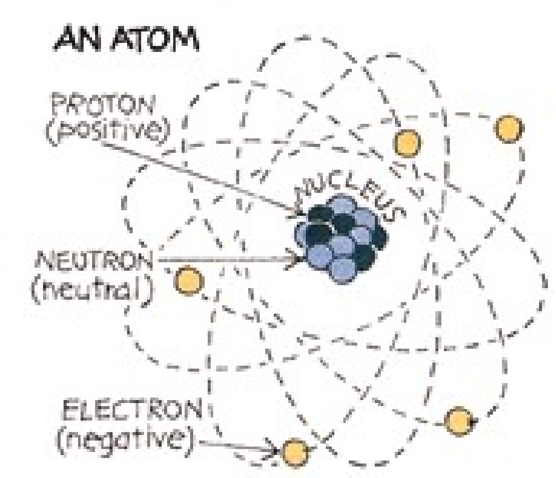
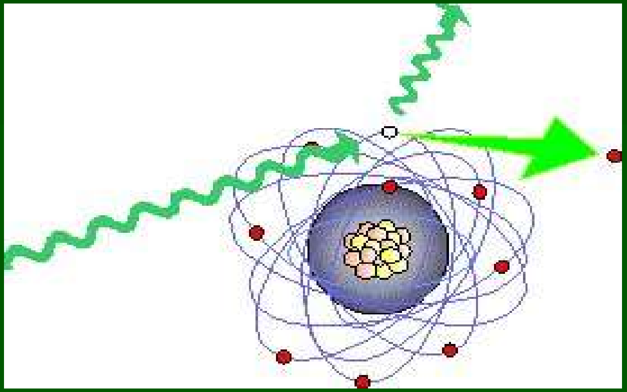
Ionizing radiation and its biological effects

1) Basic concepts
2) Sources of ionizing radiation
3) Consequences of exposition to the ionizing radiation
4) Ionizing radiation in the medicine
5) Practical

What is ionizing radiation

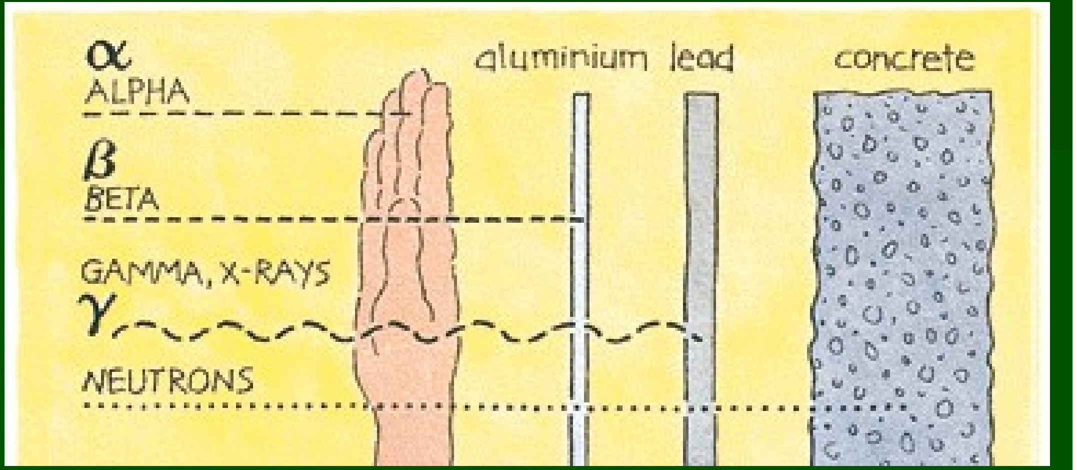
- **particle** or **electromagnetic** radiation, when a particle/photon carries enough energy to **ionize** an atom or a molecule (by removing an electrone from its orbit)
  - That leads into the formation of the atoms with electric charge - ions
  - This can have important effects for the biological functions of macromolecules

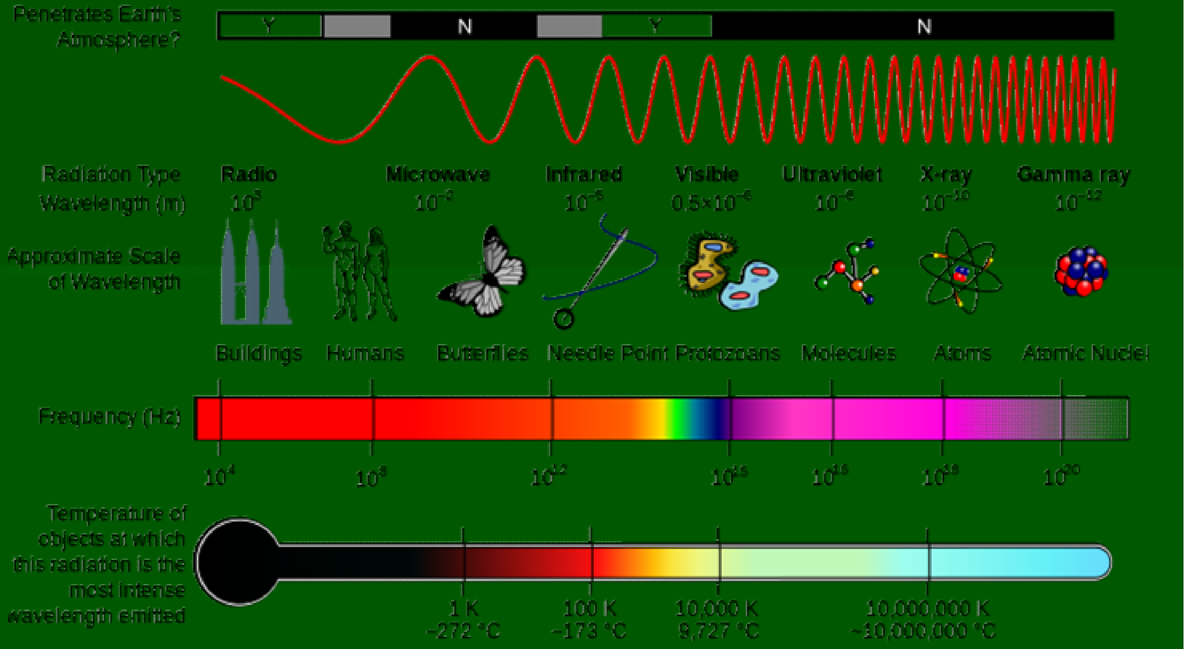




Types of ionizing radiation?

