Chapter 8 – Acute Radiation Syndrome

Chapter 14 – Radiologic Terrorism

10/28/2024

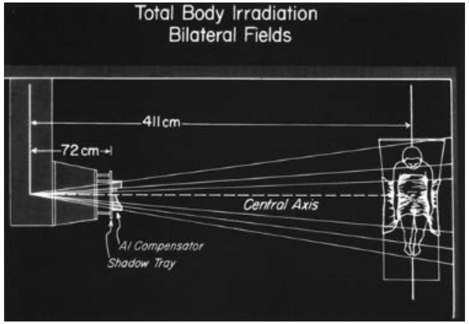
Outline

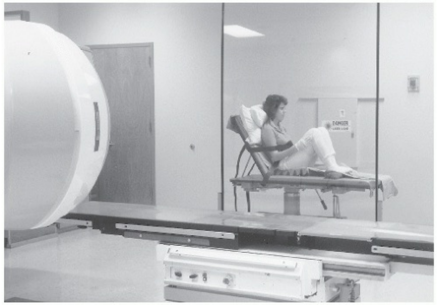
- **Total Body Irradiation in the Therapeutic Setting**
- Acute Radiation Syndrome
  - Early Lethal Effects
  - Prodromal Syndrome
  - Modes of Death
  - Value of Bone Marrow Transplant & Cytokine
- Pulmonary Syndrome
- Cutaneous Radiation Injury
- Triage and Treatment of Radiation Accident Victims
- Biological Terrorism and Dirty Bombs (Chapter 14)

Total Body Irradiation

- **Total body irradiation** (TBI) is a form of radiotherapy used primarily as part of the **preparative regimen for hematopoietic stem cell (or bone marrow) transplantation**
- TBI in the setting of bone marrow transplantation serves to destroy or suppress the recipient's immune system, **preventing immunologic rejection** of transplanted donor bone marrow or blood stem cells
- Additionally, high doses of TBI can **eradicate residual cancer cells** in the transplant recipient, increasing the likelihood that the transplant will be successful

TBI in the Setting of Transplant

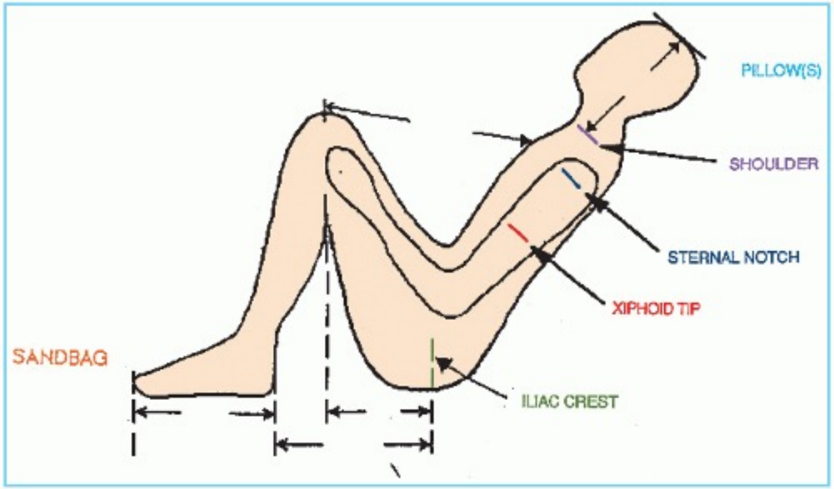


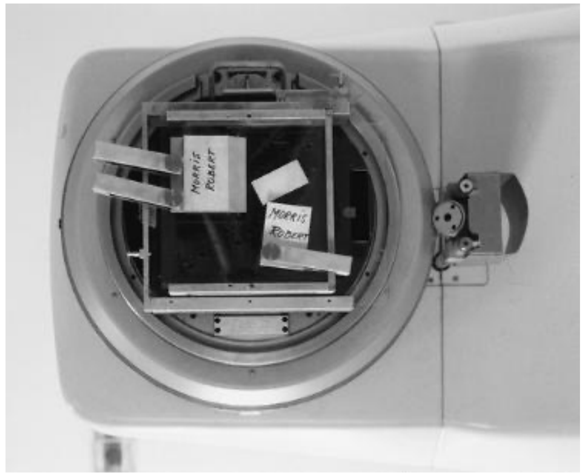


Typical U of M Protocol

200 cGy in a single fx

1320 cGy in 8 fx BID of 165 cGy per fraction





Outline

- Total Body Irradiation in the Therapeutic Setting
- **Acute Radiation Syndrome (Non-Therapeutic Setting)**
  - Early Lethal Effects
  - Prodromal Syndrome
  - Modes of Death
  - Value of Bone Marrow Transplant & Cytokine
- Pulmonary Syndrome
- Cutaneous Radiation Injury
- Triage and Treatment of Radiation Accident Victims
- Biological Terrorism and Dirty Bombs

Acute Radiation Syndrome in the Setting of TBI

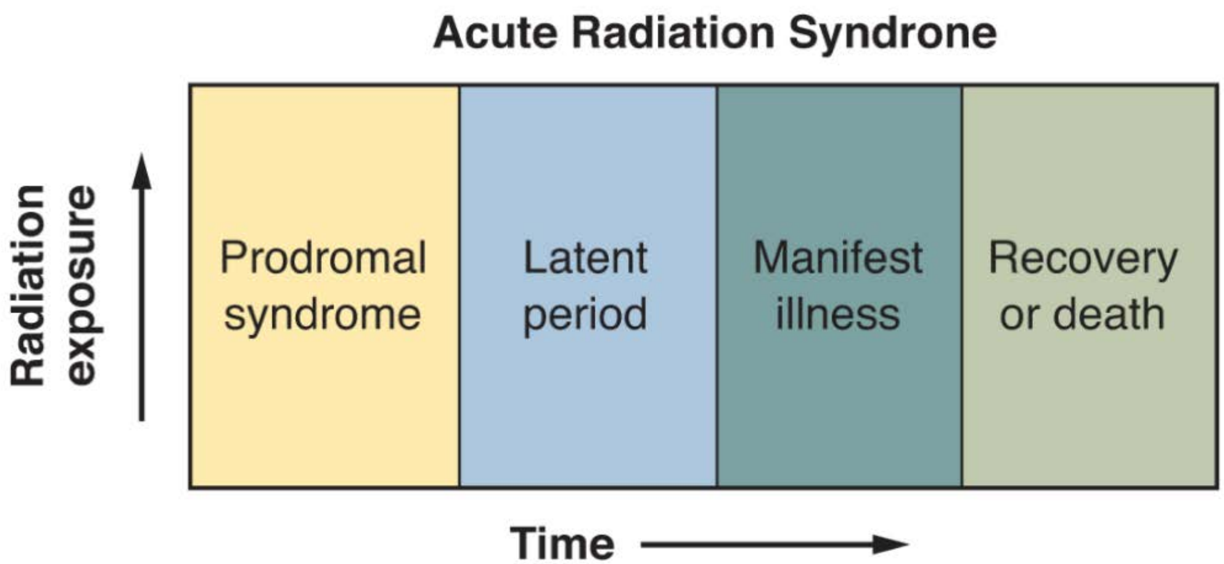
- In this lecture, we focus on the effect of TBI on *whole organism* in the **non-therapeutic setting** (i.e., accidental exposure or terrorist attack)
- Studies of TBI were popular and important in the 1950s and 1960s, supported largely by the military
- In more recent years, TBI has been of interest from the point of view of **bone marrow transplantation**, stemming from the treatment of radiation accidents, or from the rescue of patients receiving cancer therapy

Acute Radiation Syndrome (ARS)

- **Acute Radiation Syndrome** (sometimes known as radiation toxicity or radiation sickness) is an **acute** illness caused by irradiation of the **entire body** (or most of the body) by a **high dose** of penetrating radiation in a **very short period of time** (usually a matter of minutes)

- To date, about 400 humans have suffered from ARS

Stages of Acute Radiation Syndrome



Acute Radiation Syndrome

- A high-intensity exposure to radiation can result in death within a few weeks = early radiation lethality
- Death can occur via 3 distinct modes
  - **The Cerebrovascular Syndrome** (CNS Death)
  - **The Gastrointestinal Syndrome** (GI Death)
  - **The Hematopoietic Syndrome** (Bone Marrow Death)

Timeline for Acute Radiation Syndromes

DAYS

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28

CNS@1-2 days

Hematopoietic @ 18-28 days

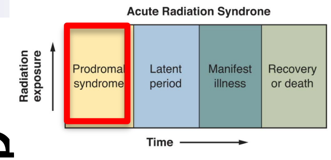
GI @5-10 days

DOSE

Hematopoietic 2.5-5 Gy

GI – 5-12 Gy

CNS > 100 Gy (20 Gy)



The Prodromal Radiation Syndrome

- Soon after irradiation, early symptoms appear, lasting for a limited period = **prodromal radiation syndrome**
- The signs and symptoms of the human prodromal syndrome can be divided into 2 main groups
- **Gastrointestinal** – anorexia, nausea, vomiting, diarrhea, cramps, salivation, fluid loss
- **Neuromuscular** – fatigue, apathy, sweating, fever, headache, hypotension

Signs

Objective, externally observable evidence of disease that a medical professional can perceive. Examples include fever, swelling, skin rash, high blood pressure, and high blood glucose.

Symptoms

Subjective evidence of disease that a patient experiences. Examples include complaints, pains and discomforts, and disturbances of function.

The Prodromal Syndrome

TABLE 8.1. *Symptoms of the Prodromal Syndrome*

Neuromuscular	Gastrointestinal
Signs and Symptoms to be Expected at About 50% Lethal Dose	
Easy fatigability	Anorexia
	Vomiting/nausea
Additional Signs to be Expected after Supralethal Doses	
Fever	Immediate diarrhea
Hypotension	

Survival possible

Survival unlikely

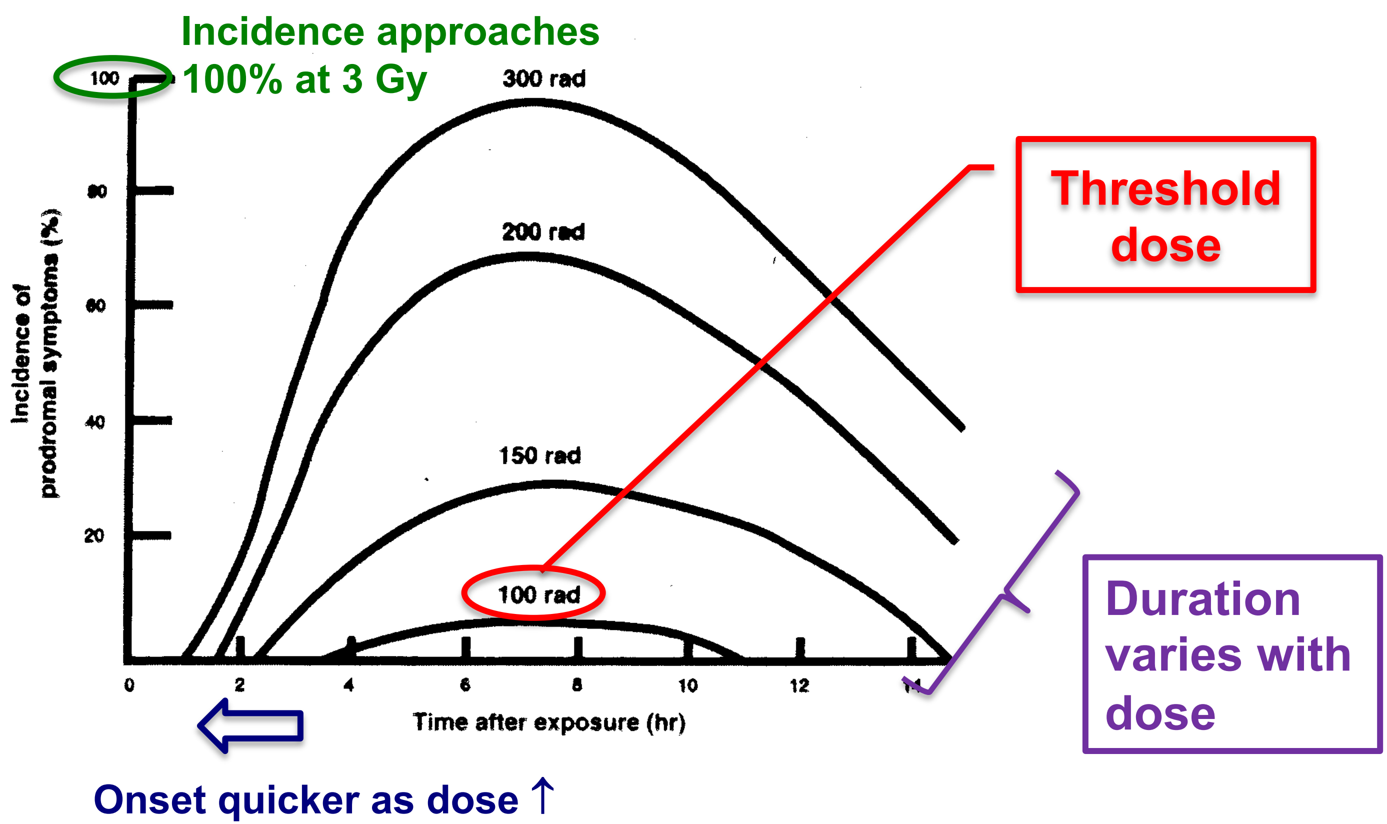
Can be used as a biological dosimeter to triage

