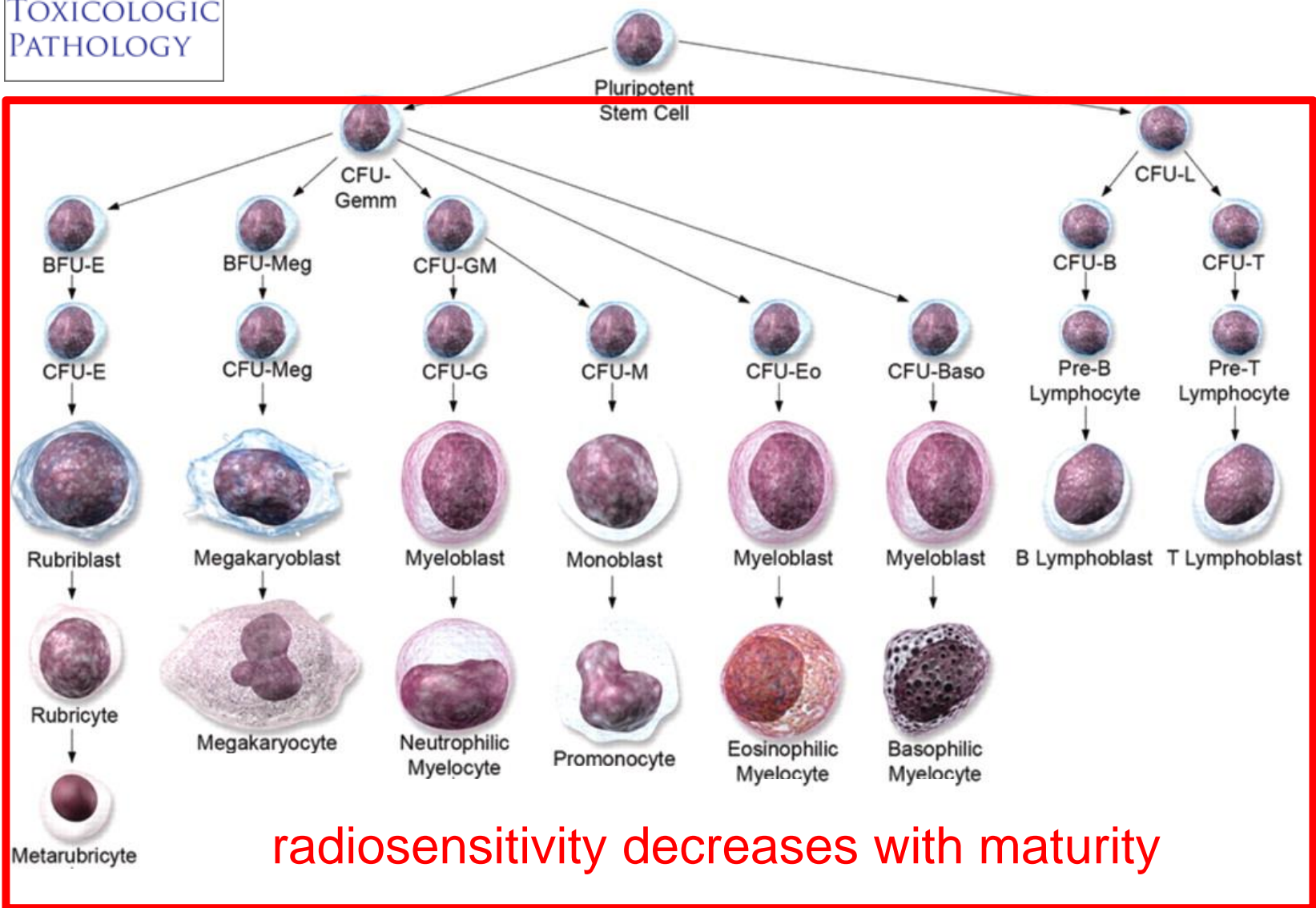
**Dose:**  $\geq 0.5$  Gy (lymphocytes)

**Cause of death:** infection



Pluripotent  
Stem Cell

radioresistant?  
hypoxic niche?

