MPHY3892 Radiobiology

Lecture 4

Effects of Radiation on Normal Tissues

Effect of Cell Death on Tissue

- Reproductive cell death is random; each cell has a finite probability of being killed by radiation
- For a given dose, a certain proportion of cells will be killed. This proportion is never zero
- A macroscopic lesion is not observed in tissue until a significant proportion of cells are killed above which the effect becomes noticeable $\Rightarrow$ THRESHOLD DOSE
- Threshold dose varies greatly from one tissue to another
- Little variation in threshold dose with mammalian species

Tissue Damage

- Appearance of effect at tissue level depends on mitotic rate
- Timescale:
  - hours for intestinal epithelium and bone marrow
  - days for skin and mucosa
  - months for lung and kidney

In addition to reproductive cell death other phenomena play a role in tissue damage:

- Interdependence of cells
  - cells do not react to radiation as autonomous units
  - are linked to adjacent cells by intercellular junctions
  - cells receive and emit short- and long-range micro-environmental signals (e.g. growth factors and inhibitors of cell division)
  - thus lesions in irradiated cells can elicit effects in neighbouring layers of non-irradiated cells – this is called a "bystander effect"
- Injury to cell membrane

  e.g. acute erythema (redness of skin) is associated with injury to $_2$ cell membrane of blood vessels

Risk of Tissue Damage

Risk: $R = 1 - e^{-H}$

where hazard function $H = \ln 2 \cdot \left(\frac{D}{D_{50}} \right)^{v}$

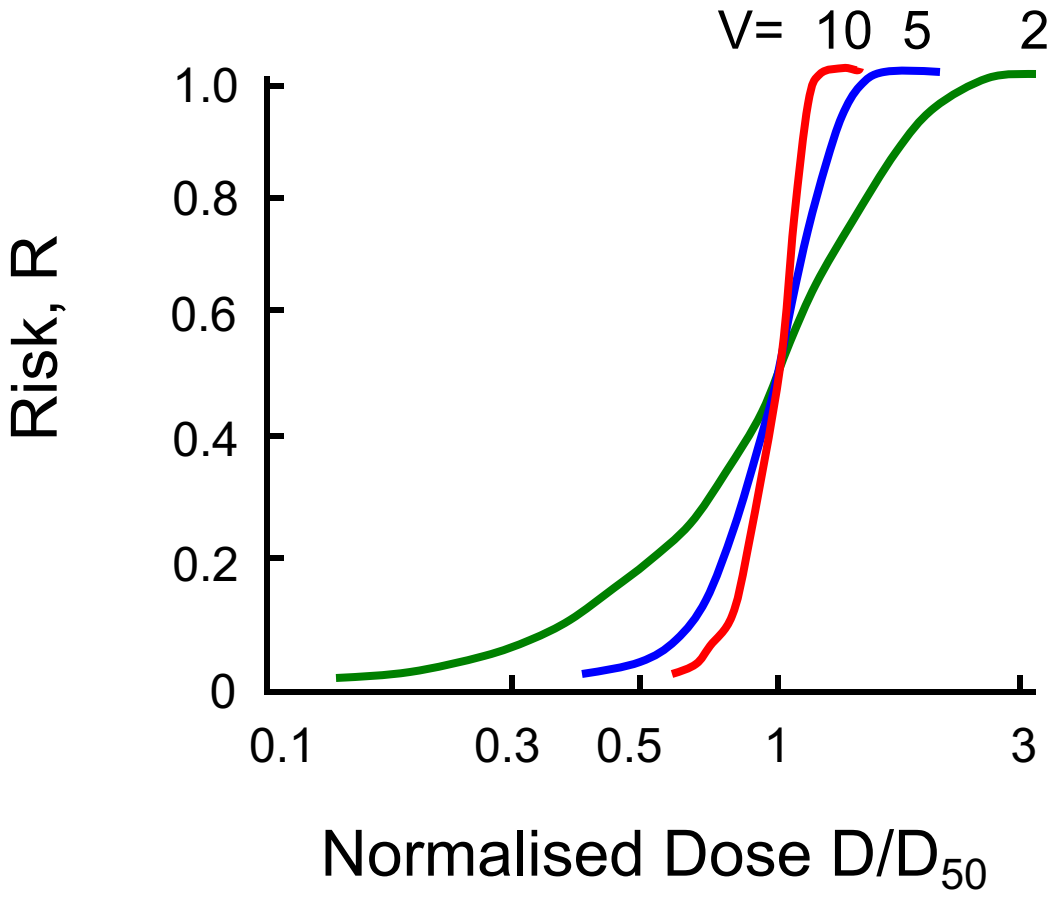
D_{50} = dose at which effect is observed in 50% of population
(e.g. LD_{50} - 50% lethal dose for lethal effects)

D - radiation dose

V - shape factor indicating sharpness of rise in response above threshold dose

Threshold dose T is proposed as the dose that yields a risk of 1%

Deterministic Dose-Response Curves

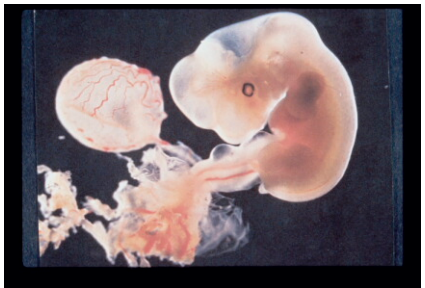


Symptom	Organ	Threshold Dose T (Gy)	Shape Factor V
Mortality			
Bone Marrow Syndrome	bone marrow	1.5	6
GI Syndrome			
internal	small intestine	9.8	10
external	colon	23	10
Embryonic	fetus:		
	1-18 days	0.12	2
	18-150 days	0.37	3
	150-270 days	1.5	6
Morbidity			
Prodromal			
vomiting	abdomen	0.49	3
diarrhoea	abdomen	0.55	2.5
Lung Fibrosis	lung	2.7	5
Skin Burns	skin	6	5
Hypothyroidism	thyroid	2.3	1.3
Thyroiditis	thyroid	140	2
Cataracts	eye lens	1.3	5
Suppression of Ovulation	ovaries	0.85	3
Suppression of Sperm Count	testes	0.46	10