The Prodromal Syndrome

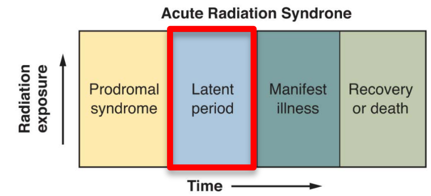
- Threshold **~ 1 Gy**
- As dose increases
  - Incidence increases
  - Severity of symptoms increases
  - Onset time for symptoms decreases from a few hours to a few minutes
- Duration of symptoms varies with dose

Several of these parameters are illustrated in the next diagram

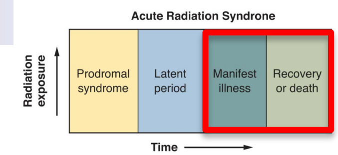
Dose and Incidence of Prodromal Symptoms



Latent Stage



- The prodromal phase is followed by a latent stage before the final ARS develops
- During latent stage, the patient may seem and feel relatively well for hours or even weeks
- The duration of the latent stage is inversely proportional to the dose



The Cerebrovascular Syndrome

- Death due to cerebrovascular syndrome is also known as **CNS death**
- Occurs at dose in excess of about **100 Gy** **(20 Gy)**
- Exposed individuals show prodromal symptoms within 5-15 minutes (e.g., severe N/V), which gradually diminish in intensity until merging with the fatal cerebrovascular syndrome
- As doses increases, mean survival time decreases, but death usually occur within **48 hours**

The Cerebrovascular Syndrome

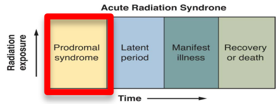
- Also called Neurovascular Syndrome or Acute Incapacitation Syndrome
- **Major symptoms** include *disorientation*, *loss of coordination*, *respiratory distress*, *diarrhea*, *convulsive seizure* and *coma*
- **Mechanism of action** is not fully understood, but likely due to disruption of nerve impulses and/or leakage of vessels that cause an increase in fluid content of the brain

Cecil Kelley – Los Alamos, 1958

- On December 30, 1958, an accident occurred in the Los Alamos plutonium-processing facility
- Cecil Kelley, an experienced chemical operator was working with a large mixing tank. The solution in tank was supposed to be "lean", typically less than 0.1 grams of plutonium per liter. However, the concentration on that day was 200 times higher. When Kelley switched on the stirrer, the liquid in the tank formed a vortex and the plutonium containing layer went critical releasing a huge burst of neutrons and gamma radiation estimated to be 39 Gy and 49 Gy in a pulse that lasted a mere 200 microseconds
- Kelley, who had been standing on a foot ladder peering into the tank through a viewing window, fell or was knocked to the floor. Two other operators on duty saw a bright flash and heard a dull thud. Quickly, they rushed to help and found Kelley incoherent and saying only, "I'm burning up! I'm burning up!".

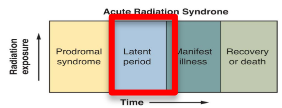
http://listverse.com/2010/03/25/10-famous-incidences-of-death-by-radiation/

Cecil Kelley – Los Alamos, 1958



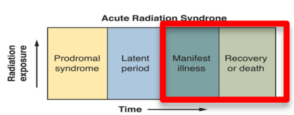
- He was rushed to the hospital, semiconscious, retching, vomiting, and hyperventilating. At the hospital, Kelly's bodily excretions were sufficiently radioactive to give a positive reading on a detector.

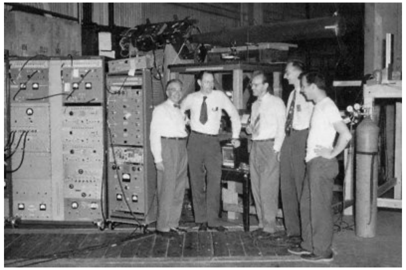
- Two hours after the accident, Kelley's condition improved as he regained coherence.



- However, it was soon clear that Kelley would not survive long. Tests showed his bone marrow was destroyed, and the pain in his abdomen became difficult to control despite medication.

- Kelley died 35 hours after the accident.





Robert Peabody – Wood River Junction, RI, 1964

- The Wood River Junction nuclear facility was designed to recover highly enriched uranium in scrap material from fuel element production.
- On July 24, 1964, technician Robert Peabody was working with a tank containing radioactive Uranium-235 in a sodium carbonate solution, which was being agitated by a stirrer.
- Intending to add a bottle of trichoroethane to remove organics, he mistakenly added a bottle of uranium solution to the tank, producing a criticality excursion accompanied by a flashlight and the splashing of about 20% of the tank's contents (about 10 liters) out of the tank
- This criticality exposed the 37-year-old Peabody to a fatal radiation of 22 Gy neutron and 66 Gy of gamma rays

Robert Peabody – Wood River Junction, 1964

- Ninety minutes later, a second excursion happened when a plant manager returned to the building and turned off the agitator, exposing himself and another administrator to doses of up to 1 Gy without apparent ill effect.

- Members of the local Hope Valley Ambulance Squad responded to render aid, initially transporting Peabody to Westerly Hospital; the hospital was not equipped for such a patient, the ambulance was turned away and the ambulance transported the patient to Rhode Island Hospital in Providence.
- Day 1 – headache, vomiting, diarrhea
- Day 2 – restless; hypotension; impaired vision
- He died at 49 hours after the incident

Woods River Junction patient 24 h post-TBI (100 Gy; died 49 h). Goans and Wald. BJR 2005

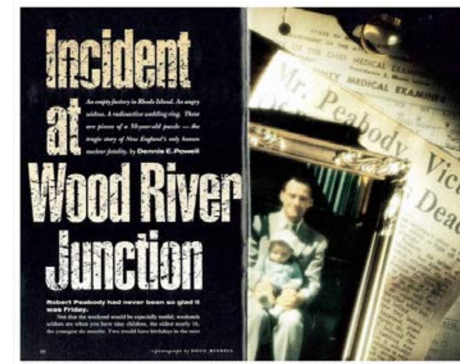
Robert Peabody – Wood River Junction, 1964

NEW ENGLAND HISTORY

Nuclear Fatality at Wood River Junction | *Yankee* Classic

An empty factory in Rhode Island. An angry widow. A radioactive wedding ring. These are pieces of a decades-old puzzle — the tragic story of New England's only known nuclear fatality in July of 1964.

Dennis E. Powell · July 6, 2022 · Read Comments (19)



"Incident at Wood River Junction" by Dennis E. Powell | *Yankee Magazine*, October 1994

https://newengland.com/today/living/new-england-history/nuclear-accident-at-wood-river-junction/

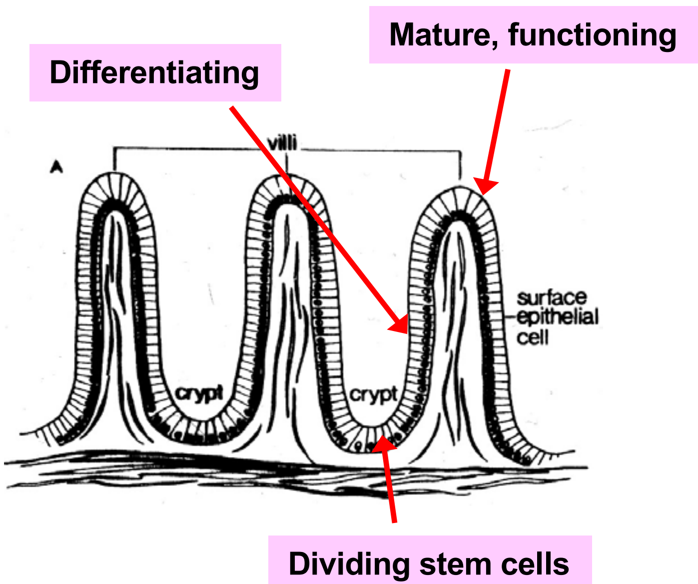
The Cerebrovascular Syndrome

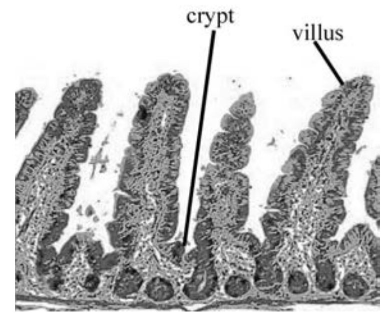
- At such very high doses, GI or Hematopoietic syndrome would be inevitable were the victims to survive long enough
- Death from cerebrovascular syndrome occurs so quickly that damage to all other systems is expressed but is not the primary cause of death

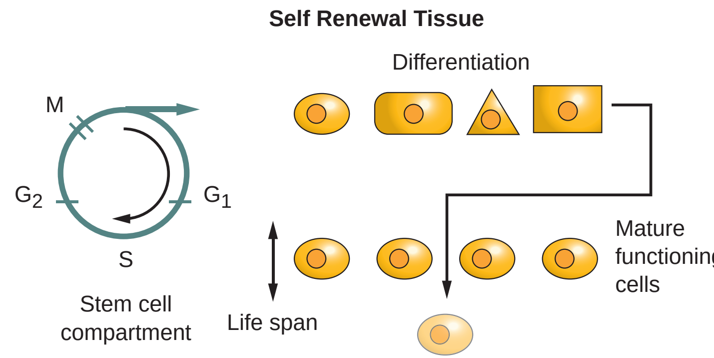
The GI Syndrome

- Occurs at doses more than **10 Gy**
- Prodromal symptoms start a few hours after exposure, but depending upon the dose, there is often a **"latent period"** before symptoms return
- **Major symptoms** include *nausea*, *vomiting*, *prolonged diarrhea*, *loss of appetite*, *lethargy*, *dehydration*, *emaciation*, *exhaustion*
- Death follows in about **5-10 days**

The GI Syndrome

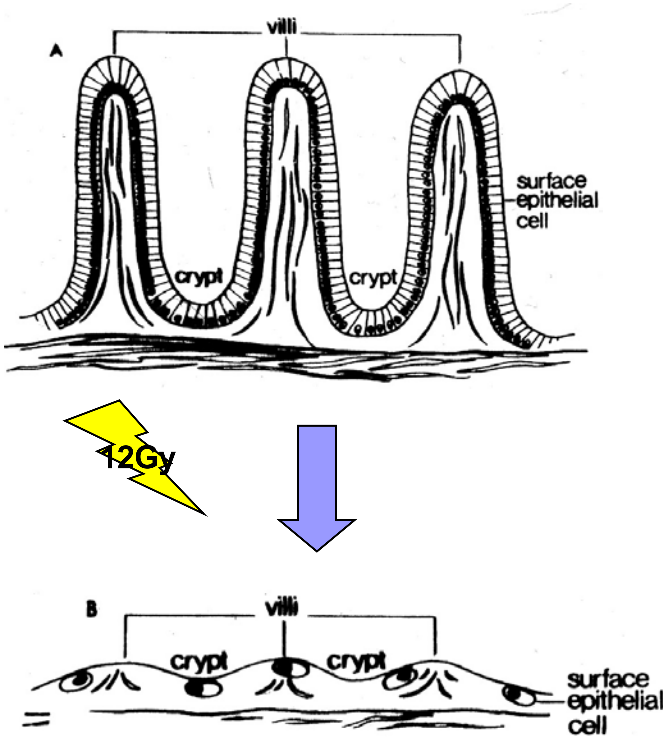






The normal lining of the intestine is a classic example of **self-renewing tissue**

The GI Syndrome



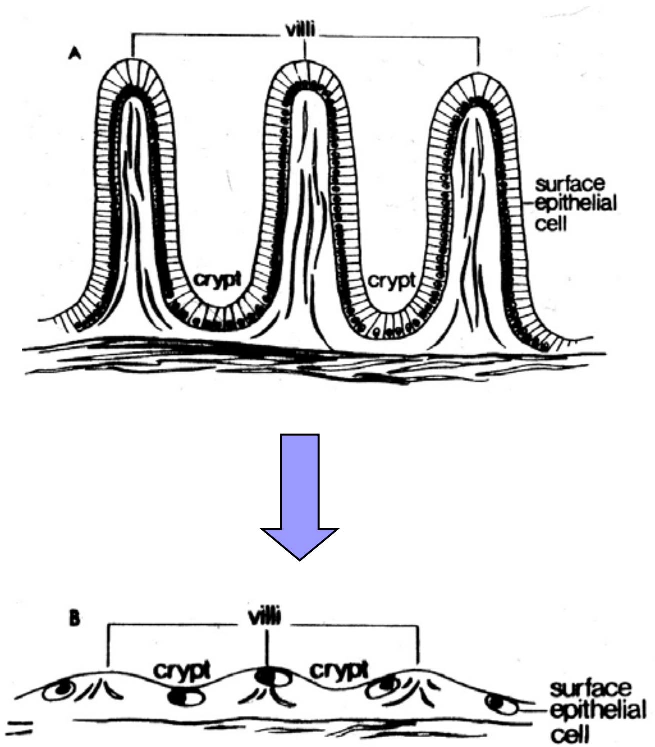
Completely denuded villi

Recall from Chapter 3 – very high radiation doses (100 Gy) is necessary to cause the breakdown of all cellular functions in nonproliferating systems
In contrast, the **mean lethal dose** for loss of reproductive capability is usually less than **2 Gy**

A 10 Gy dose kills dividing cells in the crypts, though not seriously affect the function of mature, fully differentiated cells