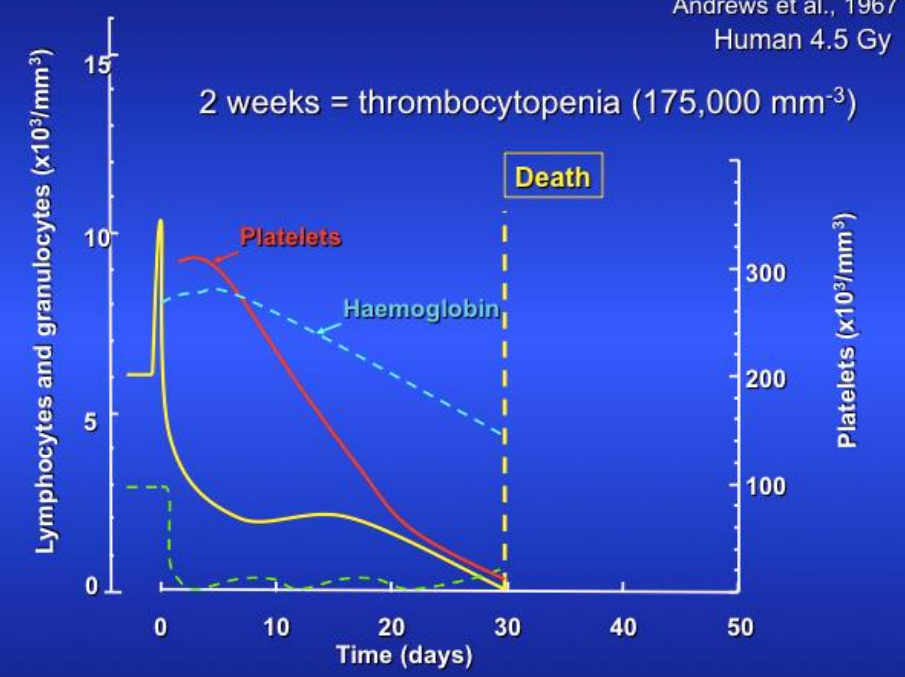
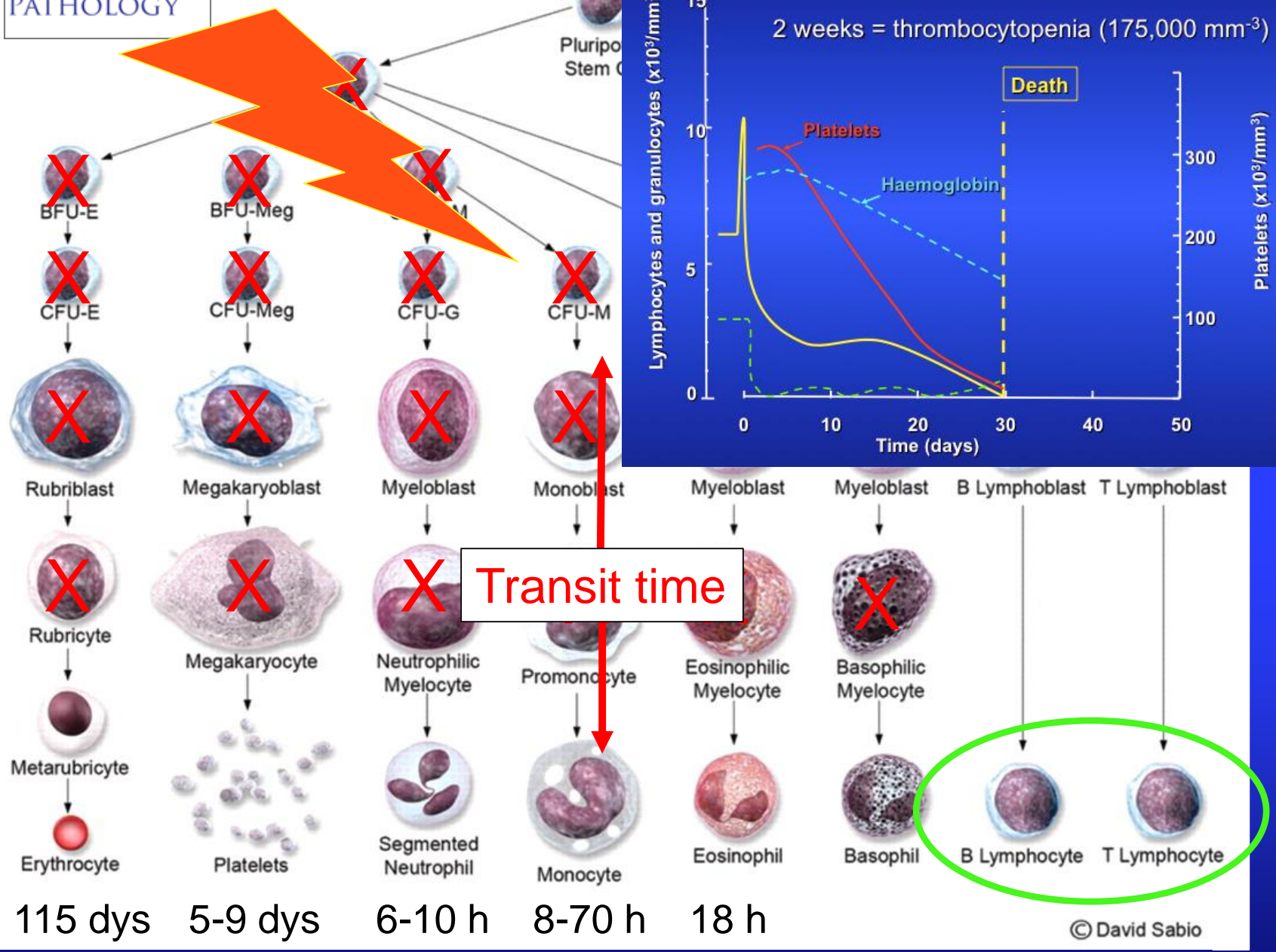