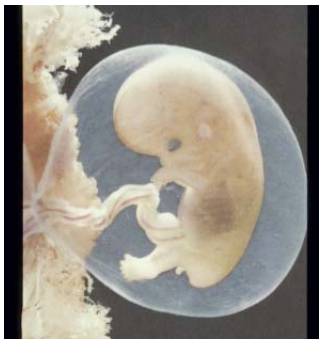
Fetal Radiation Risk

- Radiation risks are most significant during organogenesis and in the early fetal period, somewhat less in the 2nd trimester, and least in the 3rd trimester
- Malformations have a threshold of 100-200 mGy or higher and are typically associated with central nervous system problems
- Termination of pregnancy at fetal doses of less than 100 mGy is **NOT** justified based upon radiation risk

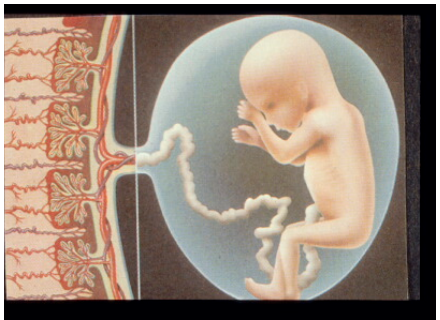
Most risk



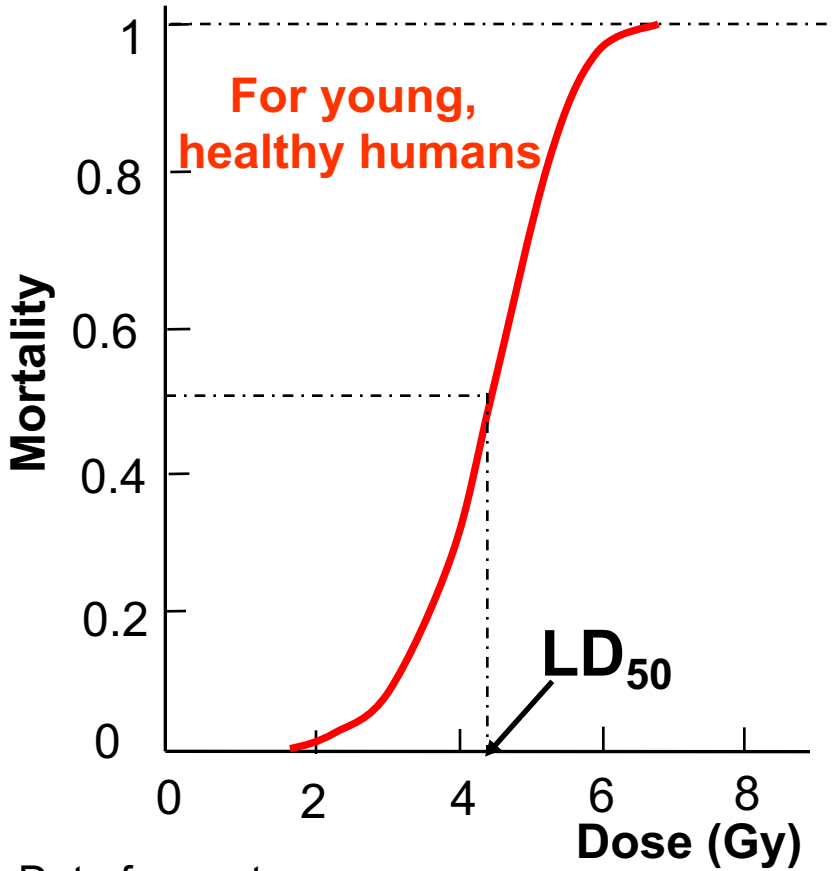
Less



Least



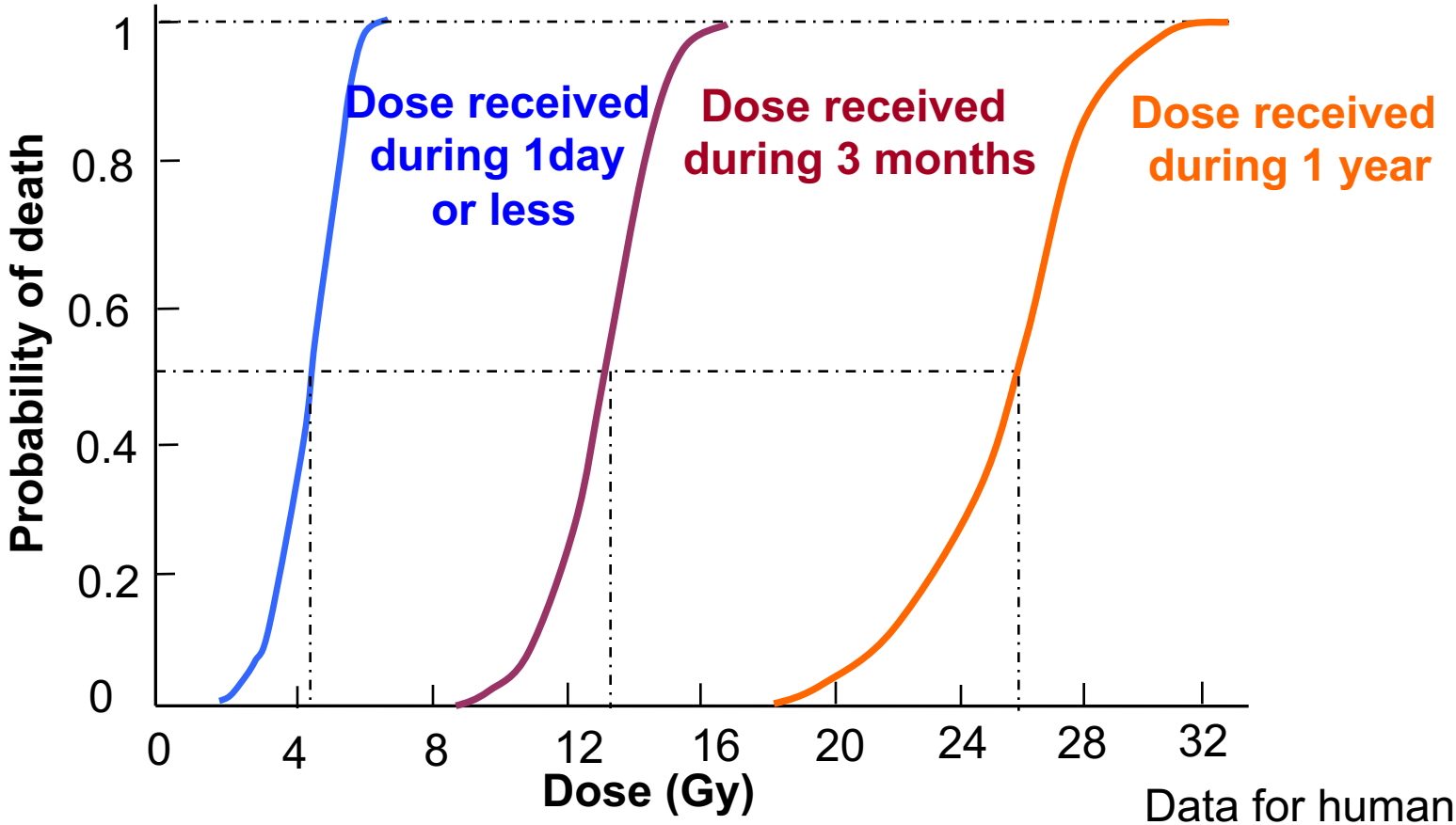
Mortality Following Whole Body Irradiation