As the surface of the villi is sloughed off and rubbed away, there are no replacement cells → the lining of the intestine becomes completely denuded

The GI Syndrome



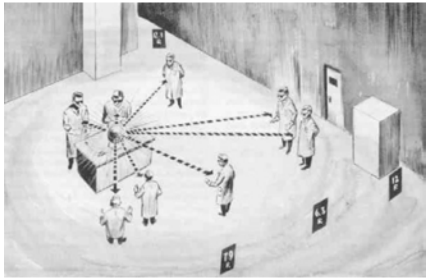
Completely denuded villi

The delay between the time of irradiation and the onset of the symptoms (i.e., **latency period**) is **dictated by the normal life span of the mature functioning cells**

In small rodents, complete denudation takes 3-4 days; in human, it may take **10 days** after the radiation

Louis Slotin – Los Alamos 1946

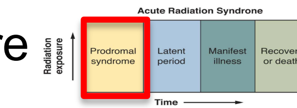
- Louis Alexander Slotin was a Canadian physicist and chemist
- As part of the Manhattan Project, Slotin performed experiments with uranium and plutonium cores to determine their critical mass values
- On 21 May 1946, Slotin accidentally began a fission reaction, which released a burst of hard radiation.
- "The blue flash was clearly visible in the room although it (the room) was well illuminated from the windows and possibly the overhead lights,"
- "The total duration of the flash could not have been more than a few tenths of a second. Slotin reacted very quickly in flipping the tamper piece off."
- Various estimates of total body exposure range from 11 to 20 Gy



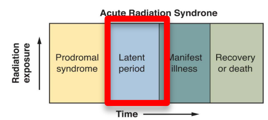
https://www.sciencealert.com/the-chilling-story-of-the-demon-core-and-the-scientists-who-became-its-victims-plutonium-bomb-radiation-wwii

Louis Slotin – Los Alamos 1946

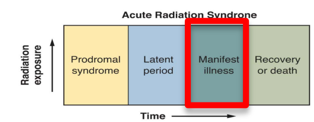
- He vomited several times within the first few hours of the exposure



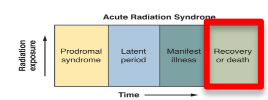
- On admission, his temperature and pulses rates were slightly elevated; physical exam was otherwise within normal limits. He remained relative well in the next few days.



- On day 6, he developed signs of severe paralytic ileus
- On day 7, liquid stools with occult blood were noted

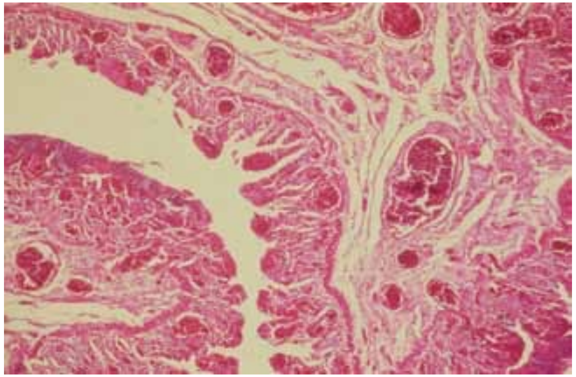


- He developed signs of circulatory collapse and died 9 days after irradiation



Louis Slotin – Los Alamos 1946

- On autopsy, most of the gastrointestinal tract showed atrophy and sloughing, most pronounced in the jejunum and ileum



Intestinal specimen illustrating villous atrophy, congestion, and hemorrhage

The GI Syndrome

- All individuals who received a dose large enough for a GI death have already received far more than enough radiation to result in hematopoietic death
- Death occurs before the full effect of the radiation on the blood-forming organs has a chance to express

At the time of death of Louis Slotin, jaundice and spontaneous hemorrhages were observed for the first time

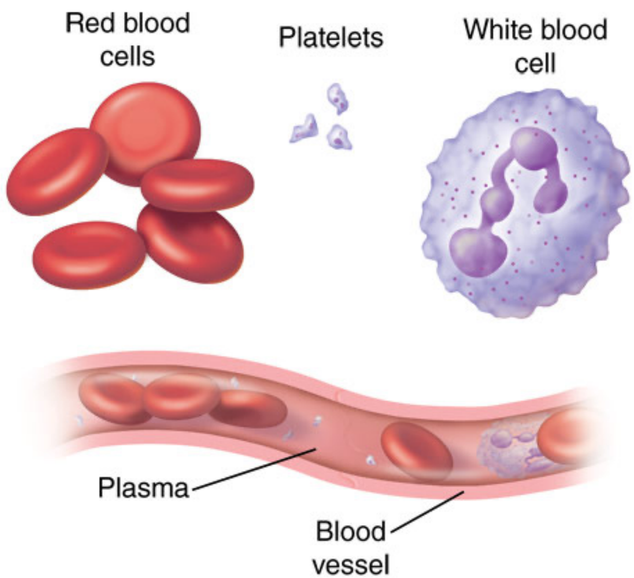
The Hematopoietic Syndrome

- Death due to hematopoietic syndrome is also known as **bone marrow death**
- Occurs at doses of **2.5 - 5 Gy**
- Following the prodromal symptoms, there is a **latency period of ~ 3 wks**
- Victims then begin to experience *chills*, *fatigue*, *hemorrhages in the skin*, *ulceration in the mouth*, *anemia*, and *epilation*
- Death is caused by **infection** (lymphocyte and granulocyte depression) or **hemorrhage** (platelet depletion)

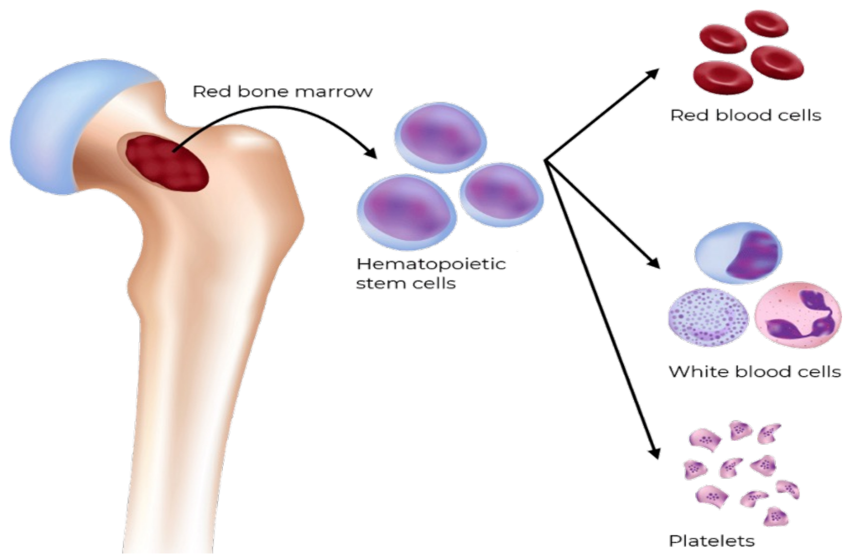
Hematopoietic Syndrome

- The blood-forming organ is another example of **self-renewal tissue**
- The mitotically active **stem cells** are particularly radiosensitive (no shoulders, and a **D_0 ~ 1 Gy**)
- The transit time from stem cell to fully functioning cell differ for the various circulatory blood elements

Blood Cells



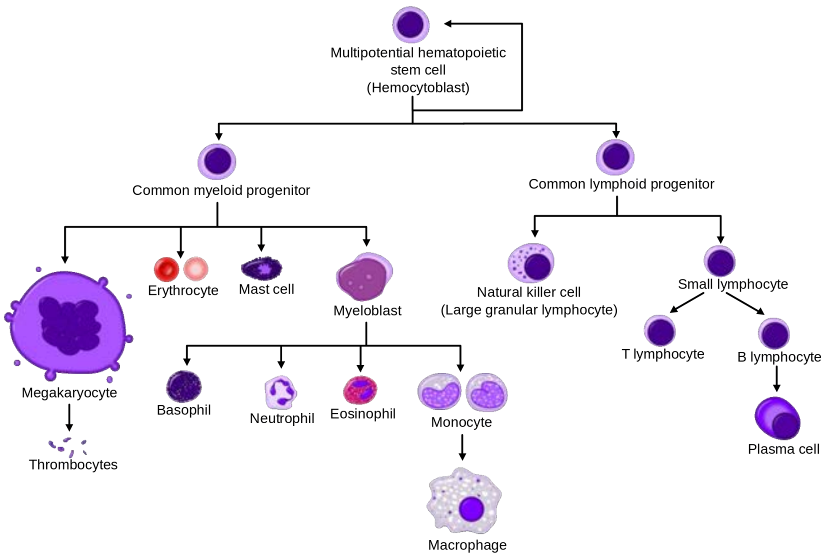
Peripheral Blood



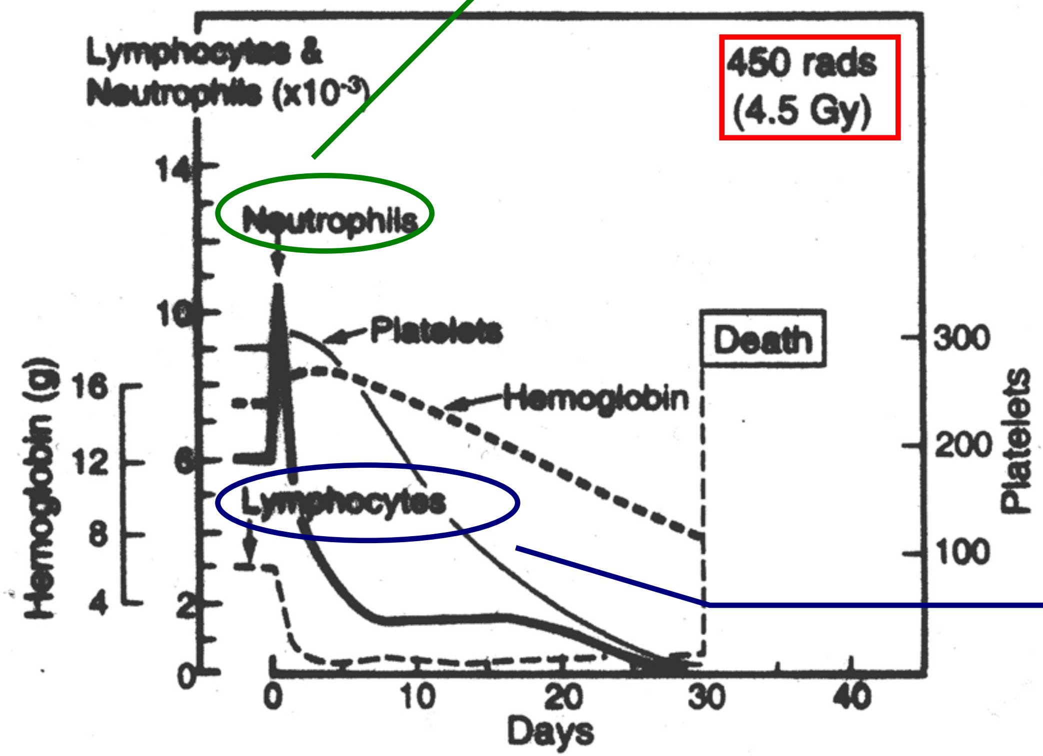
Bone Marrow

Hematopoiesis

- Hematopoiesis is the process of creating new blood cells in the body.
- All blood cells start off as hematopoietic stem cells, and then differentiate into **myeloid cells** (erythrocytes, megakaryocytes, monocytes, neutrophils, basophils, or eosinophils) or **lymphoid cells** (T-lymphocytes and B-lymphocytes).