- α = α–particles (helium ${}^{4}_{2}He$ nuclei)
- β = electrones (β^-) or positrones (β^+)
- γ, X-rays = electromagnetic waves (photons)
- neutrons
- protons
- fission fragments
- cosmic rays (particles – e.g. muons)





Physical quantities and their units

- Dose of ionizing radiation obtained by a person is expressed as **absorbed dose,** with unit **gray** (Gy)
  - 1Gy = 1 J/kg (older - rad = 1/100 Gy)
- The same dose in Gy in various types of radiation leads into different biological effect (1Gy of α-radiation has higher effect than 1Gy of β-radiation) → the biological effect is expressed as **equivalent dose**, with unit **sievert** (Sv; older - rem = 1/100 Sv)
  - Regardless the type of the radiation, 1 Sv leads into the same biological effect
    - example: 1Gy=1Sv for X-rays, γ- or β-radiation; 1Gy=2-10Sv for protons; 1Gy=3-20Sv for neutrons (depending on their energy) and 1Gy=20Sv for α-radiation and fission fragments

Contact of ionizing radiation with the organism – comparison of effects

- Irradiation from the distant source (neutrons > γ >> β*; $\alpha = 0$)
- Contact of the emitter and the body surface (γ > β*; α ~ 0; there are no neutron emitters)
- Contact of the emitter and the inner environment - contamination (α > β > γ; there are no neutron emitters)

* body surface

Equivalent dose vs. effective dose

- Both have Sv for the unit
- Equivalent dose: adjustment for the radiation type
- Effective dose: adjusts also for the features of irradiated tissue (multiplies by a specific coefficient: gonads/blood marrow/GIT > parenchymatous organs > brain/bone/skin)
- It suppose a more severe effect/higher probability with increasing dose of radiation
- By definition, the effective dose expressed in Sv is questionable in:
  - > 10 Sv (higher than lethal dose)
  - < 100 mSv (empirically, the correlation of the dose and the disease is not clear)

Sources of ionizing radiation?*

- Natural (2.1 mSv/year)
  - cosmic (0.3 mSv/year)
    - exposition increases with the altitude and latitude
  - earth sources (0.4 mSv/year)
    - radioactive decay of natural radioisotopes (in soil and rock)
  - radon (1.1 mSv/year)
    - gas, formed by radioactive decay
    - most abundant isotope $^{222}_{86}Rn$ comes from radium $^{226}_{88}Ra$ (originally from $^{238}_{92}U$)
    - undergoes α-decay with several following decays in short time
  - nutrients (0.3 mSv/year)
    - mostly $^{40}_{19}K$

- Artificial (2.0 mSv/year)
  - medicine (1.9 mSv/year)
    - diagnostics, therapy, sterilization
  - other artificial (<0.1 mSv/year)
    - consumer products
    - nuclear fallout (nuclear tests, Chernobyl…)
    - nuclear energetics

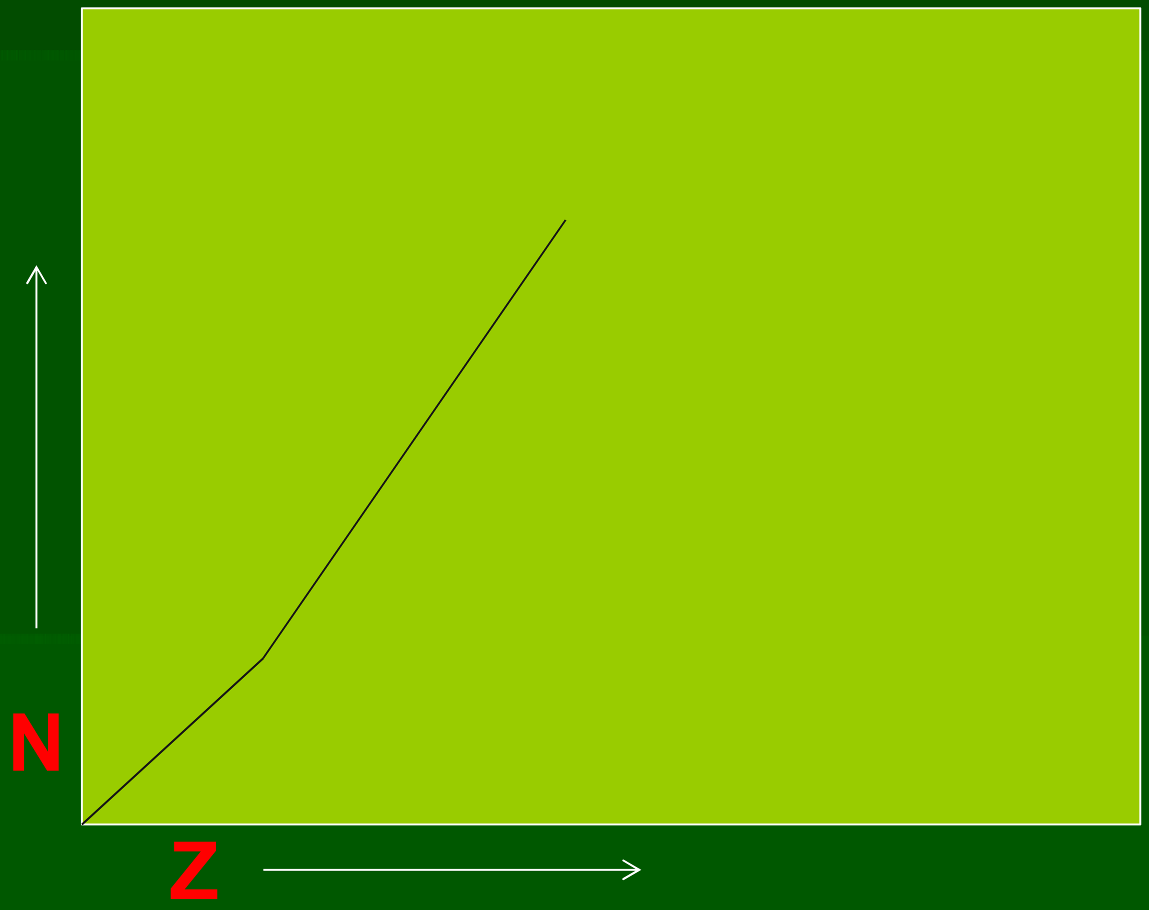
* Germany 2005

What is a radioactivity?