Data for acute γ-rays

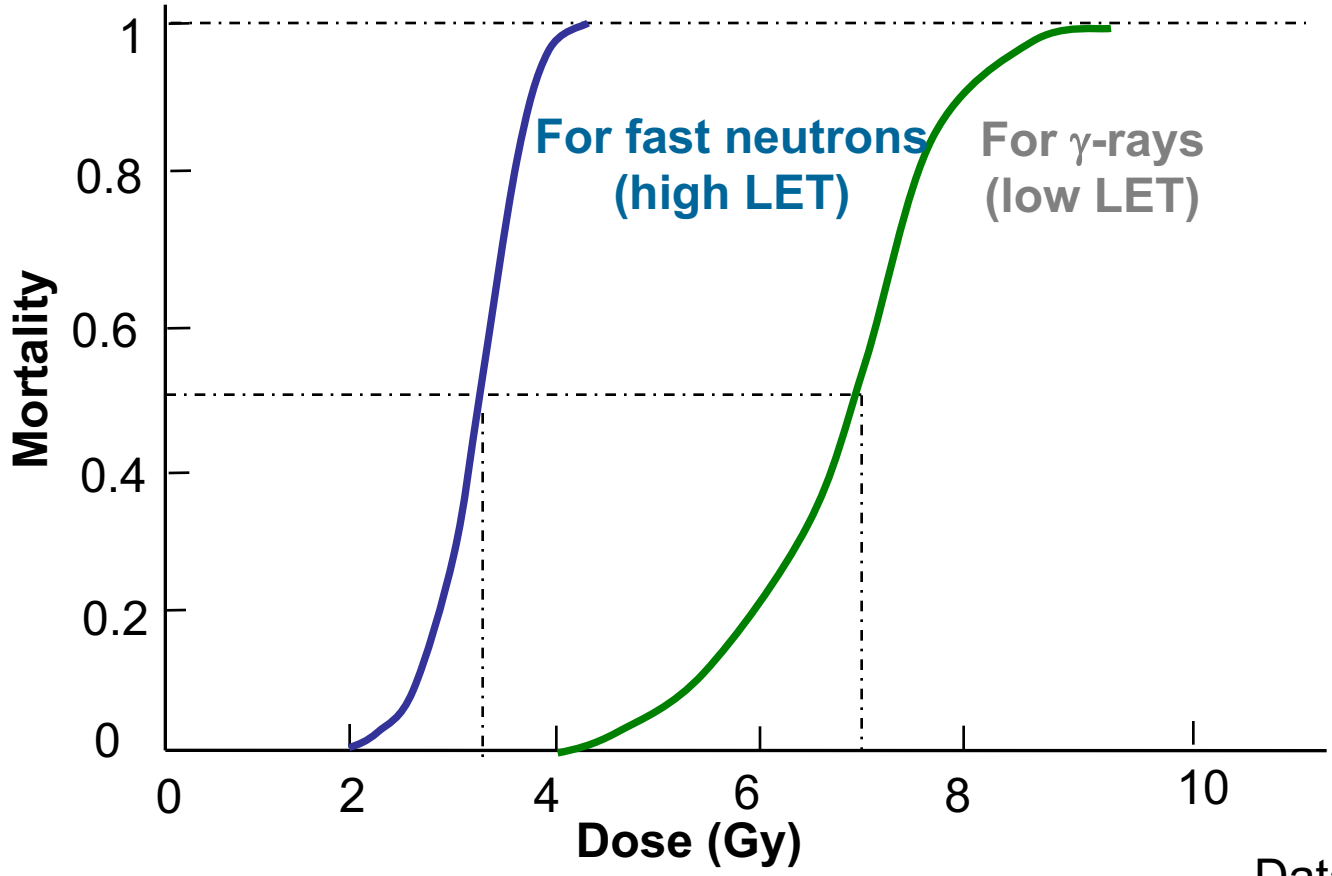
- LD_{50} - 50% Lethal Dose
- LD_{50} = 4.5 Gy for young, healthy humans at 60 days after single total-body exposure to γ-rays, without medical intervention
- 50% Lethal Dose LD_{50} can be almost doubled by supportive treatment, nursing and antibiotics