radiosensitivity decreases with maturity

Radiosensitive precursor compartment

**TOXICOLOGIC PATHOLOGY**

Andrews et al., 1967  
Human 4.5 Gy



# GI Syndrome

**Critical cells:** Epithelial lining of the g.i. tract

**Dose:**  $\geq 10$  Gy (damage occurs at lower doses; sparing of bone marrow increases required dose)

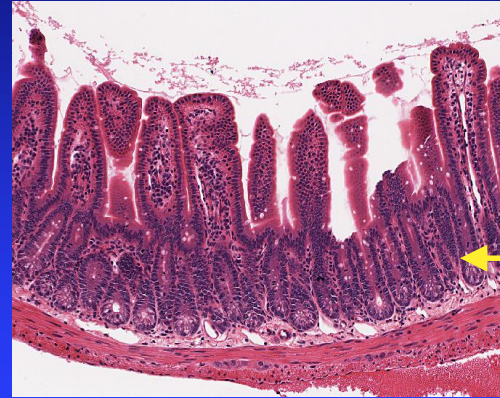
**LD<sub>50/7</sub>:** sterilization of crypt stem cells

**Cause of death:** infection



# GI Syndrome

0 Gy



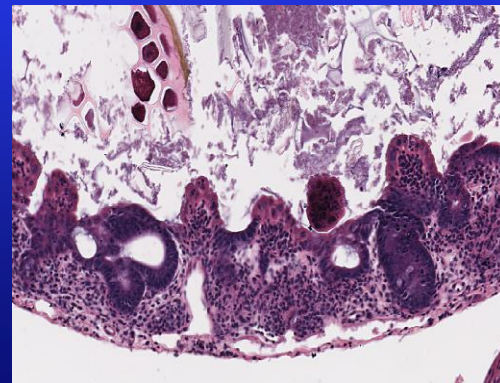
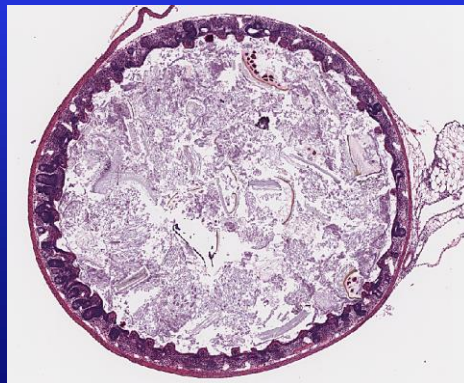
stem cells