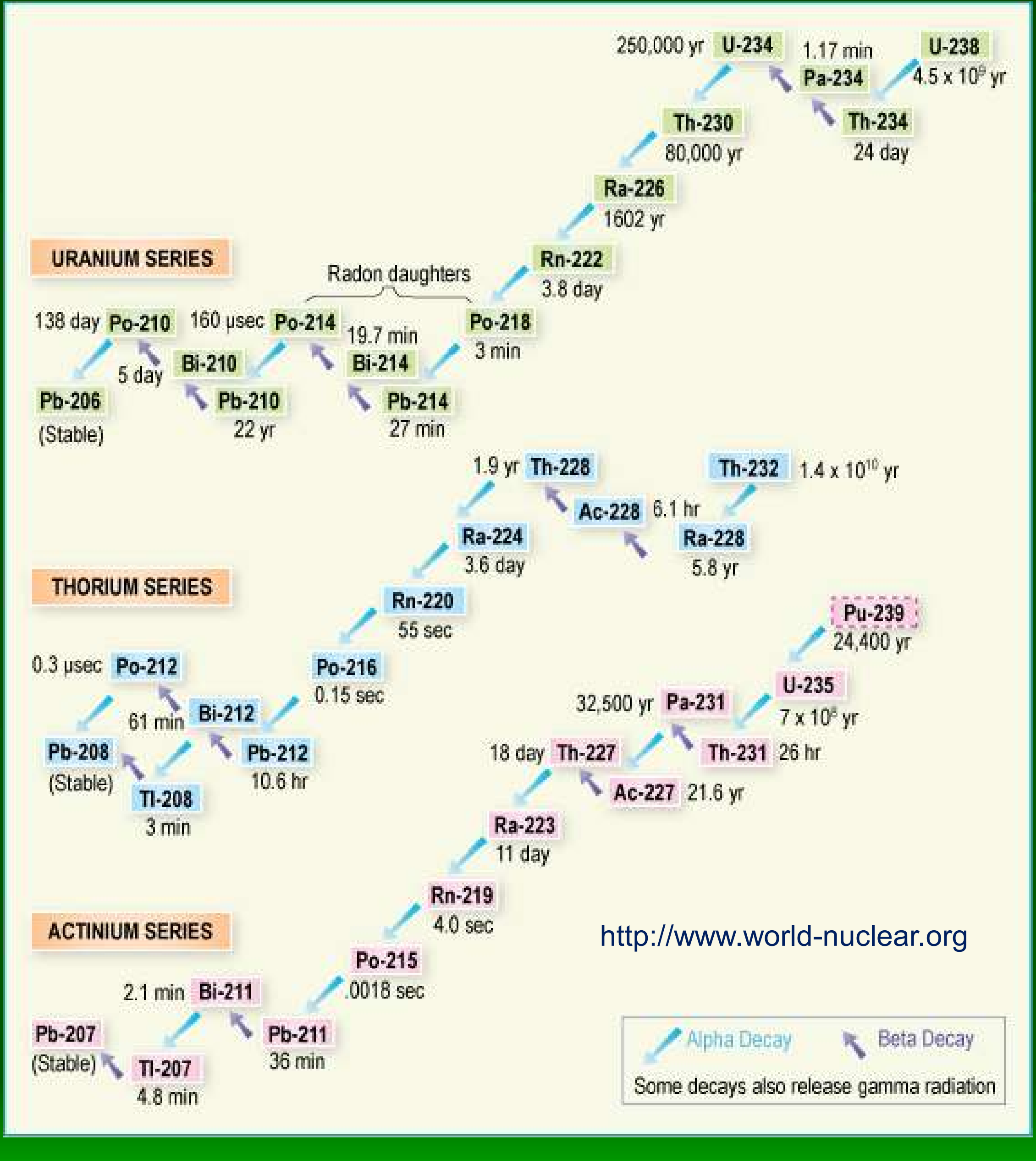
- Most atoms occuring in the nature are stable
- Some of them have an excess of internal energy (in fact that means high mass per 1 nucleon – $E=mc^2$) that is released during their disintegration when new nuclides and elements are formed =“**radioactive decay**”
- Most stable atoms have typical ratio of protons and neutrons in the nucleus
  - during the decay, an excess of internal energy is released as γ-rays or particle
- radioactivity of a radioactive matter is expressed in **becquerels** (Bq)
  - 1 Bq=1 radioactive decay of 1 atom/s (former 1 curie = $3{,}7 \times 10^{10}$ Bq)

Stable and unstable nuclides

- Atoms situated on the left and up from the black line have too many neutrons - β- -decay
- Atoms on the right and down have too many protons – β+ -decay or electron capture
- Atoms on the right and up are too big altogether – α- decay (or nuclear fission)
- Atoms on the left and down are stable, but under extreme temperatures (stars, thermonuclear bomb) they can undergo the nuclear fusion



Radioactive decay chains



http://www.world-nuclear.org

Grays, sieverts, becquerels

- Equivalent or effective dose (Sv) cannot be measured directly, but only estimated
- Radioactivity cannot be easily converted into absorbed dose
  - It depends on the way of contact with a source, its biological availability, excretion, and on the properties of radioactive nuclide
  - Example: potassium of own body: 5 kBq ~ 200 µGy/year ~ 200 µSv/year

Choose the most significant radioactive source in the environment...