Effect of Dose over a Period of Time



Data for humans

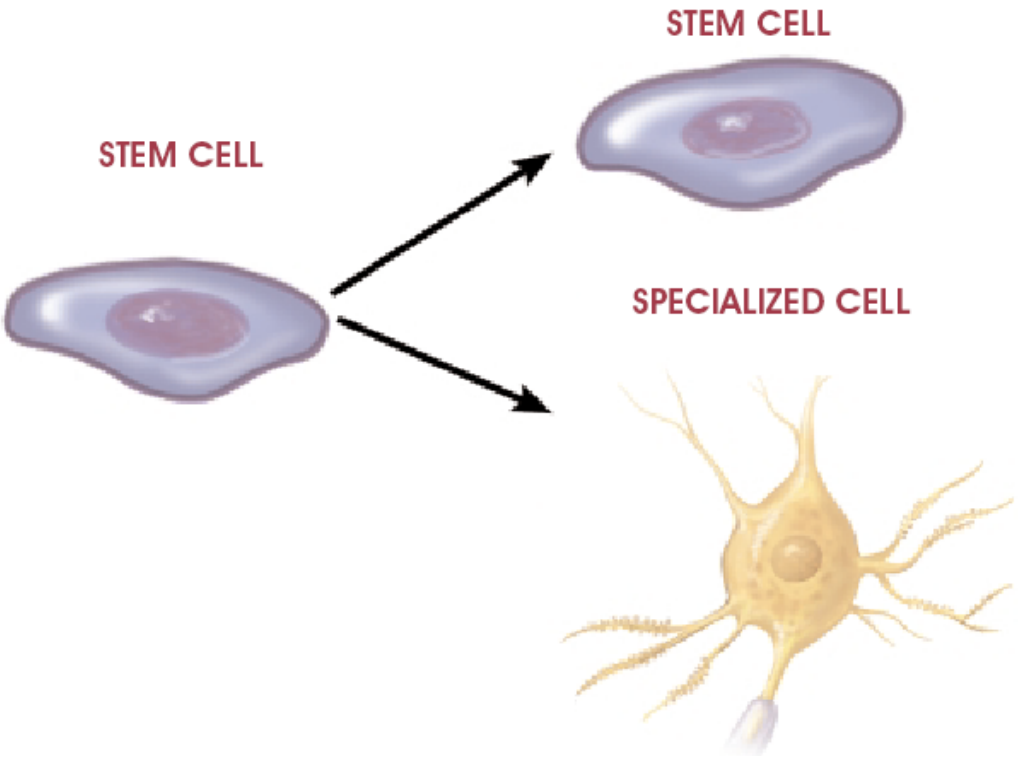
Mortality Following Whole Body Irradiation: Effect of LET



Data for mice

Cell Categories and Tissue Models

- Cell Categories in most of the tissues:
  - Stem cells
  - Differentiated cells
  - Maturating cells
- Two tissue models:
  - Hierarchical model
  - Flexible model



Cell Categories: Stem Cells

- Divide large number of times
- Produce identical stem cells and cells which will differentiate
- Proliferation capacity of stem cells remains constant for a given organism during its life time, but the number of mitoses for each stem cell is limited (to about 60)
- Most stem cells are in G_0 phase (time out of cycle) at any given time but can rapidly enter into cycle after stimulation
- A clonogenic cell is a stem cell capable of generating a colony of at least 100 cells
- Mean lethal dose for stem cells D_o = 1Gy (but could be as low as 0.1Gy for certain stem cells)

Cell Categories: Differentiated Cells

- functional cells
- incapable of division
- all cells of a given type will have a similar lifespan (e.g. 120 days for red blood cells)
- large variation of lifespan between different types of cells
- very radio-resistant
- cells which are differentiated but capable of proliferation when stimulated (e.g. hepatocytes in liver) have lower radiosensitivity (D_o = several Gy) because they seldom divide

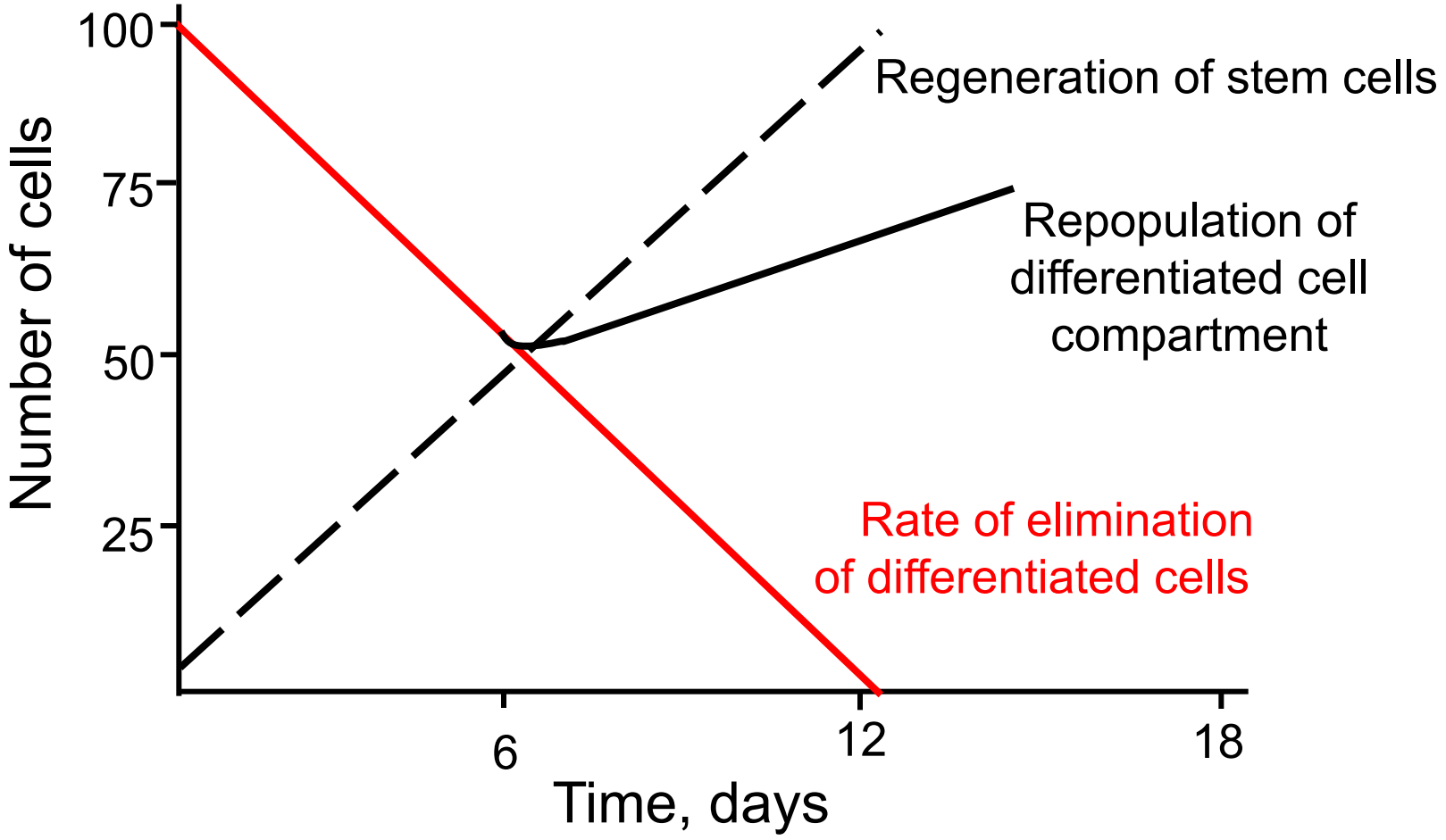
Cell Categories: Maturating Cells

- cells in the process of maturation from stem cells to differentiated cells
- multiplying whilst completing their differentiation
- radiosensitivity of maturating cells is lower than that of stem cells and diminishes as differentiation becomes complete