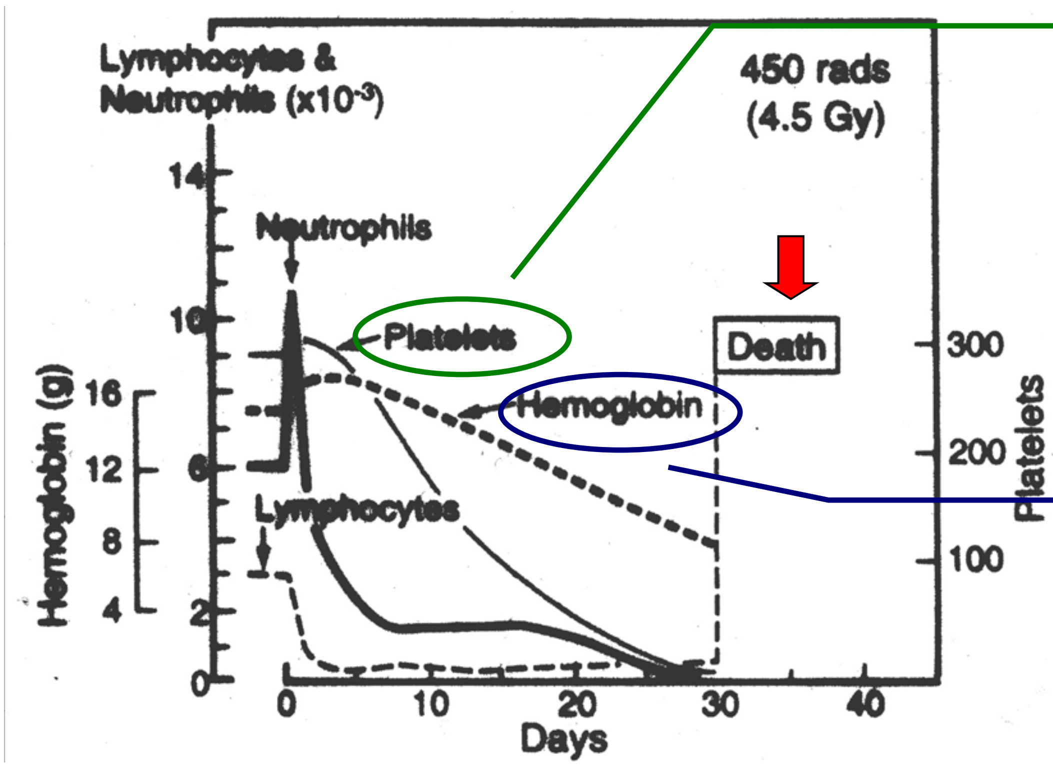
The Hematopoietic Syndrome



There is a temporary increase in the number of granulocytes because of the mobilization of the reserve pool, followed by a rapid fall by the end of the 1st wk, reaching minimum at 18-20 days

Lymphocytes are among the most sensitive cells in the body; lymphopenia occurs rapidly and at dose as low as 0.3 Gy

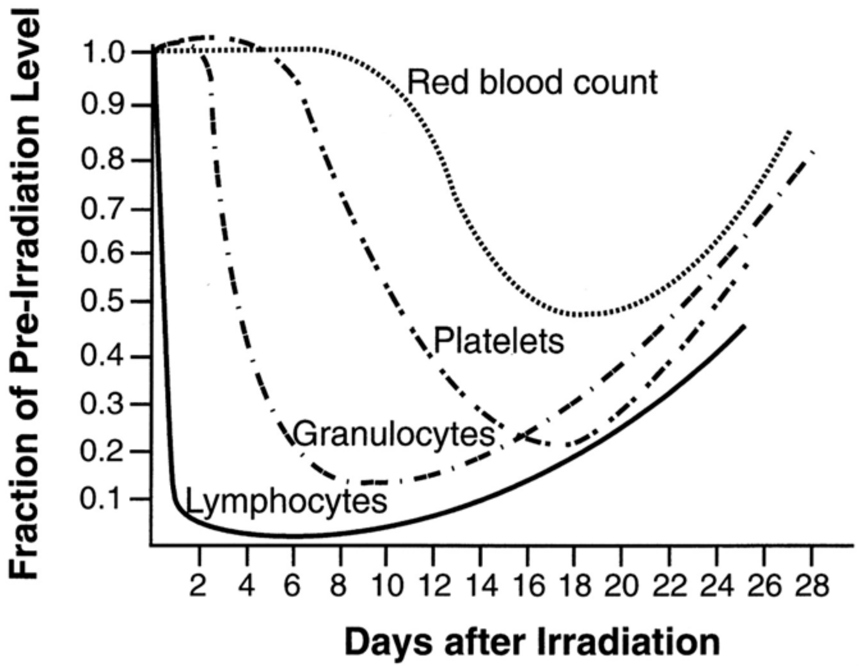
The Hematopoietic Syndrome



Bleeding and anemia are usually caused by hemorrhage resulting from platelet depression

RBC live for ~ 120 days; anemia from red blood cell depression usually does not occur

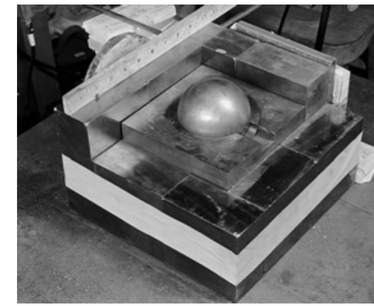
The Hematopoietic Syndrome



The time at which nadir occurs is a combination of the radiosensitivity of the stem cells and the lifetime of the mature functioning cells

Pattern of depletion and recovery of circulating blood elements

Harry Daghlian – Los Alamos, 1945



- Harry Daghlian was an American physicist with the Manttattan Project whose job was to measure the threshold at which the plutonium would become supercritical, the point where a nuclear chain reaction would unleash a blast of deadly radiation
- On **August 21, 1945**, he surrounded the plutonium sphere with bricks made of tungsten carbide, which reflected neutrons shed by the core back at it, edging it closer to criticality
- Brick by brick, Daghlian built up these reflective walls around the core, until his neutron-monitoring equipment indicated the plutonium was about to go supercritical if he placed any more
- He moved to pull one of the bricks away, but in doing so accidentally dropped it directly onto the top of the sphere, inducing supercriticality and generating a glow of blue light and a wave of heat
- He was exposed to a mixture of neutrons and γ-rays of an estimated dose of 6.35 Sv

Harry Daghlian – Los Alamos, 1945

Hospital Course

- Day 1: Nausea, anorexia, vomiting
- Day 2: greatly improved, except for numbness in his hand
- Day 3: Erythema on the front of the body
- Day 5: Rise of temperature
- Day 10: Nausea and cramps
- Day 12: Acute mucositis of mouth and tongue
- Day 17: epilation of body hair
- Day 24: died with white cell count close to 0

Blood Counts

- **Red cells**: little change until the time of death
- **Platelets**: dropped, but restored by platelet transfusion, then dropped again
- **White cells**: initial rise but eventually fell to zero by the time of death

Y-12 Critical Incident

- **The Y-12 National Security Complex** is a United States Department of Energy National Nuclear Security Administration facility located in Oak Ridge, Tennessee, near the Oak Ridge National Laboratory.
- It was built as part of the Manhattan Project for the purpose of enriching uranium for the first atomic bombs.
- In the years after World War II, it has been operated as a manufacturing facility for nuclear weapons components and related defense purposes.

Employees of the Manhattan Project operating calutron control panels at Y-12, in a US government photo by Ed Westcott.

1958 criticality incident

At 11 p.m. on **16 June 1958** a criticality accident occurred in the C-1 Wing of Building 9212 at the facility, then operating under the management of Union Carbide. In the incident, a solution of highly enriched **uranium** was mistakenly diverted into a steel drum, causing a fission reaction of 15–20 minutes duration.

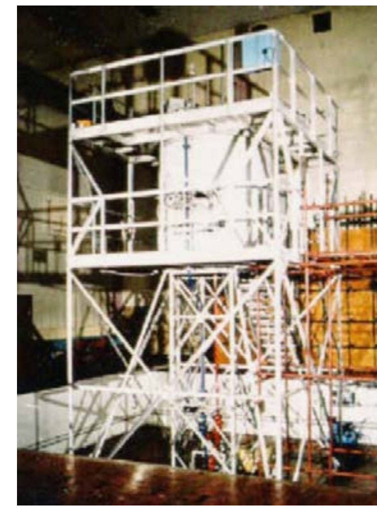
Wikipedia

1958 Vinča Accidents

- The **Vinča Institute of Nuclear Sciences** is a nuclear physics research institution near Belgrade, Serbia.
- Since its founding, the institute has also conducted research in the fields in physics, chemistry and biology.
- The scholarly institute is part of the University of Belgrade.

Vinca Institute of Nuclear Sciences logo

In **October 1958**, there was a criticality accident at one of the research reactors. Six workers received large doses of radiation; one died shortly afterwards. The other five survived with 4 receiving the first ever bone marrow transplants in Europe.



The first nuclear reactor - zero power bare critical assembly RB was assembled in 1958.

Wikipedia

Y-12 and Vinča Accidents

Vol. 179, No. 3 191

Criticality Accidents in Vinca, Yugoslavia, and Oak Ridge, Tennessee

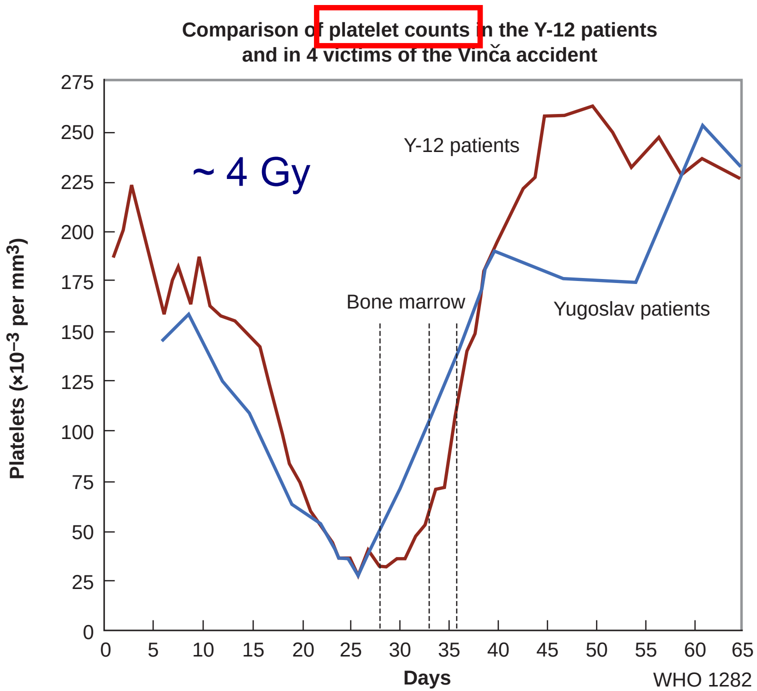
Comparison of Radiation Injuries and Results of Therapy

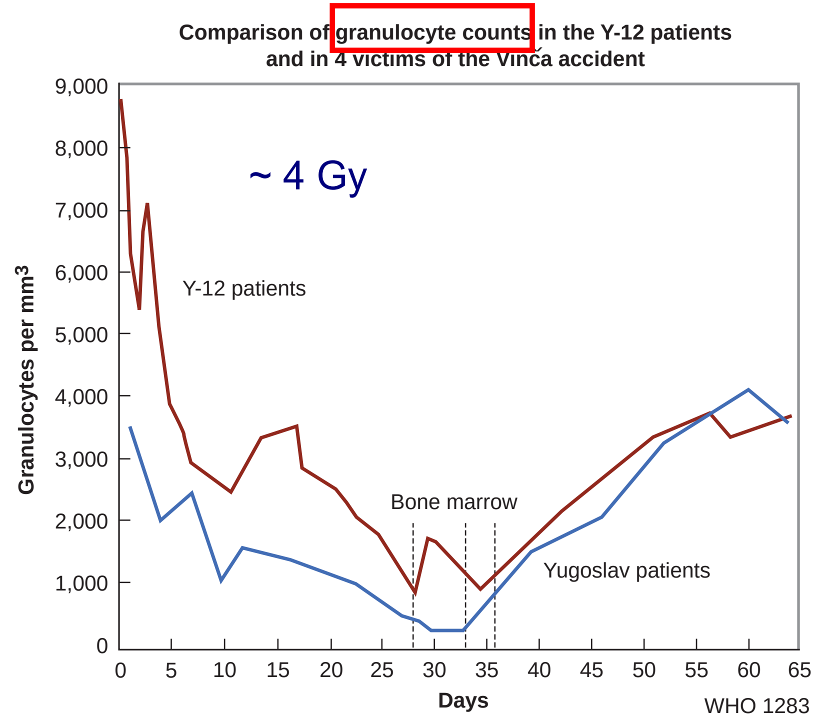
Gould A. Andrews, M.D., Oak Ridge, Tenn.

J.A.M.A., Jan. 20, 1962

Major accidents involving radiation from nuclear reactors occurred in Oak Ridge, Tenn., and in Vinca, Yugoslavia, in 1958. The 2 accidents were in some ways similar, and both contributed information on the treatment of total-body radiation injury. After the Y-12 accident at Oak Ridge, the 5 exposed men recovered with supportive care. The 6 Yugoslavian radiation victims were moved to Paris, where 1 died, and 5, including 4 who had received bone-marrow injections, recovered. Efforts to evaluate the significance of the marrow treatment have involved consideration of physical measurements of radiation dose, biological evidence of severity of injury, and evidence for and against success of the marrow graft, but have not proved its value in these cases. A comparison of the 2 accidents helps to give perspective on these problems.