10 Gy



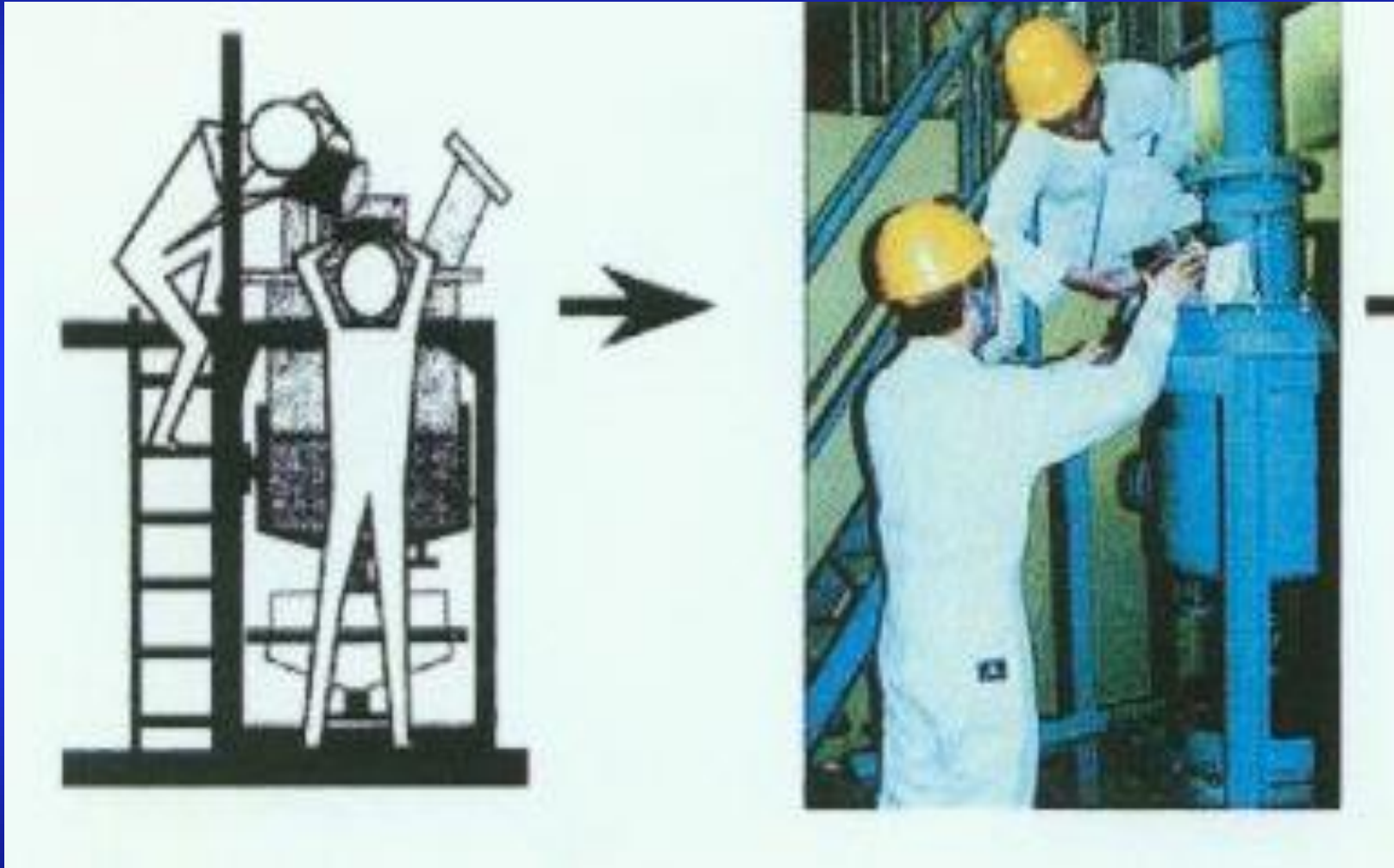
Ulceration, stenosis, ileus, perforation

14 Gy





**Incident:** September 1999, Tokai-mura,  
3 workers





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3 workers

**Dose:**

Worker A: TBI: 18 Gy; ~30 Gy G.I. tract  
small intestine: 12 – 5 Gy  
(neutrons) + 22 – 15 Gy ( $\gamma$ -  
rays )

Immediate: nausea, vomiting, loss of  
consciousness, diarrhea (1 hr)

Admission: febrile, hypotensive, drowsy,  
abdominal pain

**Incident:** September 1999, Tokai-mura,  
3 workers

**Dose:**

Worker A:

Treatment: cytokines (G-CSF), BMT (day 2),  
PBCT, tract decontamination

Symptoms: respiratory failure, severe skin  
lesions, g.i. bleeding, diarrhea  
(4 wks)

**Death:** 82 days

# Acute Radiation Syndromes (ARS)

- Hematopoietic
- Gastrointestinal
- Multi-organ syndrome (MODS/MOFS)
- Cardiovascular/CNS