Hierarchical Tissue Model

- There are 3 cellular compartments in this model : stem cells, maturating cells and differentiated cells
- Damage begins to be expressed after a latent period proportional to lifespan of differentiated cells
- As the dose is increased, the stem cell compartment is progressively depleted
- When almost all the stem cells have been killed by radiation, no more new differentiated cells are formed

Hierarchical Tissue Model



Hierarchical Tissue Model

- Stem cells are killed $\Rightarrow$ the number of cells diminishes steadily at a rate depending on the death of cells by ageing, a rate is the same whenever the dose $\Rightarrow$ the time for damage is independent of dose
- Recovery can depend on dose: at high doses regeneration is accelerated because the stimulus for regeneration is more intense when the cellular depletion is greater
- Surviving maturating cells can contribute initially to increase in production of new cells
- Proliferation of stem cells is required for recovery of the hierarchy

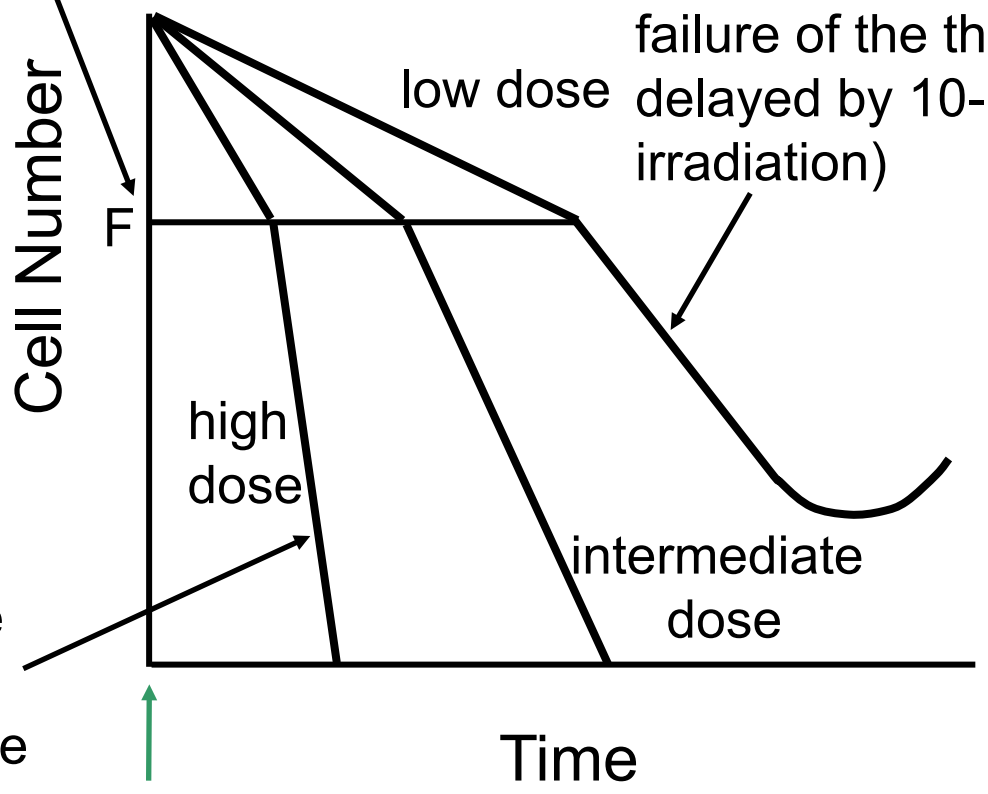
Flexible Tissue Model

- There are no compartments and no cellular hierarchy in this model
- The model assumes that after the damage, all cells, including differentiated cells, enter mitosis
- A dead cell is replaced by the division of another cell
- Thus radiation creates non-viable cells. Increase in mitosis will cause an avalanche of non-viable cell death $\Rightarrow$ rapid expression of damage
- Then the time for damage expression is a function of dose
- Sub-clonogenic cells (having infrequent division) are significant for maintaining cell population for a certain time

Flexible Tissue Model

F - critical level beyond which compensatory proliferation is set in motion and a large number of cells entry into the cell cycle

If the dose is small, damage is expressed much later, as the cells divide infrequently and the lesions remain concealed for a long time (e.g. functional failure of the thyroid may be delayed by 10-15 years after irradiation)



Death of a large number of cells in the avalanche phenomenon

Irradiation at time zero

Tissue in Reality

- Most tissues are more realistically represented by hierarchical/flexible hybrid models
- Most of cell population is sub-clonogenic, with a minority of stem cells
- Two important features of the flexible model remain:
  - accelerating decline of population size with time (avalanche effect)
  - shape of dose-response curve depends on the properties of sub-clonogenic cells
- There is a theoretical possibility of radioprotection by post-irradiation stimulation of stem-cell proliferation

Whole Body Irradiation

Whole-body Dose (Gy)	Main Cause of Death	Timescale of Death
(< 2)	(radiation lifeshortening)	
2 - 10	damage to bone marrow	10 - 30 days
10 - 100	damage to intestinal epithelium	3 - 5 days
> 100	damage to central nervous system	mins - 48 hrs