Blood Counts Following Exposure

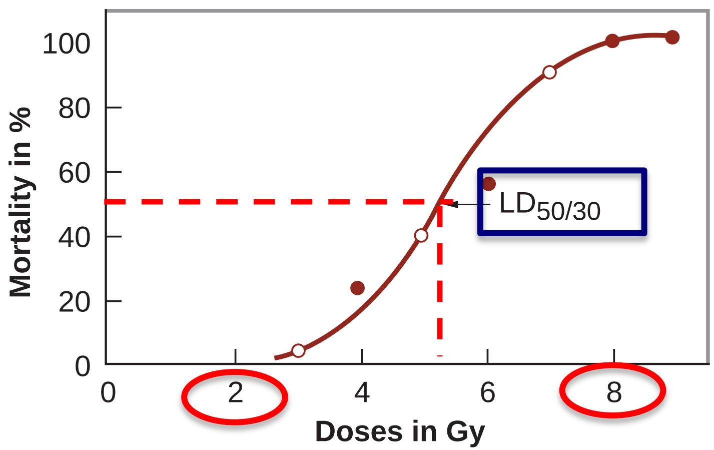




Depression and recovery of circulating blood elements in victims of the Y-12 reactor accident at Oak Ridge, TN, and 4 accidentally exposed Yugoslav scientists

The Mean Lethal Dose

Mortality rate of rhesus monkeys at 30 days after a single dose of TBI



$LD_{50/30}$ for rhesus monkey = 5.3 Gy

LD_{50}

The dose of that causes a mortality rate of 50% in an experimental group within a specified period of time; also called **50% lethal dose** or **mean lethal dose**

The peak incidence of BM death for human occurs at about 30 days, but death continue for up to 60 days → the LD_{50} is expressed as **$LD_{50/60}$**

The Mean Lethal Dose

- Many factors influence the response of the individual to TBI
- The very young and the old appear to be more radiosensitive than the young adults
- The female, in general, appears to have a greater degree of tolerance to radiation than does the male
- The best estimate of $LD_{50/60}$ for young healthy adults without medical intervention is ~ **3.5 Gy** **(3.2-3.6 Gy)**
- LD50 was estimated to be **7 Gy** – antibiotics and supportive care

The Mean Lethal Dose

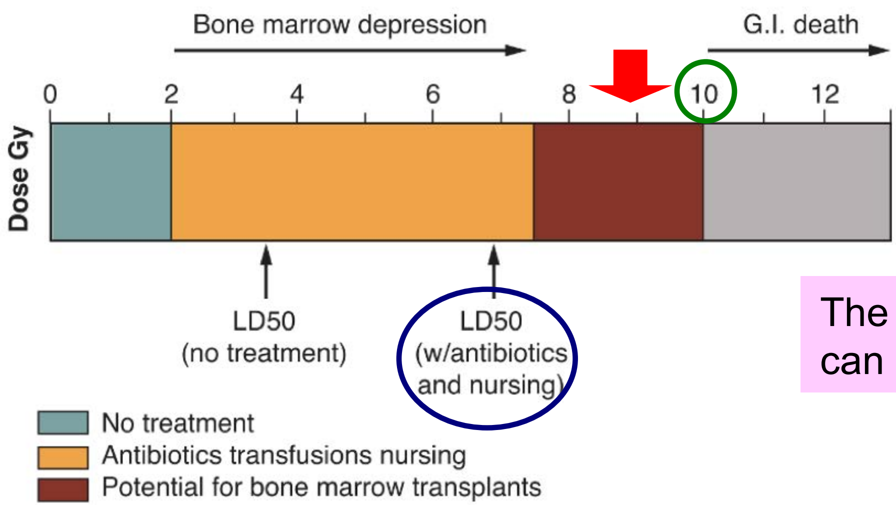
TABLE 8.2 The 50% Lethal Doses for Various Species from Mouse to Human and the Relation between Body Weight and the Number of Cells that Need to Be Transplanted for a Bone Marrow "Rescue"

Species	Average Body Weight, kg	50% Lethal Total Body Irradiation, Gy	Rescue Dose per kg $\times 10^{-8}$	Relative Hematopoietic Stem Cell Concentration
Mouse	0.025	7	2	10
Rat	0.2	6.75	3	6.7
Rhesus monkey	2.8	5.25	7.5	7.3
Dog	12	3.7	17.5	1.1
Human	70	4	20	1

Rabbits	8
Goldfish	20
Cockroaches	>>20

Studies of total body irradiation on various species were popular and important in the 1950s and 1960, supported largely by the military

Value of Bone Marrow Transplant



There is no instance on record of a human having survived a dose in excess of 10 Gy

The window of dose within which a transplant can be effective is narrow, ie, **8-10 Gy**

In primates, the LD_{50} can be raised by a factor of 2 by appropriate treatment, including careful nursing and antibiotics, and the same may be assumed for humans

Value of Bone Marrow Transplant

- 4 exposed Yugoslav scientists
  - All of the grafts were rejected, but the exposed individual survived anyway (~ 4 Gy rather than initially estimated 7 Gy)
- 13 Chernobyl accident victims
  - Only 2 survived
  - 1 showed autologous bone marrow repopulation (i.e., recovery of own marrow)

Only one possible successful transplant that saved a life, and even that has been questioned

Value of Cytokine Therapy

- Cytokines are a group of regulators that control the production of hematopoietic cells in the bone marrow.
  - For example, Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a hematopoietic-specific growth factor that plays a critical role in myeloid lineage specification.
- Filgrastim (trade name Neupogen®) is a human G-CSF produced by recombinant DNA technology that stimulates the growth of white blood cells

How about using cytokine to treat hematopoietic syndrome?

Cytokine Therapy – Case Report, Belgium

- On March 11, 2006, an alarm went off in the facility in Fleurus, Belgium, and an operator entered the irradiation room to close the open cell door.
- He turned off the alarm, and then decided to close the access door to the irradiator.
- Following safety protocol, the cell had to be checked for the absence of personnel before closing the door, so the operator had to enter the cell to validate the reset contact switch.
- The cell included a bunker, in which the irradiation material was placed in baskets located on both sides of the source, and a 6-m deep pool underneath the concrete slab
- The source moves back and forth from bunker to pool through a concrete slab.
- At that time, the Co-60 sources were partly out of the security position, most likely in an intermediate position between the high position used for irradiation phases and the low storage position.
- As a result, the whole body of the operator was exposed to the radiation for approximately 22 seconds.

http://large.stanford.edu/courses/2017/ph241/lowet1/

Cytokine Therapy – Case Report, Belgium

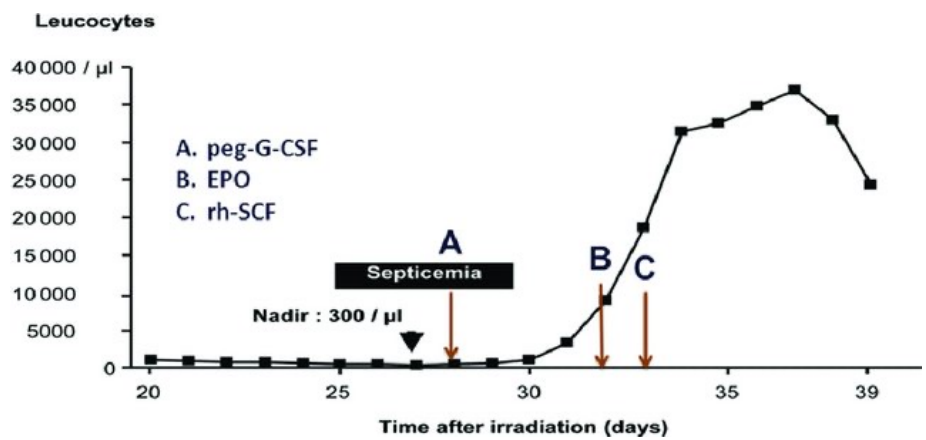
- A few hours later, he experienced nausea and vomiting but did not think it was related to the irradiation.
- Eighteen days after the incident, the victim consulted a physician because of persistent nausea, as well as intermittent diarrhea, headache and hair loss.
- It was determined the patient suffered exclusively from a hematological syndrome.
- The patient experienced a 26% drop in hemoglobin levels and had “blood poisoning” eight days after hospitalization.

Cytokine Therapy – Case Report, Belgium

- Severe hematopoietic syndrome was diagnosed, and treatment with **Neulasta** was initiated as soon as possible after the diagnosis - 28 days after exposure.
- The patient was also treated with **Erythropoietin** and given platelet transfusions.
- This cytokine treatment had an incredibly positive effect and the blood cell counts of the patient recovered quickly.
- Forty-three days after exposure, the hematopoietic syndrome was completely resolved.

Cytokine Therapy – Case Report, Belgium

- Physical dosimetry was reconstructed on site of the Sterigenics facility following the incident and the numerical simulations indicated a dose gradient between the pelvis and the skull.
- It was estimated that the patient had received a mean dose of 4.2 - 4.8 Gy.



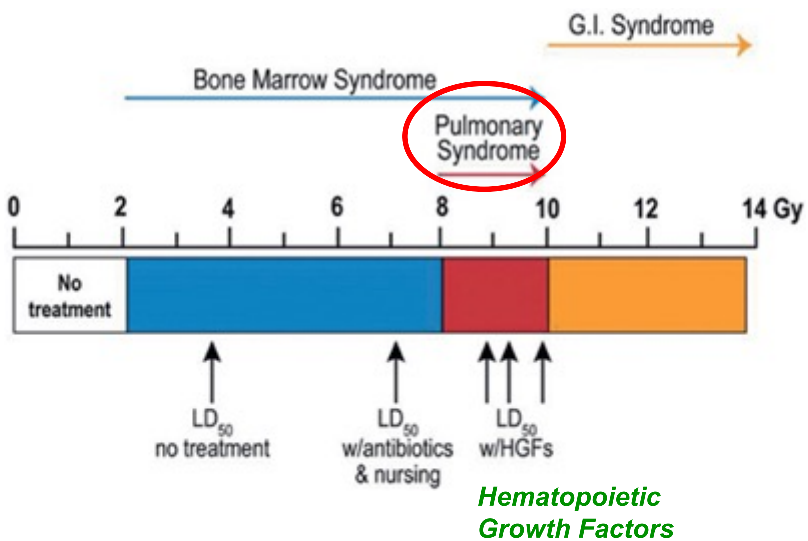
Outline

- Total Body Irradiation in the Therapeutic Setting
- Acute Radiation Syndrome
  - Early Lethal Effects
  - Prodromal Syndrome
  - Modes of Death
  - Value of Bone Marrow Transplant
- **Pulmonary Syndrome**

  Delayed radiation syndrome if individual survived
- Cutaneous Radiation Injury
- Triage and Treatment of Radiation Accident Victims
- Biological Terrorism and Dirty Bombs

Pulmonary Syndrome

- Survival with supportive care leaving open the possibility for **delayed effects** of acute radiation exposure
- Acute but delayed onset of **pneumonitis** is a major cause of death after hematopoietic syndrome



A few individuals exposed to 8 Gy or more died much later at 130 days with inflammatory pneumonitis

Pulmonary Syndrome

- Pulmonary syndrome only assumes importance now that more sophisticated countermeasures have been developed to nuclear events
- Key Premise – nuclear radiation exposure is acute, heterogeneous and non-uniform
- 90% of radiation accident victims receive highest dose to the thoracic region
- Radionuclide inhalation is another consideration

Tokaimura Criticality Accident, 1999

- Worker A was irradiated critically when a nuclear reaction was set off, while holding a funnel to pore a uranium solution into a tank
- He developed aggravating pulmonary edema and hypoxemia which required intubation and ventilator-assisted respiratory management, possibly because of uneven, but significantly high-dose, irradiation in the ventral side of the upper trunk with mixed neutron and γ-ray
- It was unclear whether the cause of hypoxemia had been radiation pneumonitis or congestive heart failure.
- The patient died before developing pulmonary fibrosis.

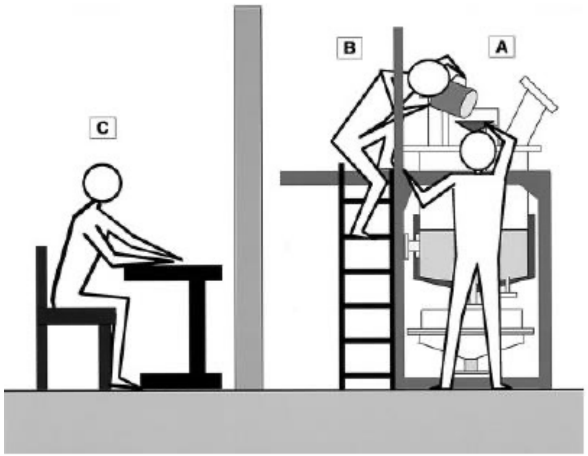


Figure 1. The positions and postures of the victims of the accident at the moment when criticality was triggered, reconstructed by interviewing Workers B and C.

An example of radiation pneumonitis

Outline

- Total Body Irradiation in the Therapeutic Setting
- Acute Radiation Syndrome
  - Early Lethal Effects
  - Prodromal Syndrome
  - Modes of Death
  - Value of Bone Marrow Transplant & Cytokine
- Pulmonary Syndrome
- **Cutaneous Radiation Injury** — Generally nonlethal, but can be debilitating
- Triage and Treatment of Radiation Accident Victims
- Biological Terrorism and Dirty Bombs

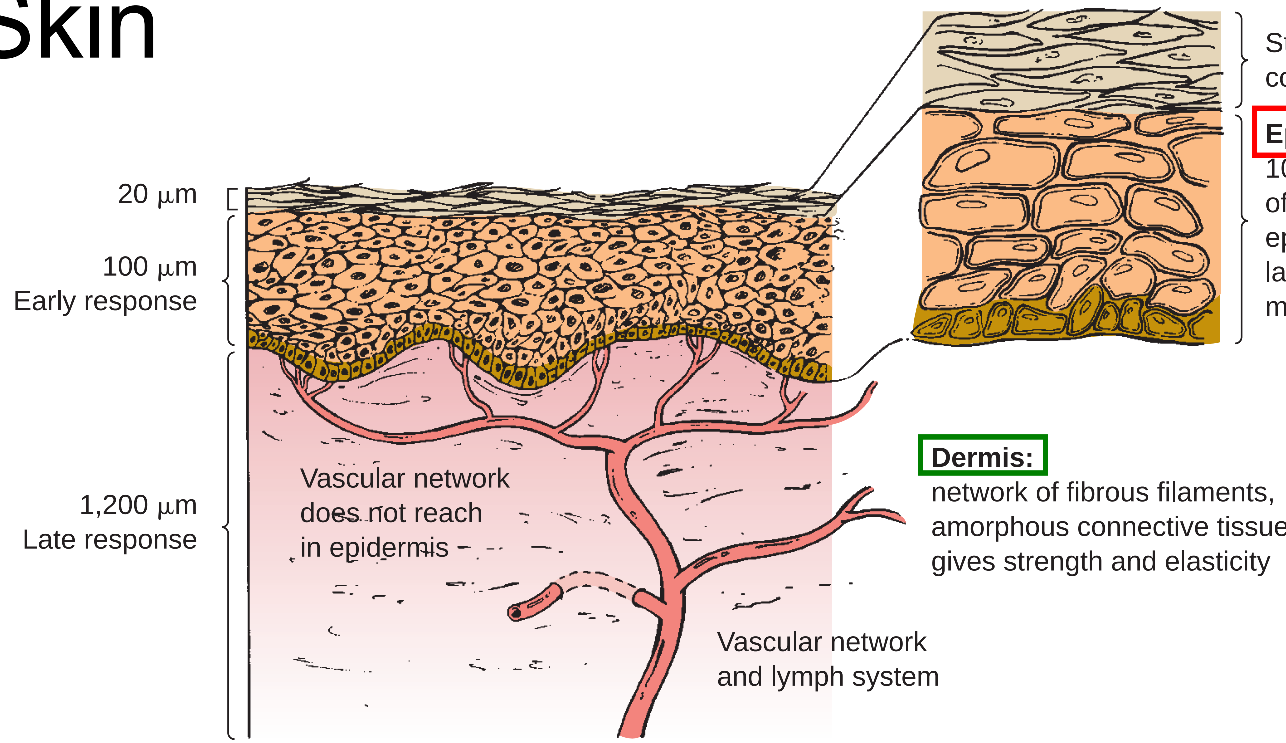
(Acute Radiation Syndrome items: Lethal or potentially lethal)