# Multiple Organ Dysfunction / Failure

**Cause:** overall host response,  
radiation-induced systemic  
response

**Dose:** >10 Gy

**Latency:** weeks to months

**Symptoms:** fever, tachycardia,  
hyperventilation, and/or  
hypocarbica

**Death:** multiple organ failure (liver,  
kidney, lungs)

# Radiation



↑ ROS

cell death

free radical scavengers  
anti-apoptotics

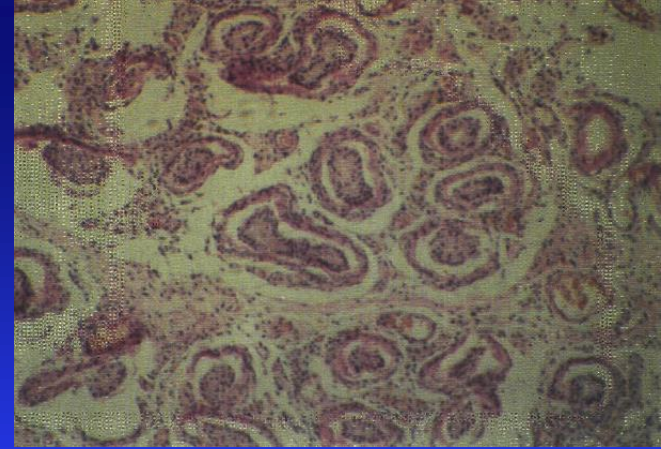


# Radiation



↑ ROS

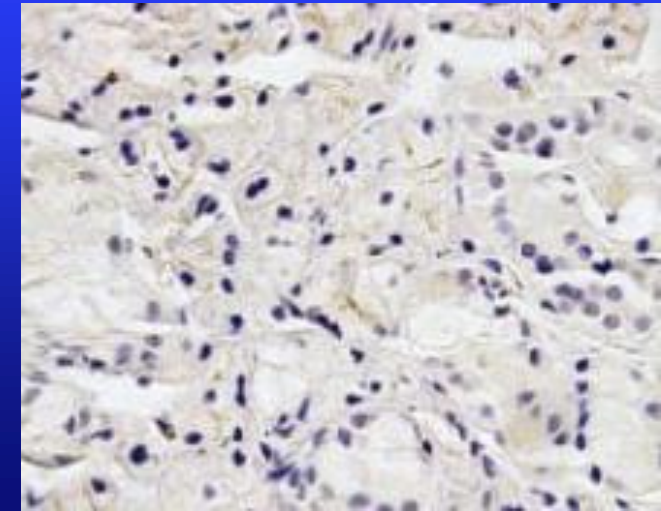
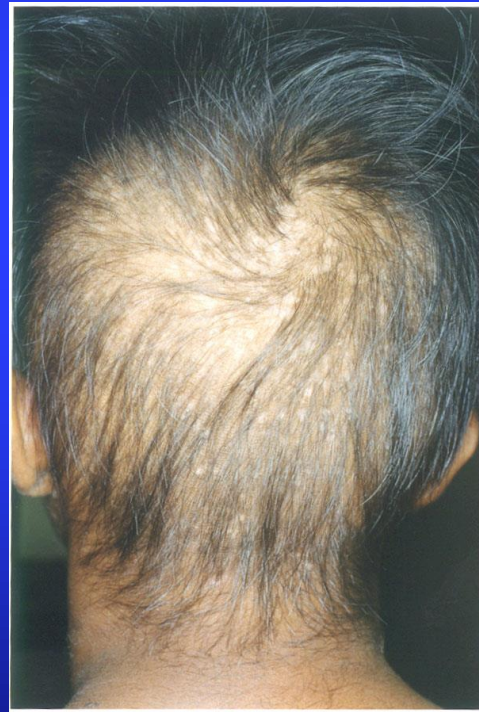
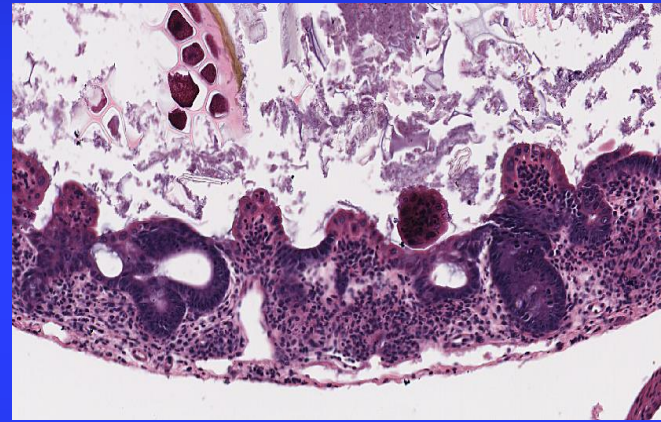
cell death