Death is caused by depletion of the stem cells of a critical self-renewal tissue

Data on Acute Radiation Syndrome in Humans

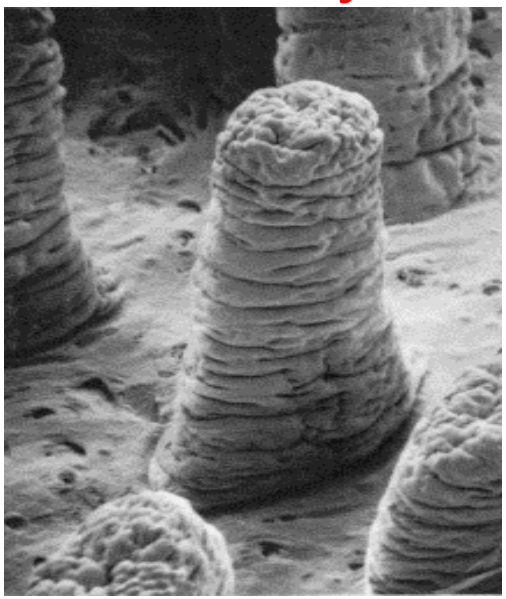
- Experiences in radiation therapy
- Studies of survivors of Hiroshima and Nagasaki in 1945
- Marshallese islanders accidentally exposed to radioactive fallout in 1954
- Victims of reported radiation accidents (403 accidents worldwide during 1944-1999):
  - 19 accidents involving nuclear reactors
  - 303 involving radiation devices (sealed radioactive sources or x-ray machines)
  - 81 involving radioisotopes
  - these 403 accidents resulted in 120 deaths
- Dose levels during accidents are usually poorly known

Cerebrovascular Syndrome (Total Body Dose > 100 Gy)

- Symptoms are associated with pathology to nerve cells and blood vessels of the brain
- Suggested cause of death - immediate increase in fluid content of the brain due to radiation induced leakage from small blood vessels resulting in build-up pressure within the skull
- At this dose all organ systems are also damaged
- Cardiovascular damage plays an important role
- In man several deaths of this type have been reported in medical literature, e.g.:
  - in 1964, accident at Uranium-235 recovery plant
  - in 1958, nuclear criticality accident at Los Alamos (USA)

Gastro-Intestinal Syndrome (Total Body Dose >10 Gy)

- Damage to cell renewal system of gastro-intestinal tract
- Damage to bone marrow also plays a part
- There is no record of a human surviving a whole-body dose > 10 Gy

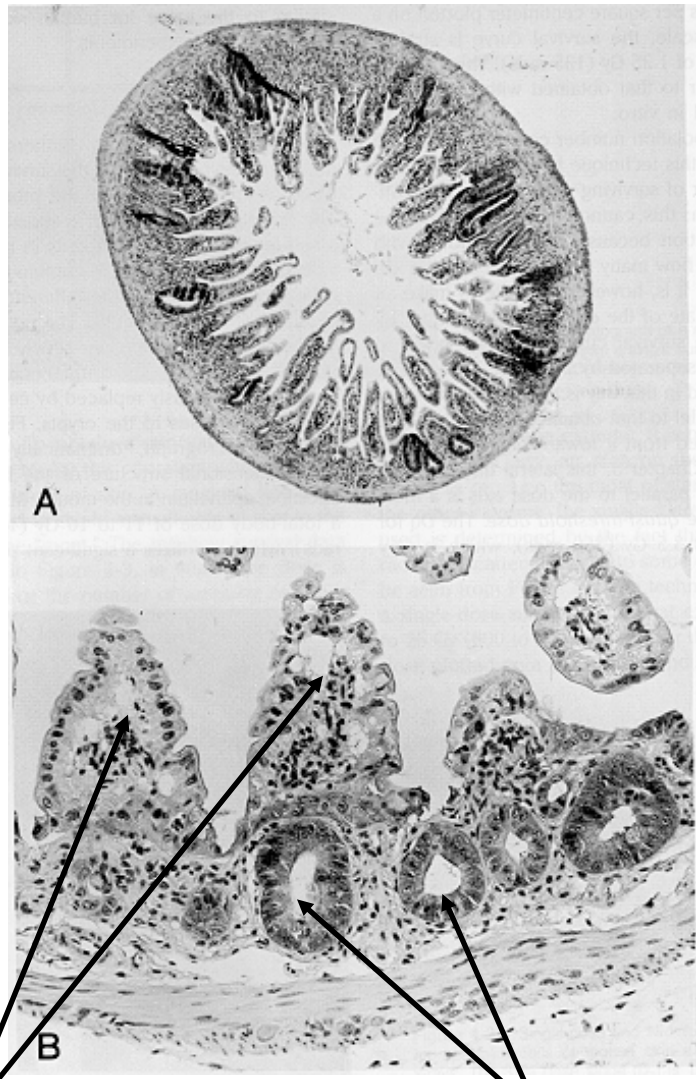


Jejunal villi of a hamster

- The normal lining of the intestine is composed of stem cells, differentiated cells and maturating functioning cells
- Cells in the villi are differentiated
- Are sloughed off with use
- Replaced from stem cells in crypt (continuous supply of new cells)

Gastro-Intestinal Syndrome

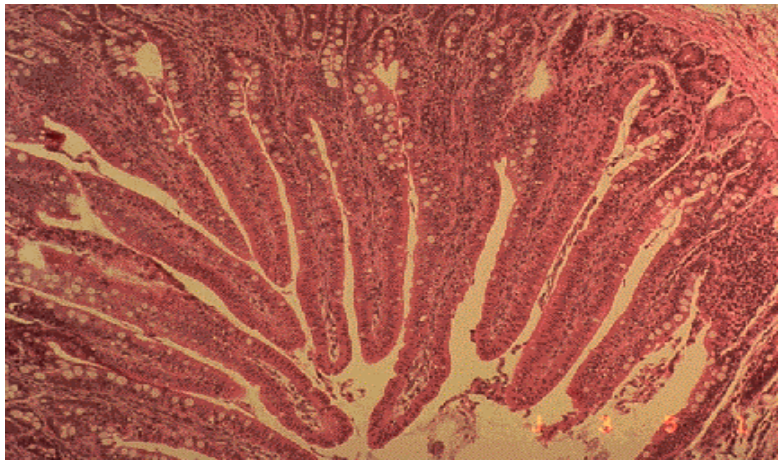
3.5 days after total body dose >10 Gy to a mouse