Cutaneous Radiation Injury

- **Cutaneous radiation syndrome** (CRS) refers to the skin symptoms of radiation exposure
- Radiation injury to the skin may occur along with hematopoetic and GI syndromes, or by itself (e.g., exposure to nonpenetrating β-particles and low energy photons)

- Symptoms and durations depend on the **dose**

Skin



Within the epidermis, the target cells for radiation damage are the dividing stem cells in the basal layer

Skin is composed of the outer layer, the **epidermis**, which is the site of early radiation reactions, and the deeper layer, the **dermis**, which is the site of late radiation reactions

Cutaneous Radiation Injury

- The threshold local dose is 3 Sv for epilation (hair loss), and 6 Sv for erythema (redness)
- Higher doses (> 10 Sv) leads to dry desquamation, moist desquamation (peeling), bullae (blister) formation, ulceration, and necrosis

Cutaneous Radiation Injury

Radiation damage differ from thermal and chemical burns and characterized by

- Delay between exposure and effect
- Tendency to undergo recurrent breakdown, even after a scar has formed

Notably, as seen at Chernobyl, when skin is irradiated with high energy **beta particles**, moist desquamation and similar early effects can heal, only to be followed by the collapse of the dermal vascular system after two months, resulting in the loss of the full thickness of the exposed skin. This effect had been demonstrated previously with pig skin using high energy beta sources.

Cutaneous Radiation Injury

The patient's skin is burned in a pattern corresponding to the dark portions of a kimono worn at the time of the explosion. Japan, circa 1945.

Harry Daghlian’s right hand received 200 Gy and left hand 30 Gy.

Wikipedia

Cutaneous Radiation Injury

- Significant radiation burns lower the LD_{50}
  - Increased risk of bleeding, infection and poor wound healing
- Management
  - Wound cleaning
  - Pain management
  - Topical anti-inflammatories
  - Antibiotics
  - Skin grafts
  - amputation

Effects of Fluoroscopic Exposures on the Skin

Epilation following an embolization procedure. Affected area is circular area of hair loss in shaved area of head (head shaved for gamma knife procedure)

Injuries to back and arm from multiple prolonged electrophysiological and ablation procedures with bi-plane fluoroscopy. Wounds on back healed into scarred areas while injury on arm required grafting.

Effects of Fluoroscopic Exposures on the Skin

Injury following three procedures involving transjugular intrahepatic portosystemic shunt placement, demonstrating disfigurement after surgical correction.

"My husband was diagnosed with a biopsy in May 2006 with a radiation burn from several heart catheterizations. We have been seeing a wound specialist since June. Along with the wound, he has been suffering with severe burning and stabbing pain and trouble breathing. We have been to pulmonary specialists, thoracic surgeons, cardiologists and pain specialists all say they have no experience with a radiation burn. We are desperate for help in this matter..."

It can affect QOL significantly

Outline

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- Pulmonary Syndrome
- Cutaneous Radiation Injury
- **Triage and Treatment of Radiation Accident Victims**
- Biological Terrorism and Dirty Bombs

Triage

- Following an event, an immediate need is to know the doses exposed
- For radiation workers, radiation badge gives accurate dosimetry
- For general public, doses will have to be estimated to allow triage

Diagnosis of ARS – Lab Test (Easiest)

Circulating lymphocytes drops after an exposure as low as 0.5 Gy as early as prodromal phase

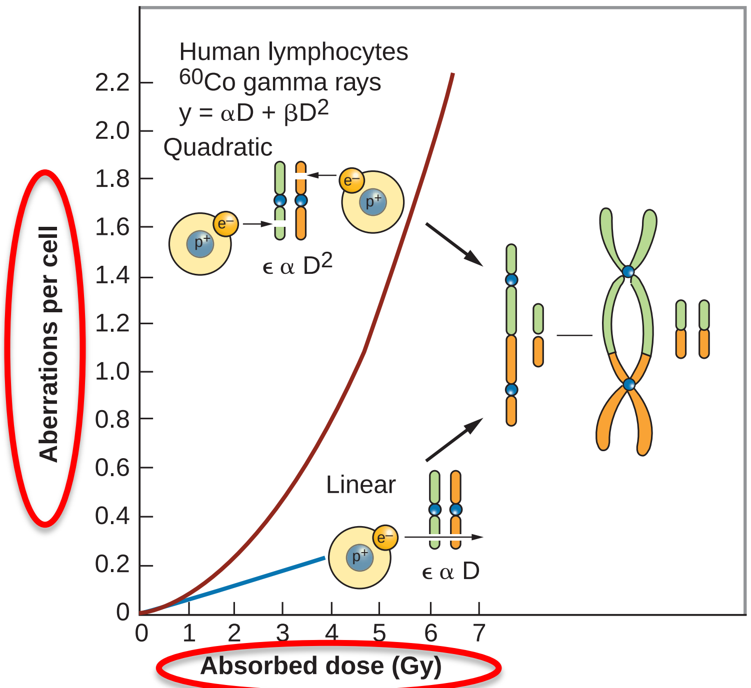
Apoptotic death

↓

Measuring drop in absolute lymphocyte count is the best and most useful laboratory test to determine the level of radiation exposure

Diagnosis of ARS – Cytogenetics (If Available)

For biological dosimetry, ***dicentrics*** historically has been the aberration of choice



Limitations

- Can only detect doses > **0.2 Gy**
- Lymphocytes disappear quickly at high doses

Scoring Lymphocyte Aberrations

Lymphocytes in the blood sample may be stimulated to divide *in vitro* by adding phytohemagglutinin (PHA)

⇩

Stopped at their 1st metaphase by addition of Colcemid after about 45 hrs of culture

⇩

Slides containing metaphase spreads stained with Giesma or FISH probes and scored

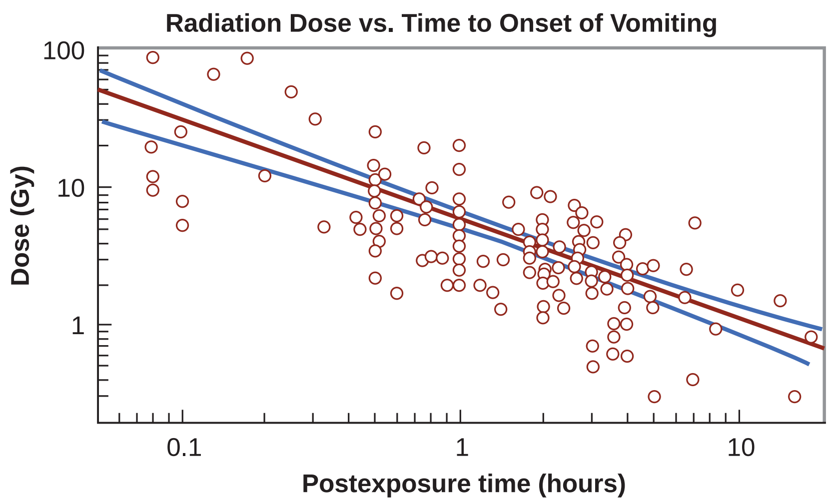
In suspected exposure case, typically 500 cells are scored

Can detect a recent total-body exposure of as low as **0.2 - 0.25 Gy**

Useful in distinguishing “real” vs. “suspected” exposures

Triage – Time to Emesis

The average time to emesis ↓ with ↑ dose (Prodromal Symptoms)

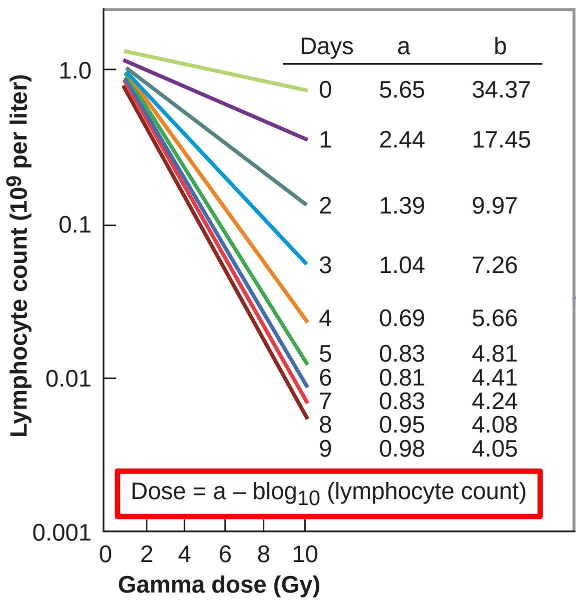


Rule of Thumb

- < 1 Gy – few will vomit
- > 2 Gy – most will vomit
- Onset < 2 hrs → dose > 3 Gy
- No vomiting by 4 hrs → severe effects unlikely

Triage – Drop in Lymphocyte Count

The rate of decline and the degree of depleted lymphocytes are directly related to the absorbed dose



Days	a	b
0	5.65	34.37
1	2.44	17.45
2	1.39	9.97
3	1.04	7.26
4	0.69	5.66
5	0.83	4.81
6	0.81	4.41
7	0.83	4.24
8	0.95	4.08
9	0.98	4.05

The higher the dose, the quicker the drop

An algorithm has been developed to estimate the approximate dose based on the depletion rate from serial blood counts at various times after exposure

IAEA and WHO Report

- The **International Atomic Energy Agency** and the **World Health Organization** jointly sponsored a report entitled ***Diagnosis and Treatment of Radiation Injuries***
- Information is based on a limited number of exposed individuals over the years
- The nature of symptoms, their severity, and the time of onset can be a useful predictor of eventual outcome in the absence of physical dosimetry

Prodromal Syndrome of ARS

TABLE 8.3 Latent Phase (Prodromal Syndrome) of Acute Radiation Syndrome

	Degree of Acute Radiation Syndrome and Approximate Dose of Acute Whole Body Exposure (Gy)				
	Mild (1–2 Gy)	Moderate (2–4 Gy)	Severe (4–6 Gy)	Very Severe (6–8 Gy)	Lethal (>8 Gy)
Lymphocytes (G/L) (days 3–6)	0.8–1.5	0.5–0.8	0.3–0.5	0.1–0.3	0.0–0.1
Granulocytes (G/L)	>2.0	1.5–2.0	1.0–1.5	≤0.5	≤0.1
Diarrhea	None	None	Rare	Appears on days 6–9	Appears on days 4–5
Epilation	None	Moderate, beginning on day 15 or later	Moderate or complete on days 11–21	Complete earlier than day 11	Complete earlier than day 10
Latency period (d)	21–35	18–28	8–18	7 or less	None
Medical response	Hospitalization not necessary	Hospitalization recommended	Hospitalization necessary	Hospitalization urgently necessary	Symptomatic treatment only

Adapted from *Diagnosis and Treatment of Radiation Injuries*, International Atomic Energy Agency, Vienna, Austria, 1998.

Critical Phase of ARS

TABLE 8.4 **Critical Phase of Acute Radiation Syndrome**

	Degree of ARS and Approximate Dose of Acute Whole Body Exposure (Gy)				
	Mild (1–2 Gy)	Moderate (2–4 Gy)	Severe (4–6 Gy)	Very Severe (6–8 Gy)	Lethal (>8 Gy)
Onset of symptoms	>30 days	18–28 days	8–18 days	<7 days	<3 days
Lymphocytes (G/L)	0.8–1.5	0.5–0.8	0.3–0.5	0.1–0.3	0–0.1
Platelets (G/L)	60–100 10%–25%	30–60 25%–40%	25–35 40%–80%	15–25 60%–80%	<20 80%–100%[a]
Clinical manifestations	Fatigue, weakness	Fever, infections, bleeding, weakness, epilation	High fever, infections, bleeding, epilation	High fever, diarrhea, vomiting, dizziness and disorientation, hypotension	High fever, diarrhea, unconsciousness
Lethality (%)	0	0–50 Onset 6–8 weeks	20–70 Onset 4–8 weeks	50–100 Onset 1–2 weeks	100 1–2 weeks
Medical response	Prophylactic	Special prophylactic treatment from days 14–20; isolation from days 10–20	Special prophylactic treatment from days 7–10; isolation from the beginning	Special treatment from day 1; isolation from the beginning	Symptomatic only

[a]In very severe cases, with a dose >50 Gy, death precedes cytopenia.