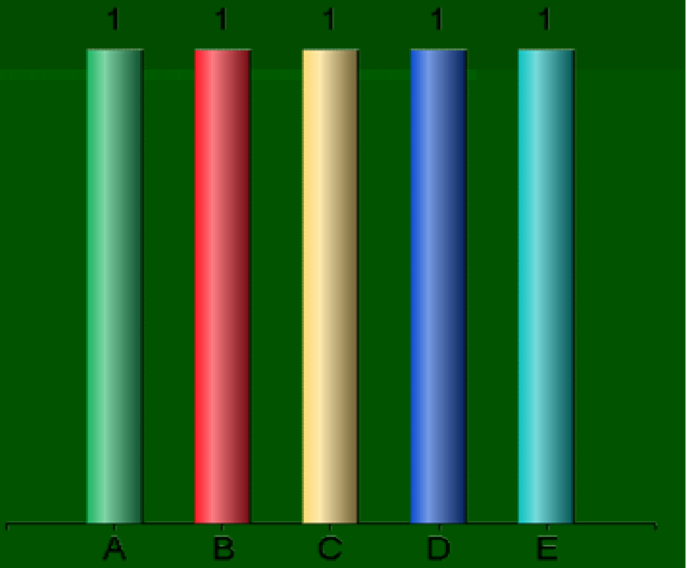
A. Potassium $^{40}_{19}K$ in the food

✓ B. Radon $^{222}_{86}Rn$ in the air (buildings, mines)

C. Uranium and thorium in the rock and soil

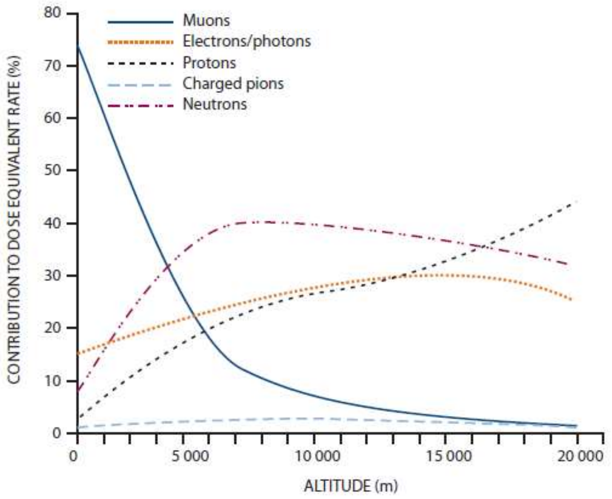
D. Fallout from nuclear tests and Chernobyl

E. Fluorescent tube starters



Cosmic rays

- Primary – 90% protons, 9% α-particles, 1% electrons, γ-rays
  - Galactic cosmic rays (steady background) vs. solar (11-year oscillations)
  - Dominate in higher layers of the atmosphere, outer space – directed to van Allen‘s belts and to magnetic poles by Earth‘s magnetic field
- Secondary – appear as a result of the interaction between primary cosmic rays and the atmosphere
  - Muons dominate at the sea level, neutrons at 10000 km (flight level)
  - Exposition increases with the altitude (↓atmosphere) and latitude (↓magnetic field)
  - Some light radioactive nuclides are also formed ($^{14}_{6}C$, $^{3}_{1}H$)

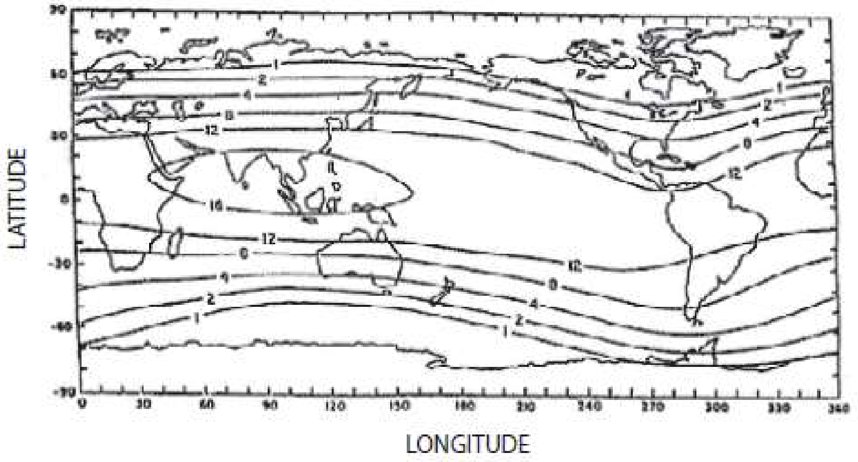


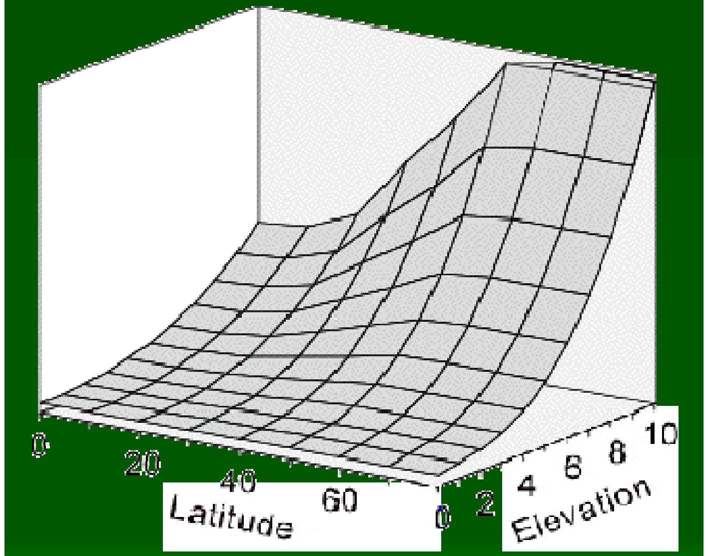
Components of the dose equivalent rate due to cosmic rays in the atmosphere

Cosmic rays – altitude and latitude effects

- Only high-energy primary cosmic rays can get through Earth‘s magnetic field at the equator
- In high altitudes (proton/neutron dominance), there is significantly higher exposition near magnetic poles (around 0.1 mSv per trans-Atlantic flight near north magnetic pole vs. 0.03 over the equator)
- In low altitudes (muon dominance), the effect is quite low (muons originate in high-energy reactions)
- Energy of the particles is measured in **electronvolts** (1 eV = 1.6×10^{-19} J)