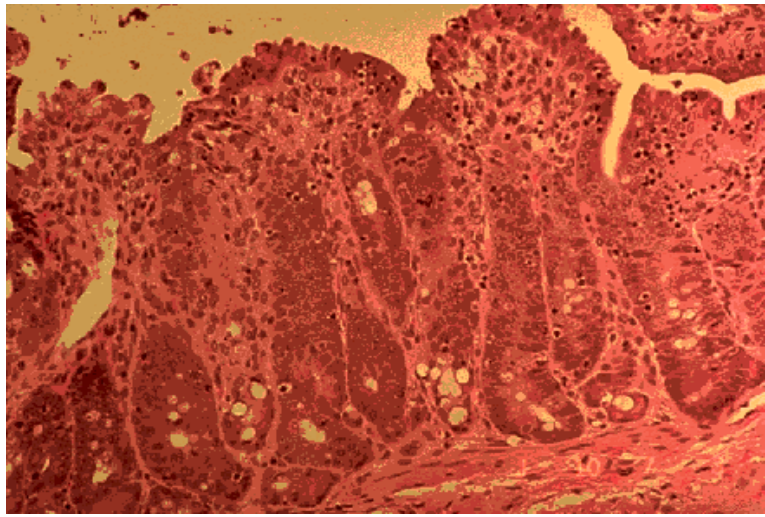
- Destruction of stem cells in the crypt turns off cell supply
- Radiation has practically no effect on differentiated cells
- Villi rapidly wear down, shorten and shrink
- Crypt mitosis picks up again (after 2-6 hours)
- Abnormal cells die after few divisions so mitosis falls again
- Regenerative wave gets weaker and takes longer as dose is increased
- At death the villi become very clearly flat

Gastro-Intestinal Syndrome

- Before Chernobyl - only 1 example in medical literature of a human suffering gastro-intestinal death:
  - in 1946 radiation accident to 32-year old man, total body dose 11-20 Gy. General condition remained good until 6th day after exposure. Death on the 9th day
  - Several firefighters at Chernobyl (USSR, 1986). Total body doses from 10 to 16 Gy. Death within 7-10 days after exposure
  - Sarov nuclear accident (1997, Russia) - one experimenter received a total body dose of 45 Gy, mainly from neutrons. Death on the 3rd day



Normal GI mucosa



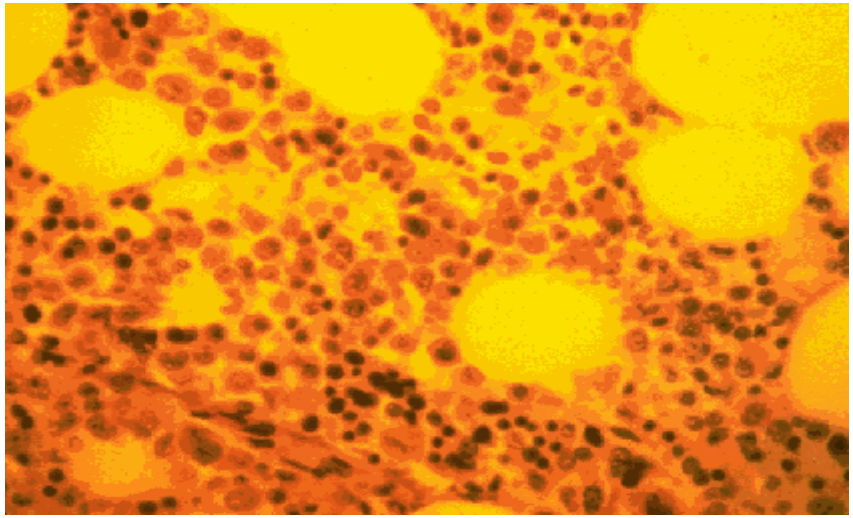
Irradiated GI mucosa

Bone Marrow Syndrome at Total Body Dose 2 - 10 Gy

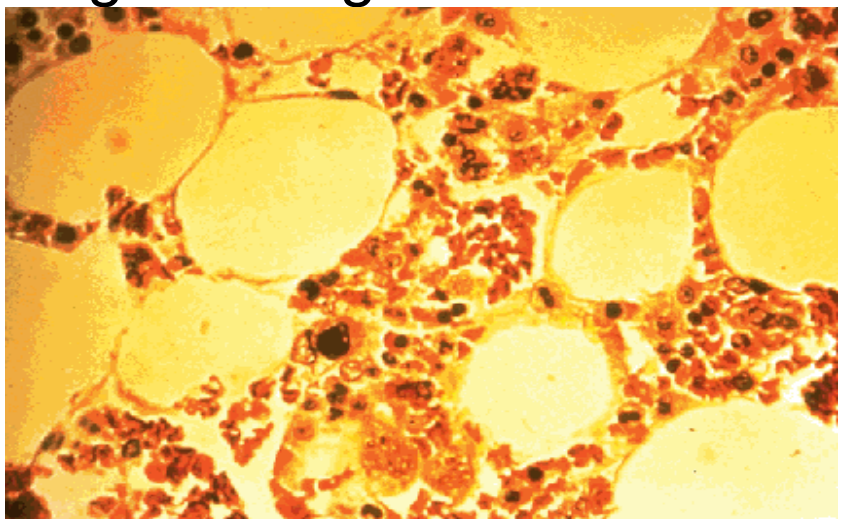
- Doses low enough for gastro-intestinal syndrome
- Depletion of the stem cells of circulatory blood cells
- Mitotic and non-mitotic death of bone marrow cells
- Number of mitoses can fall to zero in 1 hour
- Supply of mature red blood cells, white blood cells and clotting platelets diminishes or is cut
- Time when the number of circulating cells in blood reaches the minimum value is delayed for weeks

Bone Marrow Syndrome

- Regeneration will include many abnormal cells
- Dead cells from bone marrow are removed and the space is filled by leaking blood
- Circulating blood cells are not replaced when they die
  - initial gastro-intestinal symptoms will clear up in few days
  - anaemia (low red blood cells and haemaglobin)
  - haemorrhage (vessels damaged and no clotting platelets), infection
- Death unless bone marrow has begun to regenerate in time



Normal bone marrow



Irradiated bone marrow

Bone Marrow Syndrome

- Humans develop signs of Bone Marrow Syndrome and recover from it much slower than most other mammals
- Deaths continue for 60 days
- Peak incidence of death at 10-15 days
- Therapy:
  - antibiotic therapy to fight infection
  - hospital isolation to avoid infection, bleeding and physical trauma
  - bone-marrow transplant from a suitable donor (usually from a close relative) - this can only be useful after whole-body doses of 8 to 10 Gy
- Chernobyl nuclear reactor accident (USSR, 1986):
  - 35 people had severe bone marrow syndrome, 13 of them died
  - of 13 people that received bone-marrow transplant, only 2 survived:
    - bone marrow naturally regenerated in 1 case
    - bone-marrow transplant was successful in another case