stem/progenitor  
cell loss



stem cell transfusions  
cytokines/growth factors



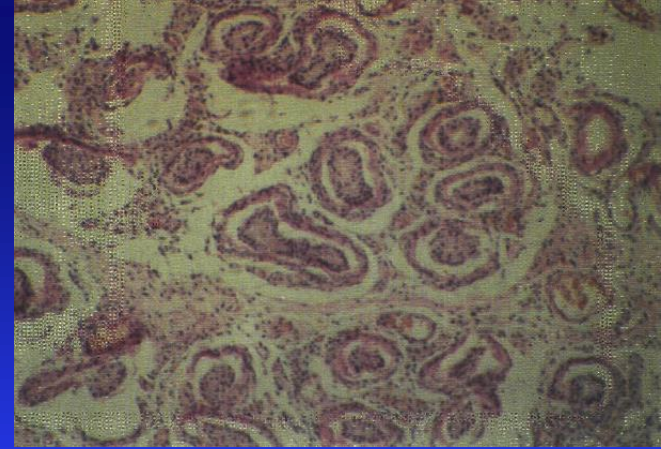


# Radiation



↑ ROS

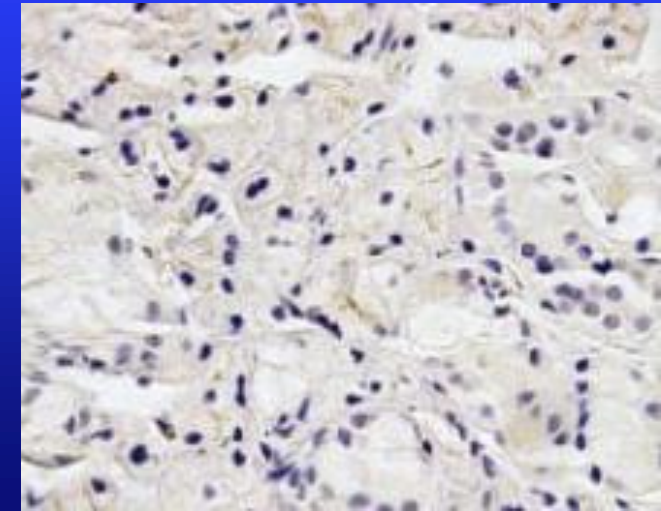
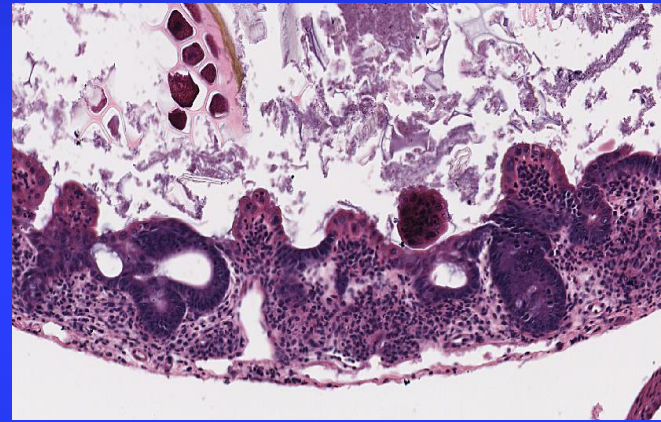
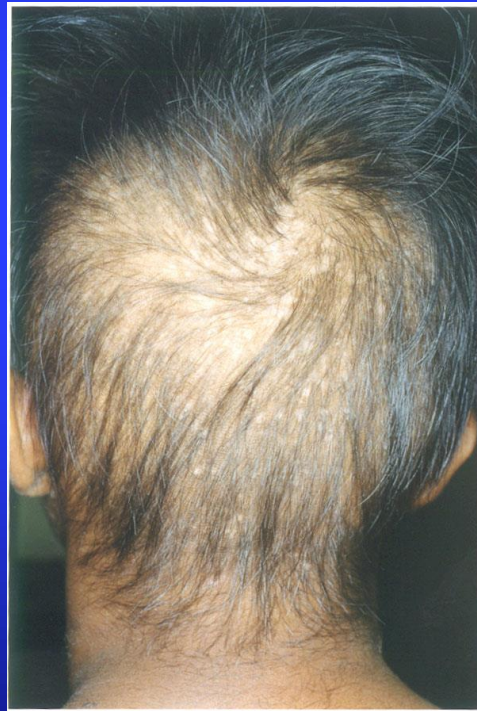
cell death



stem/progenitor  
cell loss



stem cell transfusions  
cytokines/growth factors  
mesenchymal stem cells



# Radiation



↑ ROS

cell death



stem/progenitor  
cell loss

altered barrier  
function  
(g.i., skin,  
brain)

antibiotics, antifungals  
mesenchymal stem cells  
FGF-P, anti-VEGF (BBB)