Figure III. Vertical cut-off rigidity, R_c (in GV), at 20 km altitude [S30]



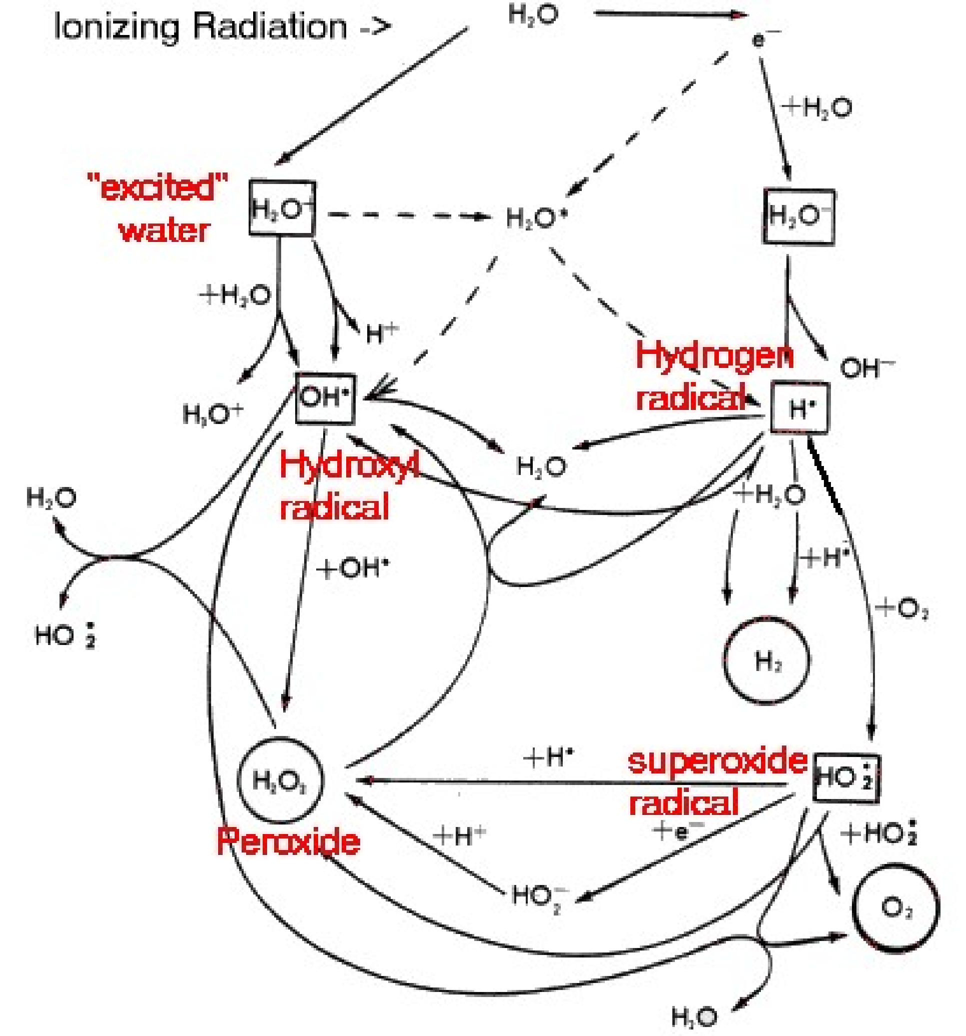


Quantities and their units - summary

Unit	Quantity	Definition	Use
Electronvolt (eV)	Particle energy	1.602 x 10^{-19} J	Defines the ionizing ability of a particle (> 10eV)
Gray (Gy)	Absorbed dose	1 J / kg of ionizing radiation	Total energy carried by ionizing radiation – e.g. in radiotherapy, measured by dosimeters
Rad	Absorbed dose	= 1 cGy	See Gray
Sievert (Sv)	Equivalent dose	1 Gy x radiation weighing factor	Accounts for a type of radiation
	Effective dose	1 Gy x radiation weighing factor x tissue weighing factor	Accounts also for the properties of irradiated tissue
Rem	Equivalent dose	1 rad x radiation weighing factor	See Sievert
	Effective dose	1 rad x radiation weighing factor x tissue weighing factor	See Sievert – both equivalent and effective dose are estimations only!
Roentgen (R)	Exposure	Ionizing radiation that creates 3.7 x 10^{10} C in 1 cm^3 of dry air	Measurement by dosimeters (1R ~ 1 rad)
Becquerel (Bq)	Radioactivity	1 decay / s	Useful in determining radioactive contamination
Curie (Ci)	Radioactivity	3.7 x 10^{10} Bq (37 GBq)	See Becquerel

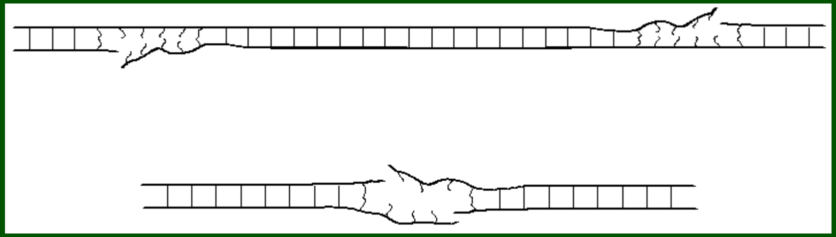
Biological effects of ionizing radiation and its consequences

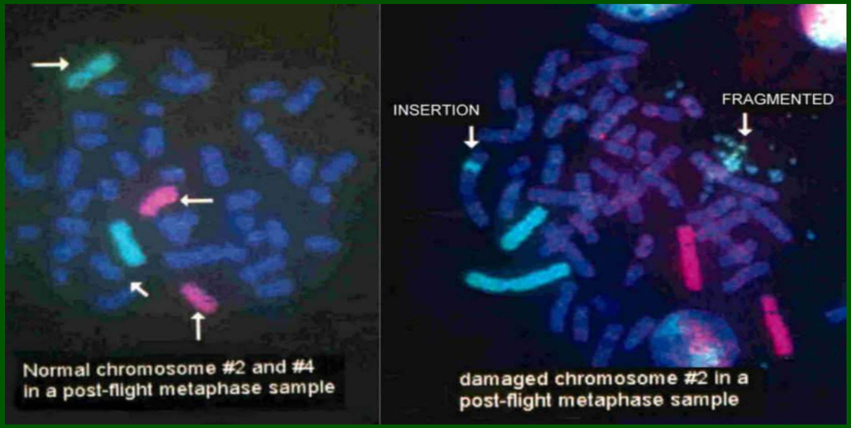
- Direct ionization of macromolecules
- Indirectly through water “radiolysis”
  - reactive oxygen species
- Consequences:
  - reparation
  - apoptosis (mostly in rapidly proliferating cells)
  - persisting change (DNA mutation)