Adapted from *Diagnosis and Treatment of Radiation Injuries*, International Atomic Energy Agency, Vienna, Austria, 1998.

Radiation Emergency Assistance Center

- The Medical Sciences Division of the Oak Ridge Institute for Science and Education operates a Radiation Emergency Assistance Center/Training Site (**REAC/TS**)
- REAC/TS provides 24-hour direct or consultative assistance in cases of radiation accidents
- Areas of expertise include cytogenetics for dose assessment, calculation of doses from internally deposited radionuclides, and laboratory facilities that include total-body counting capabilities
- Website – http://www.orau.gov/reacts

Survivors of Serious Radiation Accidents in the United States

- Heavily irradiated survivors of accidents in the nuclear industry have been followed for many years
- Their medical history mirrors that of any aging population
- An expected higher incidence of shortened lifespan, early malignancies after a short latency, and rapidly progressing cataracts has NOT been observed
- This is not to say that heavily irradiated individuals are not at increased risk, but highlights the problem of detecting an excess cancer incidence in any small irradiated population

Y-12

Eight workers were hospitalized for moderate to severe radiation sickness or exposure, but all eventually returned to work. In June 1960 the eight workers, Bill Wilburn, O.C. Collins, Travis Rogers, R.D. Jones, Howard Wagner, T.W. Stinnett, Paul McCurry, and Bill Clark filed suit against the Atomic Energy Commission. The suit was settled out-of-court. Wilburn, who had received the highest radiation dose, was awarded $18,000. Clark received $9,000.

Under the Energy Employees Occupational Illness Compensation Program, the eight later received additional compensation from the government. Most, if not all, of the eight victims were diagnosed with cancer at some point during their lives. As of June 2014, Clark was the only surviving member of the eight.

Outline

- Total Body Irradiation in the Therapeutic Setting
- Acute Radiation Syndrome
  - Early Lethal Effects
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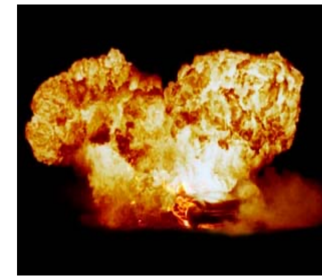
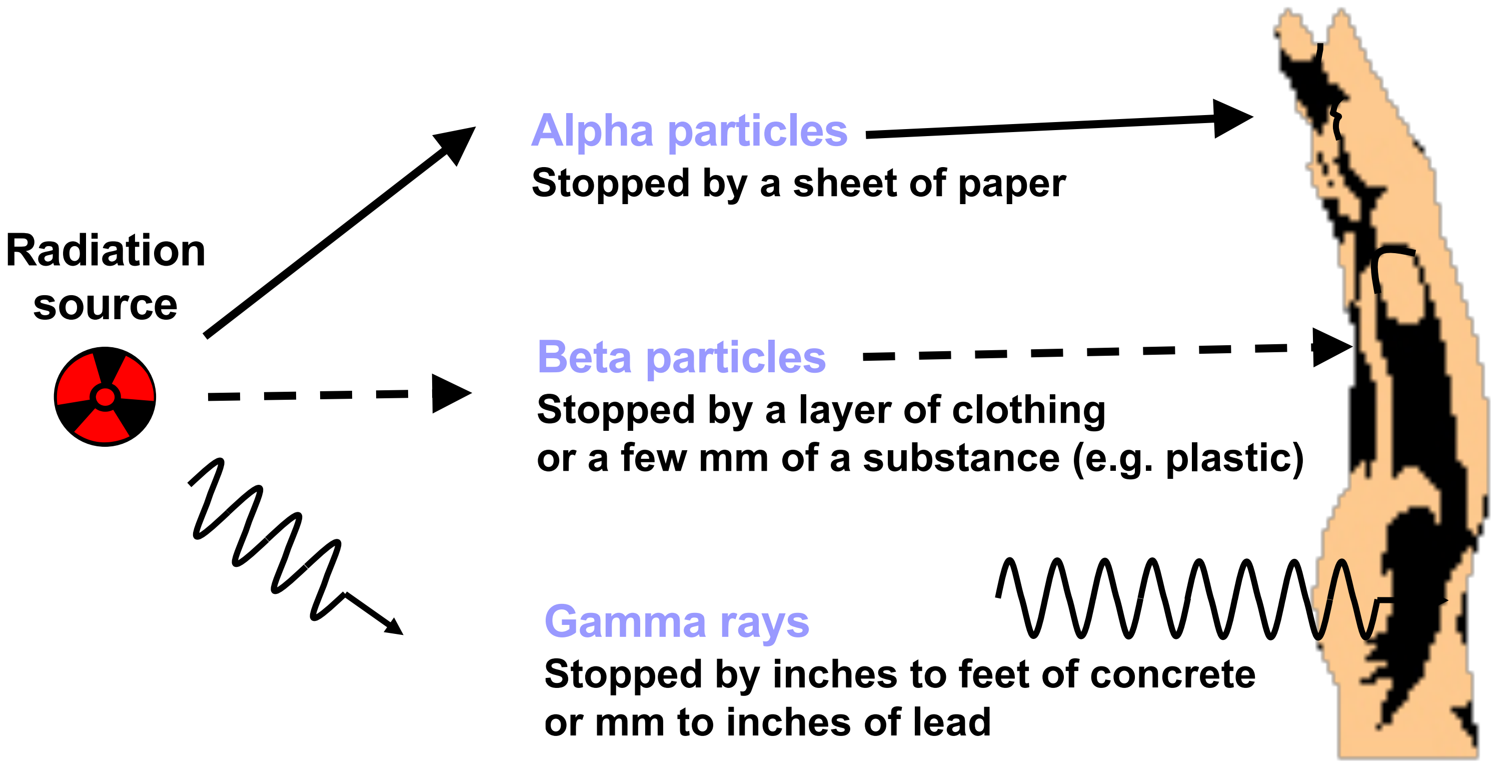
  - Modes of Death
  - Value of Bone Marrow Transplant & Cytokine
- Pulmonary Syndrome
- Cutaneous Radiation Injury
- Triage and Treatment of Radiation Accident Victims
- **Biological Terrorism and Dirty Bombs (Chapter 14)**

Scope of Radiological Terrorism



- Extremely unlikely
  - Detonation of a nuclear device
  - Attack on a nuclear power station
- Highly likely
  - "Dirty bomb" – a relatively small quantity of a radioactive material dispersed by being attached to a conventional explosive

Types of Ionizing Radiation



Examples of Radioactive Materials

Substance	Half-Life	Activity	Use
Cesium-137	30 yrs	1.5×10^6 Ci	Food irradiator
Cobalt-60	5 yrs	15000 Ci	Cancer therapy
Iridium-192	74 days	100 Ci	Industrial radiography
Hydrogen-3	12 yrs	12 Ci	Exit signs
Iodine-131	8 days	0.015 Ci	Nuclear Medicine therapy
Technetium-99m	6 hrs	0.025 Ci	Diagnostic imaging
Americium-241	432 yrs	0.000005 Ci	Smoke detectors
Radon-222	4 days	1 pCi/l	Environmental levels

In 2004, an Islamic cell was raided in London and found to have accumulated 10,000 household smoke detectors, each containing a tiny quantity of americium-241.

Sources of Radioactive Materials

Americium Smoke Detectors

Moisture Density Gauge

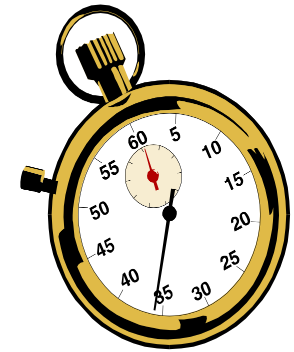
Used in the laying of tarmacadam road surfaces
Contain small quantities of both Am-241 and Cs-137

Dirty Bomb

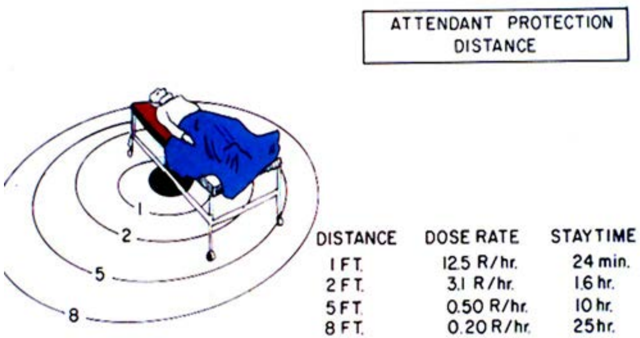
- In the event of a dirty bomb, victims can receive radiation in 3 way
  - External exposure from γ-emitting radionuclides such as Cs-137
  - External contamination of a γ-emitter
  - Ingestion of a γ-emitter (i.e., internal contamination)

Emergency Department Management of Radiation Casualties

Reducing Radiation Exposure



- **Time**
  - **Reduce time spent near radiation sources**



- **Distance**
  - **Maintain maximal practical distance from radiation source**

- **Shielding**
  - **Place radioactive sources in lead container**

“Exposed” vs. “Contaminated”

- A person who is contaminated has radioactive material on their skin or inside their body
- Individuals who are exposed but not contaminated pose no risk to the ER staff and that normal ER procedures can be used with them
- Reassurance for ER staff

Protecting Staff from Contamination

- Universal precautions
- Survey hands and clothing with radiation meter
- Replace contaminated gloves and clothing
- Keep the work area free of contamination

Key Point

It is not very likely that ED staff will receive large radiation doses from treating contaminated patients

Patient Management Priorities

Table 14.2 Patient Management Priorities

- Standard medical triage
- Attend first to critical injuries
- Decontaminate
- Remove clothing
- Survey with Geiger counter
- Open wounds
- Mouth and nose
- Intact skin
- Cease decontamination when further efforts do not reduce count and when count is less than twice background.

Treatment and Decontamination Rules

- Patient with life-threatening condition – treat, then decontaminate
- Patient with non-life-threatening condition – decontaminate, then treat
- Decontaminate wounds first, then intact skin
- Uninjured contaminated persons should NOT be directed to medical facilities, should be decontaminated on site

Treatment and Decontamination Rules

Treatment of significant medical conditions should always take precedence over radiological assessment or decontamination of patient!!!

Review Questions

Question 1

The death of a person 30-60 days following a total body radiation dose close to the LD_{50} would likely be due to damage to the:

A. heart
B. bone marrow
C. central nervous system
D. brain
E. gastrointestinal system

Timeline for Acute Radiation Syndromes

DAYS

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28

CNS@1-2 days

Hematopoietic @ 18-28 days

GI @5-10 days

DOSE

Hematopoietic 2.5-5Gy

GI – 5-12 Gy

CNS > 100 Gy (20 Gy)

Question 2

Which of the following effects from a whole-body acute exposure of radiation where survival is unlikely (supralethal dose) is most accurate?

A. Easy fatigability, anorexia, and headache lasting more than 6 days

B. Significant reduction in red blood cell count within 6 days of exposure

C. Immediate hair loss, headache, and disorientation

D. Fever, hypotension, and immediate diarrhea

The Prodromal Syndrome

TABLE 8.1. *Symptoms of the Prodromal Syndrome*

Neuromuscular	Gastrointestinal	
Signs and Symptoms to be Expected at About 50% Lethal Dose		
Easy fatigability	Anorexia Vomiting/nausea	Survival possible
Additional Signs to be Expected after Supralethal Doses		
Fever Hypotension	Immediate diarrhea	Survival unlikely

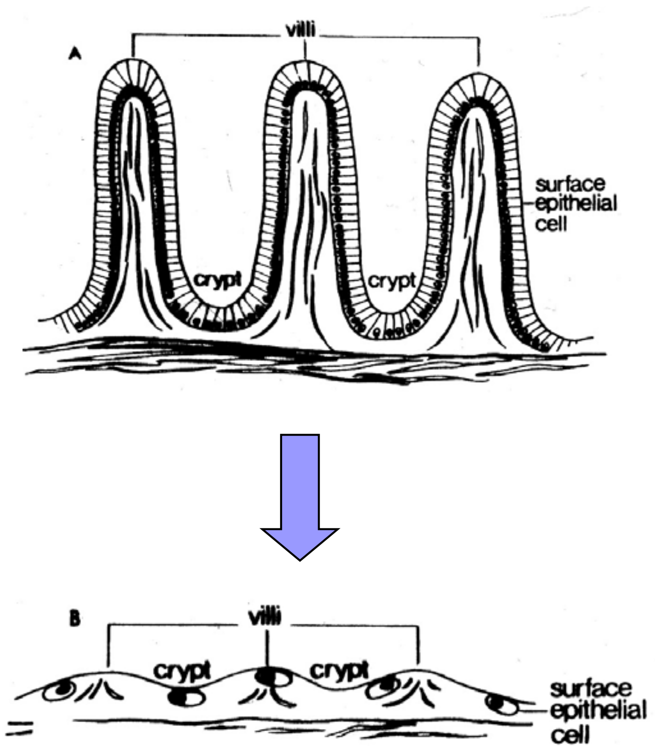
Can be used as a biological dosimeter to triage