Radiation



↑ ROS

cell death  
/ injury

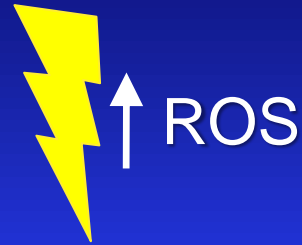
stem/progenitor  
cell loss

altered barrier  
function

mitochondrial  
damage



# Radiation



stem/progenitor  
cell loss

cell death  
/ injury

altered barrier  
function

inflammatory cell  
loss/recruitment

↑ ROS

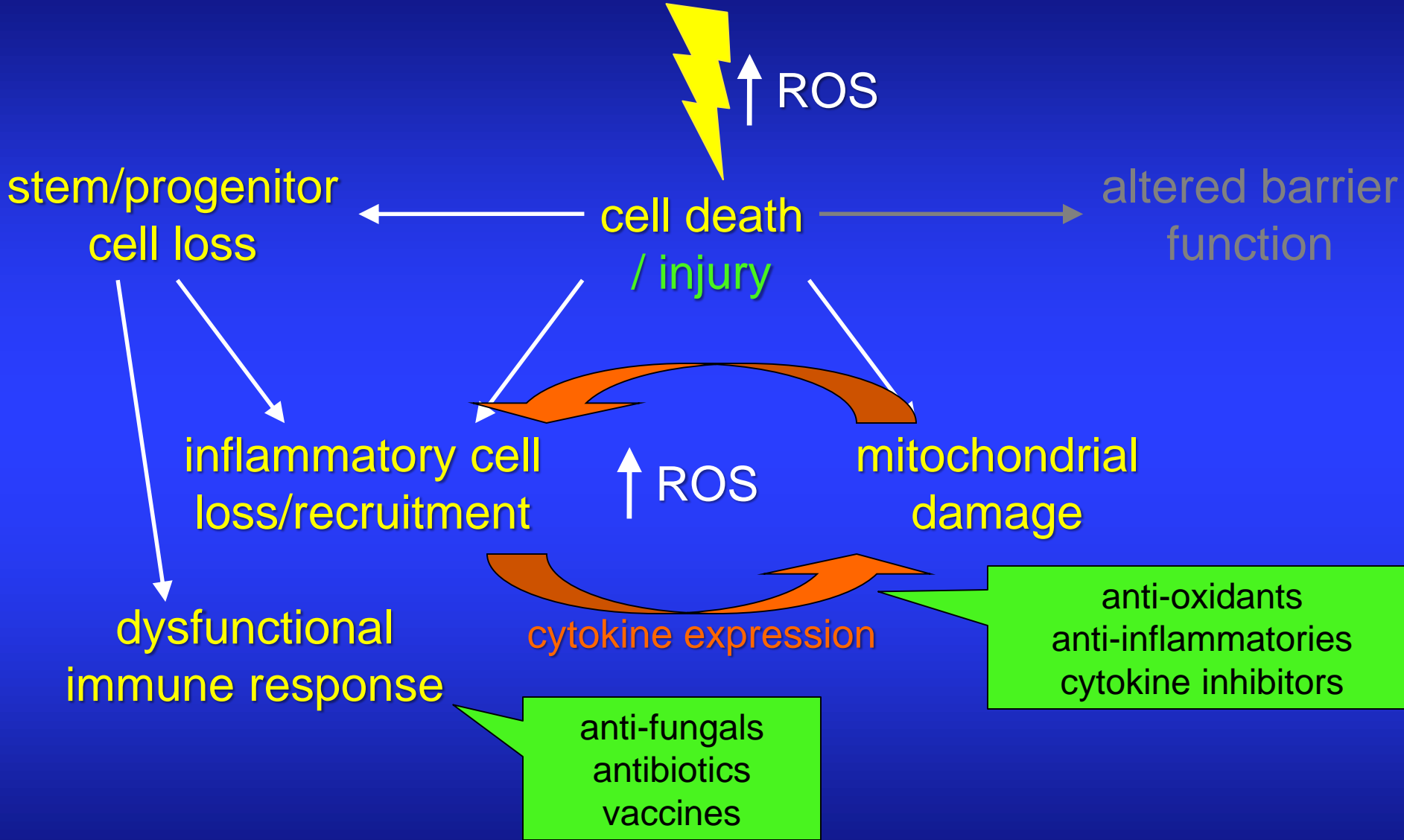
mitochondrial  
damage

dysfunctional  
immune response

cytokine expression

anti-oxidants  
anti-inflammatories  
cytokine inhibitors

anti-fungals  
antibiotics  
vaccines



# Radiation



↑ ROS

stem/progenitor  