Types and consequences of the DNA lesions

- single strand breaks (SSB)
  - around 1000 SSB per 1 cell and 1 Gy
- double strand breaks (DSB)
  - around 70 DSB per 1 cell and 1 Gy

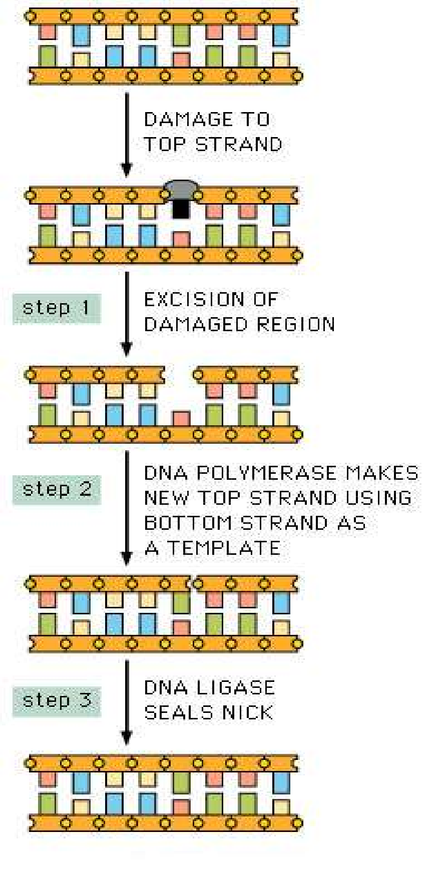




Normal chromosome #2 and #4 in a post-flight metaphase sample

damaged chromosome #2 in a post-flight metaphase sample

DNA repair



- *in situ* repair – non-specific (e.g. hydrogen donors)
- excision repair - SSB
  - base excision repair
  - nucleotide excision repair
- homologous recombination (DSB - repair using the second chromosome)
- nonhomologous end joining
  - translocation
  - insertion/deletion
- mismatch (point mutation)
- lethal (apoptosis)
- almost 100 % success in SSB, only about 75 % in DSB