Question 3

The G. I. syndrome is observed sooner than the hematopoietic syndrome because

A. there are fewer gut cells, so symptoms are seen earlier.
B. the life span of the mature GI cells is shorter than for most of the bone marrow cells.
C. the prodromal syndrome makes cells sensitive to the GI syndrome.
D. the reason is unknown

The GI Syndrome

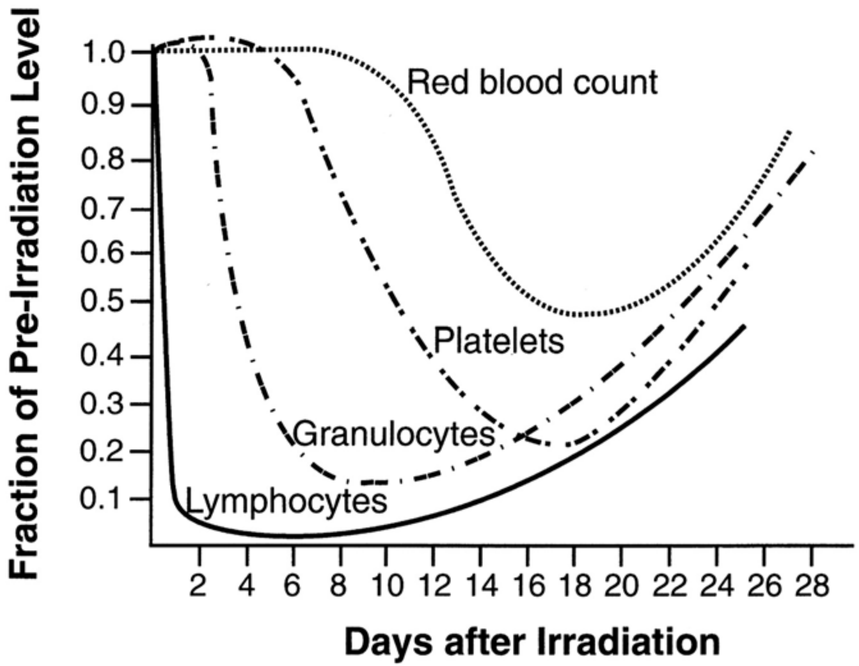


Completely denuded villi

The delay between the time of irradiation and the onset of the symptoms (i.e., **latency period**) is **dictated by the normal life span of the mature functioning cells**

In small rodents, complete denudation takes 3-4 days; in human, it may take **10 days** after the radiation

The Hematopoietic Syndrome



The time at which nadir occurs is a combination of the radiosensitivity of the stem cells and the lifetime of the mature functioning cells

Pattern of depletion and recovery of circulating blood elements

Question 4

Within 4 days of an accidental whole body radiation exposure at a nuclear power plant, 8 workers develop severe diarrhea. Assuming that 3 of the workers are female and 5 male, what is their likely prognosis?

A. All will live, but will likely develop radiation-induced cancers.
B. Approximately 50% will survive.
C. All will live, but with an increased risk of cataracts
D. They will all die in less than a month following the irradiation.
E. They men will be sterilized, but the women will remain fertile

The GI Syndrome

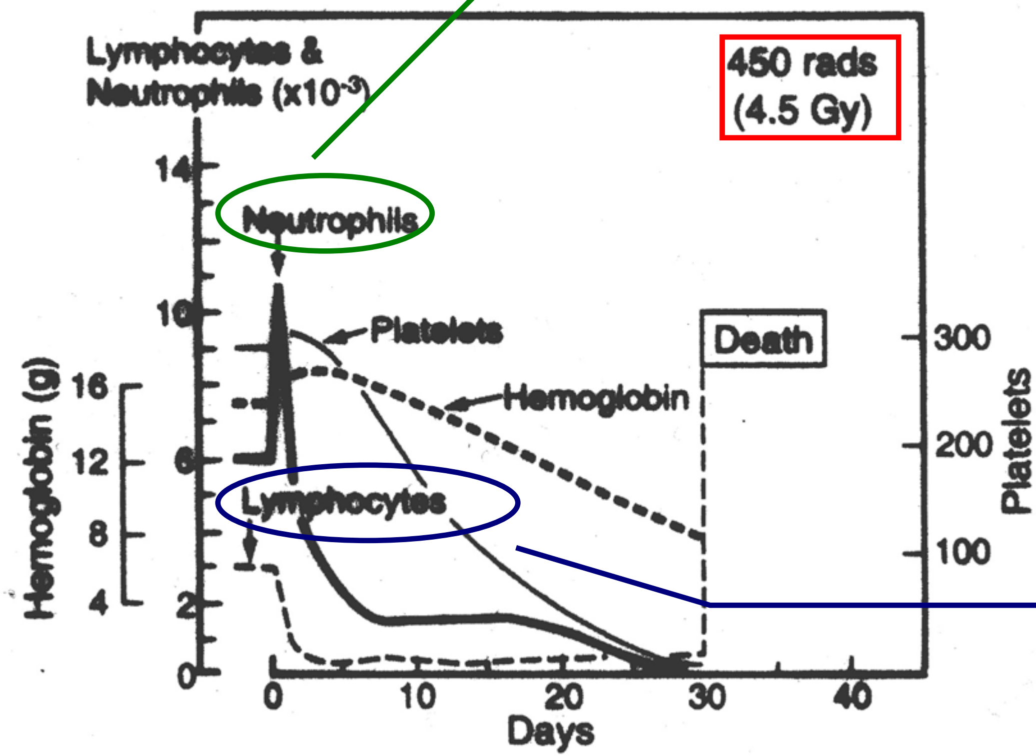
- Occurs at doses more than **10 Gy**
- Prodromal symptoms start a few hours after exposure, but depending upon the dose, there is often a **"latent period"** before symptoms return
- **Major symptoms** include *nausea*, *vomiting*, *prolonged diarrhea*, *loss of appetite*, *lethargy*, *dehydration*, *emaciation*, *exhaustion*
- Death follows in about **5-10 days**

Question 5

Immunosuppression observed within 24 hours following exposure to whole body dose of 5 Gy X-rays would be due primarily to:

A. Death of hematopoietic progenitor cells
B. Apoptosis of peripheral blood lymphocytes
C. A loss of circulating granulocytes
D. Decreased activity of NK cells
E. Inactivation of circulating antibodies

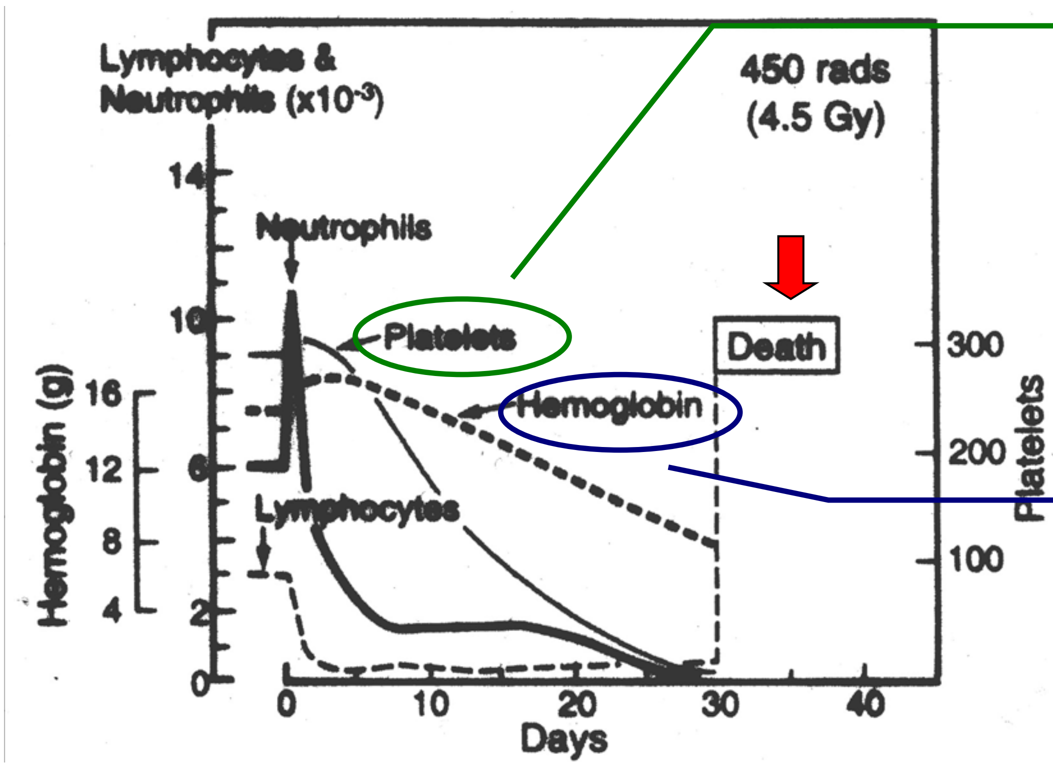
The Hematopoietic Syndrome



There is a temporary increase in the number of granulocytes because of the mobilization of the reserve pool, followed by a rapid fall by the end of the 1st wk, reaching minimum at 18-20 days

Lymphocytes are among the most sensitive cells in the body; lymphopenia occurs rapidly and at dose as low as 0.3 Gy

The Hematopoietic Syndrome



Bleeding and anemia are usually caused by hemorrhage resulting from platelet depression

RBC live for ~ 120 days; anemia from red blood cell depression usually does not occur

Question 6

Which of the following would probably NOT be noted in an individual who received an acute, whole body dose of 5 Gy of X-rays and received no medical care?

A. Infection
B. Nausea
C. Bleeding
D. Death within 1 week following irradiation
E. Epilation

Timeline for Acute Radiation Syndromes

DAYS

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28

CNS@1-2 days

Hematopoietic @ 18-28 days

GI @5-10 days

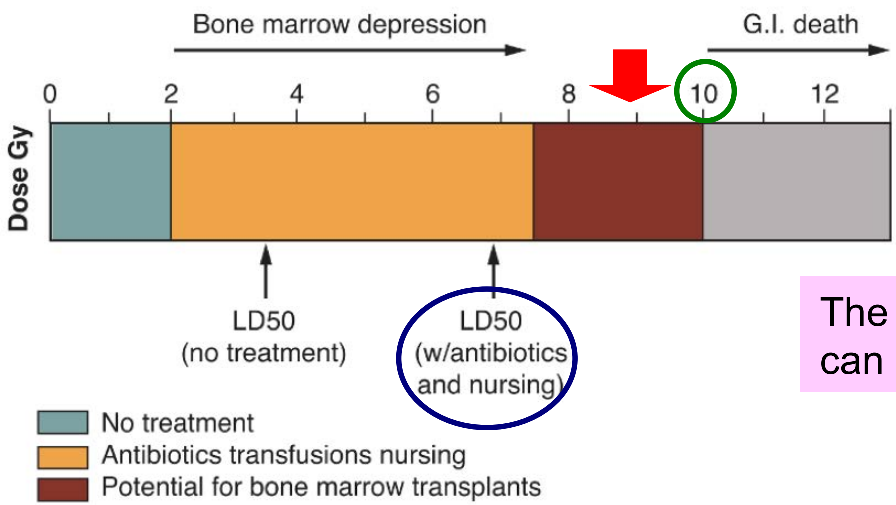
DOSE

Hematopoietic 2.5-5 Gy

GI – 5-12 Gy

CNS > 100 Gy (20 Gy)

Value of Bone Marrow Transplant



There is no instance on record of a human having survived a dose in excess of 10 Gy

The window of dose within which a transplant can be effective is narrow, ie, **8-10 Gy**

In primates, the LD_{50} can be raised by a factor of 2 by appropriate treatment, including careful nursing and antibiotics, and the same may be assumed for humans

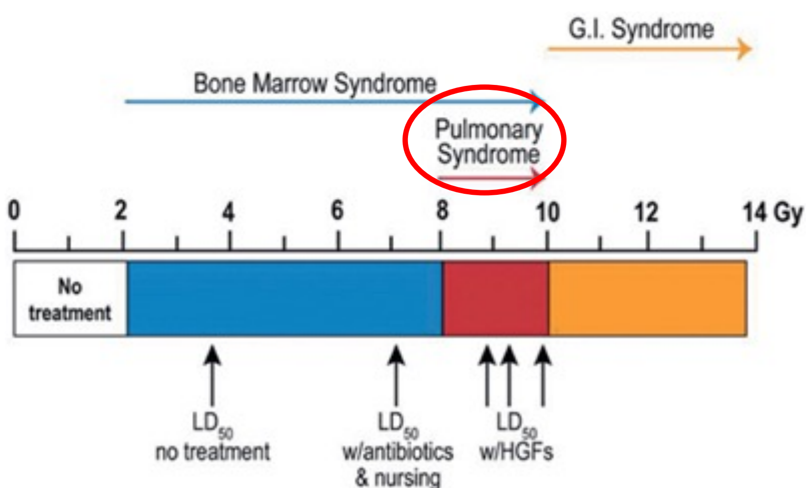
Question 7

With recent advances in supportive measures to manage acute radiation exposure, what syndrome has been seen following exposure to 8-10 Gy in modern nuclear reactor accidents?

A. Pulmonary
B. Renal
C. Endocrine
D. Musculoskeletal
E. Hepatic

Pulmonary Syndrome

- Survival with supportive care leaving open the possibility for **delayed effects** of acute radiation exposure
- Acute but delayed onset of **pneumonitis** is a major cause of death after hematopoietic syndrome



Hematopoietic Growth Factors

A few individuals exposed to 8 Gy or more died much later at 130 days with inflammatory pneumonitis