cell loss

cell death  
/ injury

altered barrier  
function

inflammatory cell  
loss/recruitment

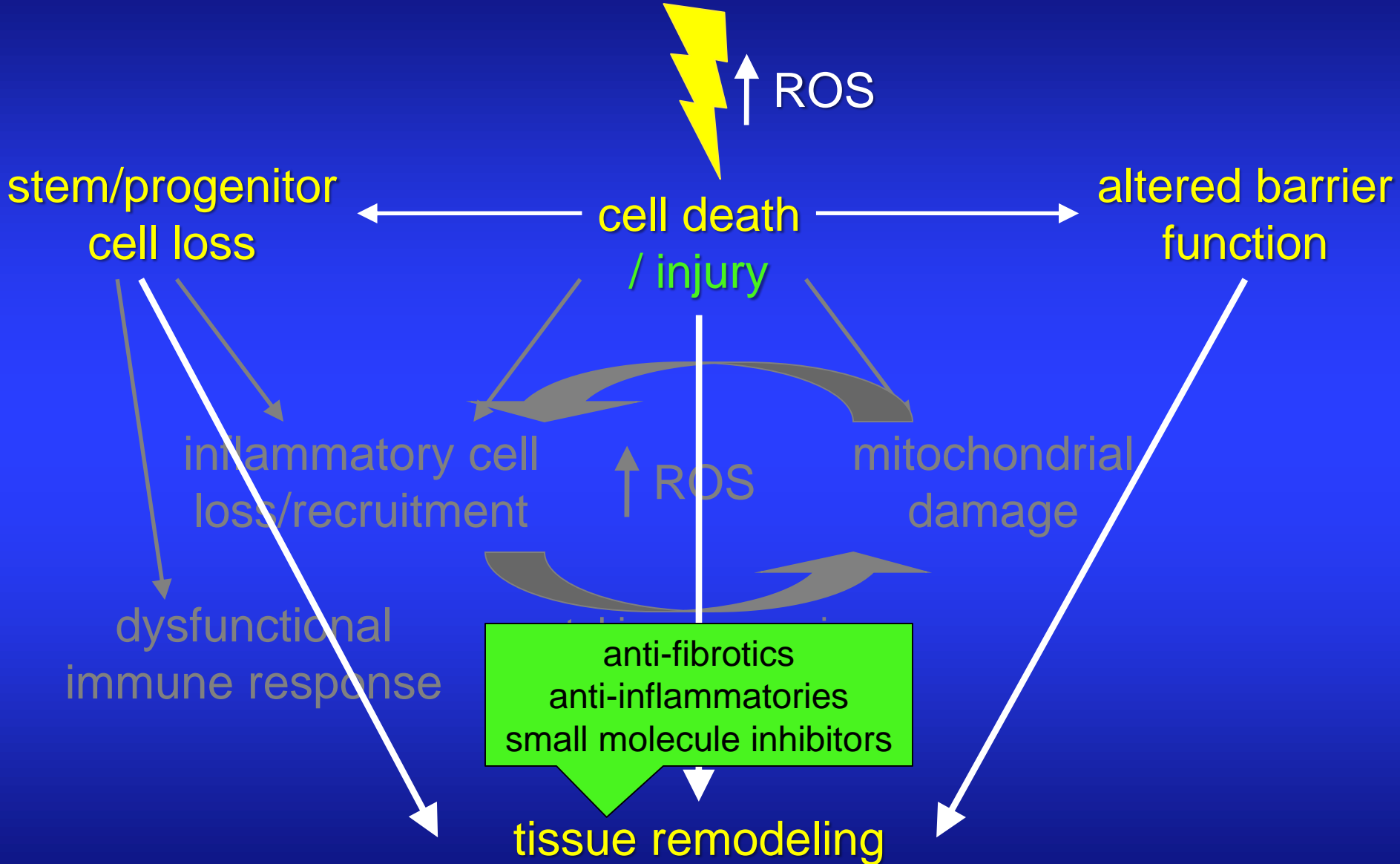
↑ ROS

mitochondrial  
damage

dysfunctional  
immune response

anti-fibrotics  
anti-inflammatories  
small molecule inhibitors

tissue remodeling



# Conclusions

- Acute radiation syndrome is now recognized as more than the simple consequence of cell death in stem cell compartment
- Multiple approaches may be needed to treat severe radiation injury
- Responding medical personnel need to look beyond immediate symptoms