Absorbed dose of ionizing radiation is expressed in…

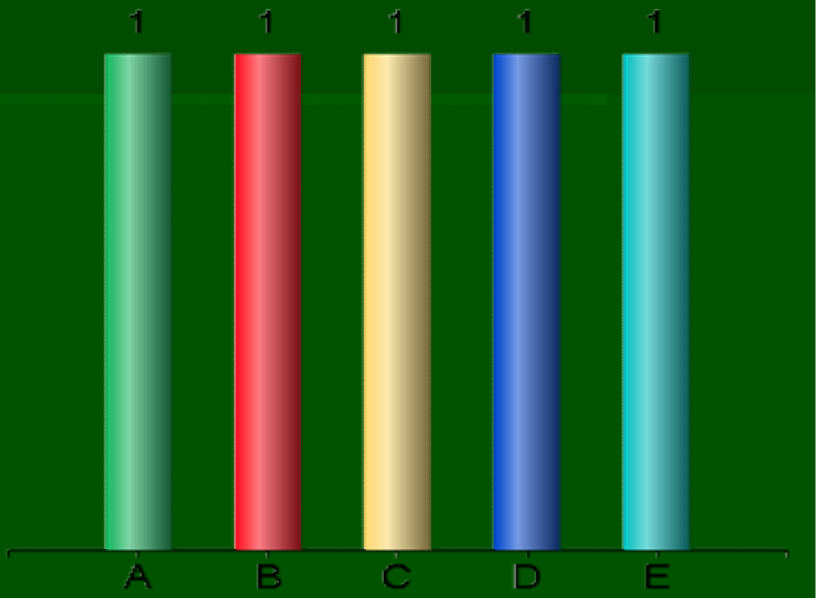
A. Sieverts

B. Becquerels

C. Electronvolts

D. Jouls

✓ E. Grays

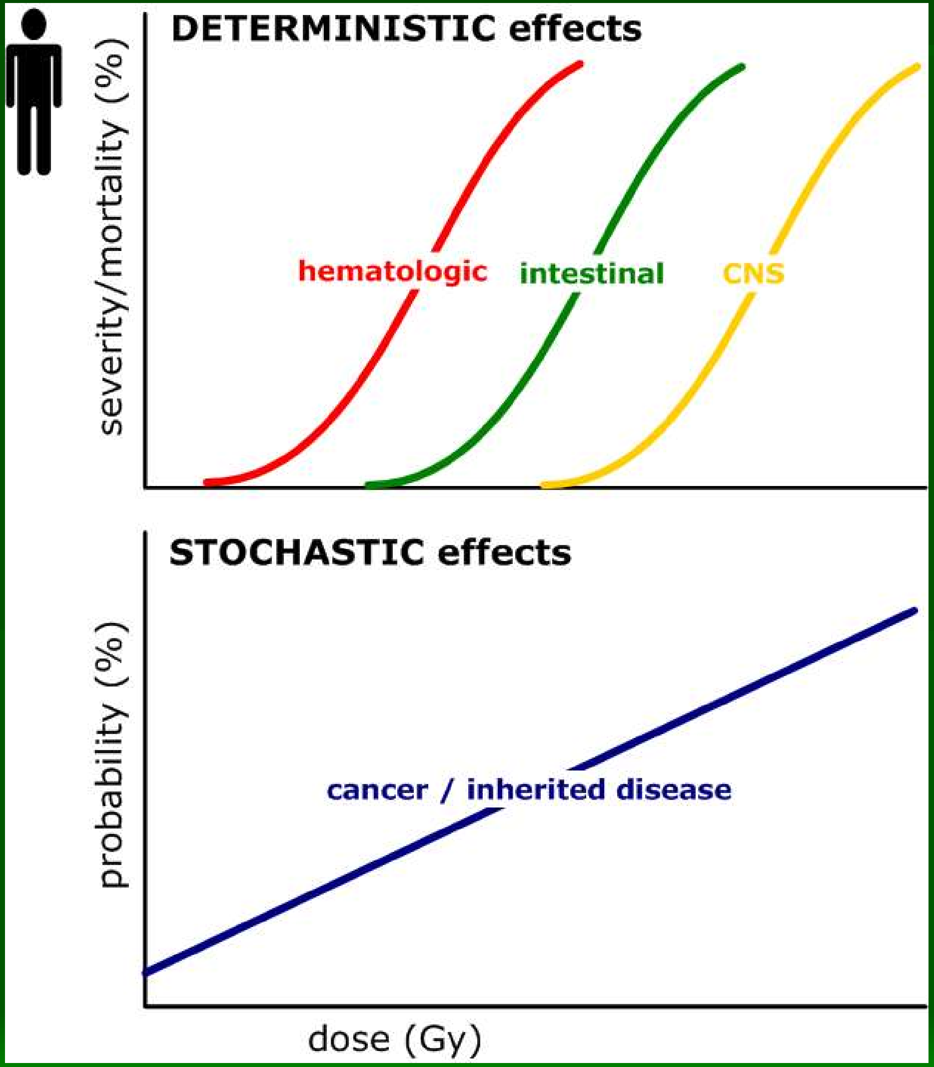


Biological effects

- Deterministic
- **Severity increases with (is determined by) the dose**
  - **specific** manifestation with the damage of typical tissues
  - the effect occurs when the **threshold dose** is reached
  - the damage is caused by destruction of the **large amount of cells**
  - the symptoms occur shortly after the exposition (**short latency**)
  - forms:
    - acute radiation syndrome
      - Whole-body absorbed dose >1Gy
    - chronic post-radiation syndrome (systemic or local)
      - sterility, cataract, postradiation dermatitis, alopecia, obliterating endarteritis, pneumonitis, …
    - damage of the fetus *in utero*

- Stochastic
  - **Probability increases with the dose** (not severity!)
  - Manifestation is **less specific**
  - Risk increases without **“safe” threshold dose**
  - The damage of **one cell** is sufficient for the effect
  - The manifestation is often delayed (**long latency**, typically years)
  - forms:
    - somatic mutations - tumours
      - leucemia, thyroid gland, lungs, mammary gland, bones
    - germinative mutation (oocyte, sperm cell) – genetic defect

Deterministic × stochastic



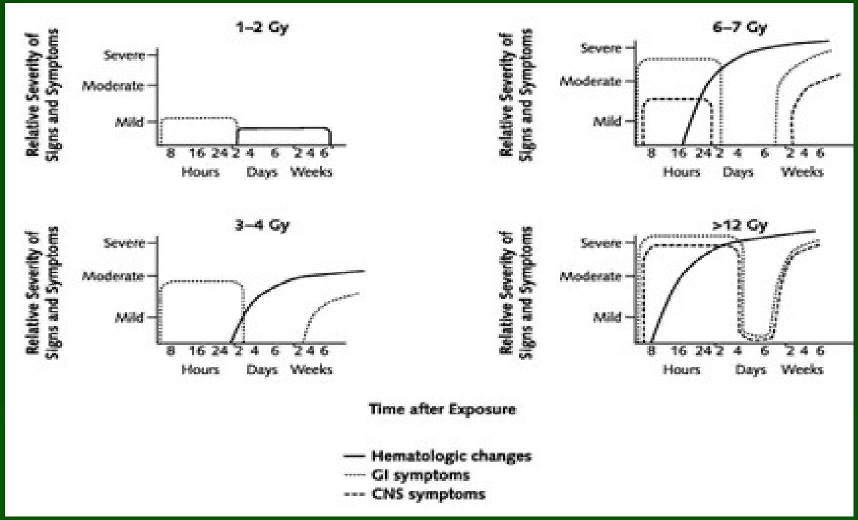
Tissue radiosensitivity

- Tissues with high rate of cell division, high metabolic turnover and high need of nutrition are particularly sensitive to ionizing radiation, roughly in following order:

1) Blood-forming tissue, intestinal epithelium, gonades
2) Skin, other epithelia
3) Eye lens, vessels, developing bone and cartilage
4) Parenchymatous organs, mature bone and cartillage, endocrinous glands
5) Brain, spinal cord, muscles

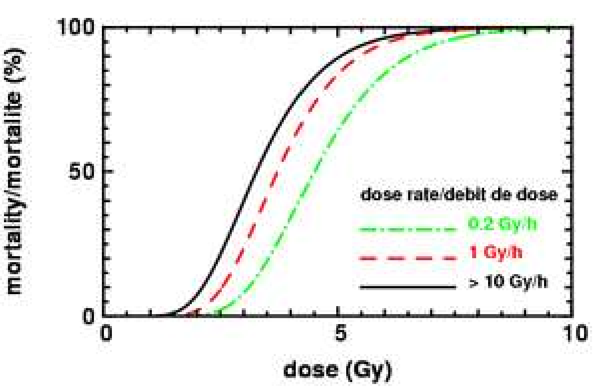
Acute radiation syndrome

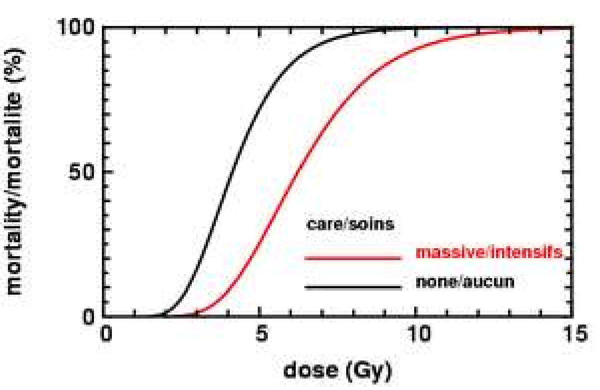
- Affects mostly **hematopoetic**, **gastrointestinal** and **cerebrovascular** system
- The course, extension and severity depend on the dose → **deterministic** effect
- Lasts from hours to months after the exposition