Case Study: **Polonium-210 poisoning** (November 2006)

Major health alert across London as police launch hunt for poison traces

DEAD SPY WAS RADIOACTIVE

LONDON'S QUALITY NEWSPAPER

Evening Standard

1.11.06 Incorporating The Evening News www.thisislondon.co.uk 50p WEST END FINAL

WEST HAM SOLD FOR £108 MILLION NEWS PAGE 5, SPORT BACK PAGE

SPY PILL 'WAS RADIOACTIVE'

Doctor's new theory in

Jowell

Properties of Polonium-210

- Is an alpha particle emitting radionuclide:

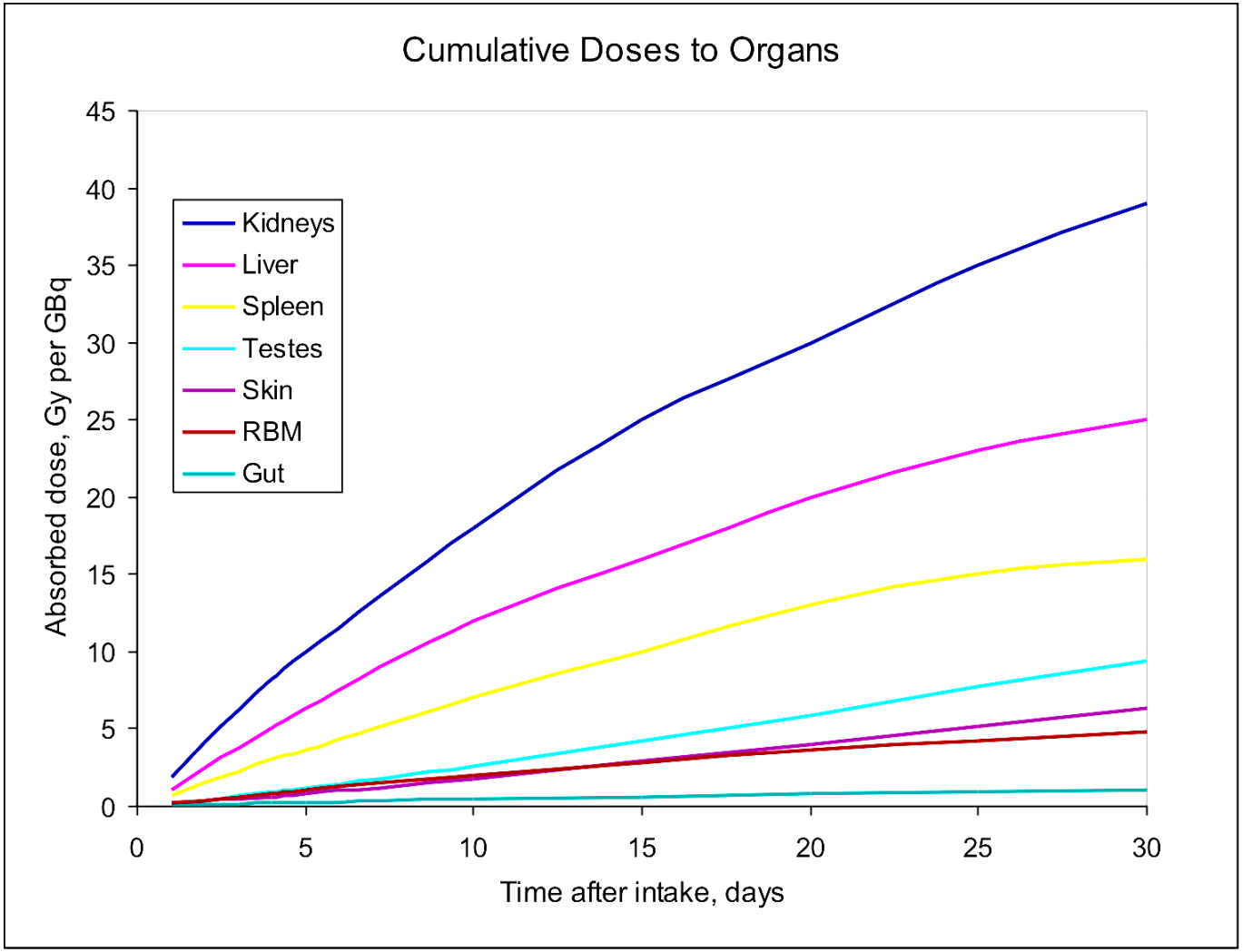
$$^{210}_{84}\mathrm{Po} \longrightarrow {}^{206}_{82}\mathrm{Pb} + \alpha$$

- Alpha particles have energy of 5.3 MeV. Their range is very short (50 μm). They produce the biological damage.
- Half–life of Po-210 is 138 days
- Po-210 can be extracted from uranium-bearing rocks
- Is manufactured by bombarding Bi-209 with neutrons:

$$^{209}_{83}\mathrm{Bi} + n \longrightarrow {}^{210}_{83}\mathrm{Bi} \longrightarrow {}^{210}_{84}\mathrm{Po} + \beta$$

- Has high specific activity: 1 GBq = 10μg as chloride (1 Bq is 1 disintegration per second)
- Soluble (as chloride) in aqueous solution
- High uptake in soft tissues: liver; kidney; spleen; red bone marrow (RBM); hair follicles

Cumulative doses to organs after ingestion of Po-210 (assuming 10% absorption to blood)



John Harrison et al., *Journal of Radiation Protection* **v. 27** (2007) pp.17-40

Dosimetry

- Litvinenko case (November 2006) – ingestion of about 2 GBq of Po-210 has been estimated* (assuming 10% absorption to blood)
- Red Bone Marrow:
  - 50% Lethal Dose LD_{50} (3.5 - 4Gy) is reached 10 days after ingestion of 2GBq of Po-210
  - 100% Lethal Dose LD_{100} (5Gy) is reached 2 weeks after ingestion
  - Is Red Bone Marrow transplant any use?
- 2GBq of Po-210 gives:
  - kidney dose 4Gy/day (LD_{50} = 6Gy)
  - liver dose 2Gy/day (LD_{50} = 8Gy)
- Excretion of ingested Polonium-210 from the patient :
  - in faeces (99%)
  - in urine (0.9%)
  - through skin (0.1%)

*John Harrison et al. J. Rad. Prot 27 (2007) 17- 40