ARS – lethal dose

- LD 50 (i.e. the dose leading into 50% mortality) is cca 5 Sv, LD 100 is cca 10 Sv
- Most data are available from Hiroshima/Nagasaki survivors
- Nuclear weapons – typically a combination of:
  - γ-rays, neutrons (approx. 15 % of the total energy of explosion)
  - thermic damage (approx. 35 %)
  - shock wave (approx. 50 %)





Phases of ARS

- 1) Prodromal phase (hours to days after the exposition)
- 2) Latency phase (partial recovery, hours to weeks depending on the dose)
- 3) Manifest disease phase (usually weeks)
- 4) Recovery (up to 2 years) or death

higher absobed dose → shorter phase duration and worse prognosis

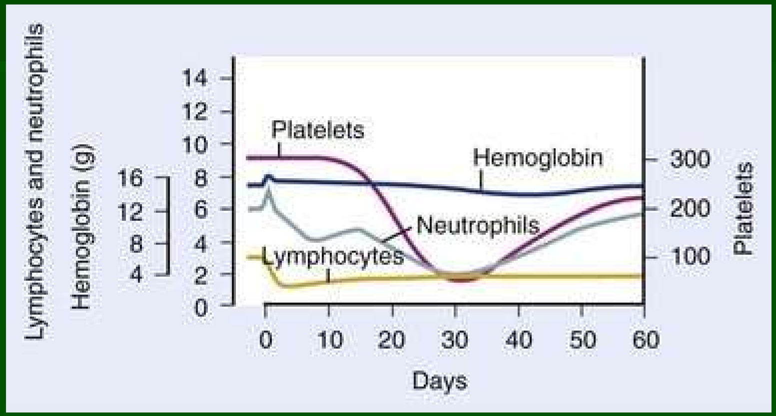
Forms of ARS

- Hematopoetic syndrome (>1Gy)
  - 1) reticulocytopenia, lymfopenia + granulocytosis
  - 2) granulocytopenia (→ imunodeficiency)
  - 3) trombocytopenia (→ bleeding)
  - 4) anemia (→ hypoxia)
- GIT syndrome (>6-10Gy)
  - early (hours) – nausea, vomiting, diarrhea
  - delayed (days) – loss of intestinal wall integrity
    - malabsorption, dehydratation, toxemia/sepsis, ileus, bleeding
- Cerebrovascular syndrome (>cca 50 Gy)
  - damage of the hematoencephalic barier
  - headache, cognitive disorders, desorientation, ataxia, spasms, exhaustion and hypotension
- Skin damage
  - erythema, burns, oedema, impaired healing of sores
  - epilation

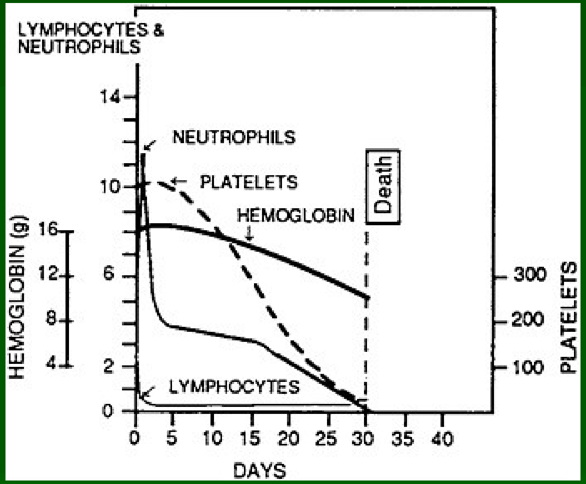
Hematopoetic syndrome

- Irradiation of the bone marrow (>1Gy) leads into exponential destruction of cells - **hematological crisis**
  - Hypoplasia to aplasia of the bone marrow + peripherous pancytopenia (infections, bleeding)
- Subpopulation of the **stem cells** is selectively more **radio-resistant**, (perhaps because most cells are in G_o phase)
  - necessary for the regeneration
- anemia is a delayed consequence (erythrocytes ~120 days)!
- massive **stress reaction** (glucocorticoids) contributes to lymphopenia (cytolytic effect) and paradoxicaly postpones the onset of granulocytopenia (the granulocytes stored in the spleen and bone marrow are released)

2 Gy



5 Gy



Blood count changes depending on the dose

- Neutrophil count tends to undergo an initial surge and transient remissions before the critical period
- Symptomatic anemia is rare and is usually a consequence of gastrointestinal bleeding (thrombocytopenia + GIT form)

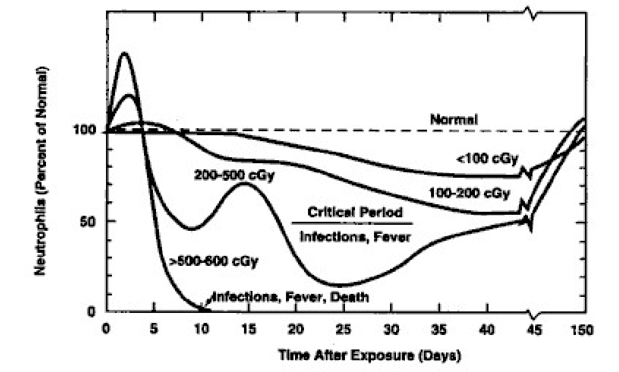


Figure 6-II. Smoothed Average Time-Course of Neutrophil Changes in Human Cases from Accidental Exposure as a Function of Dose

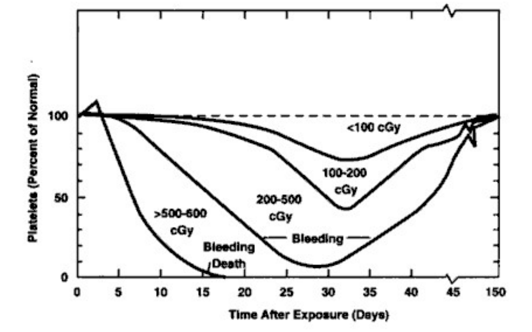


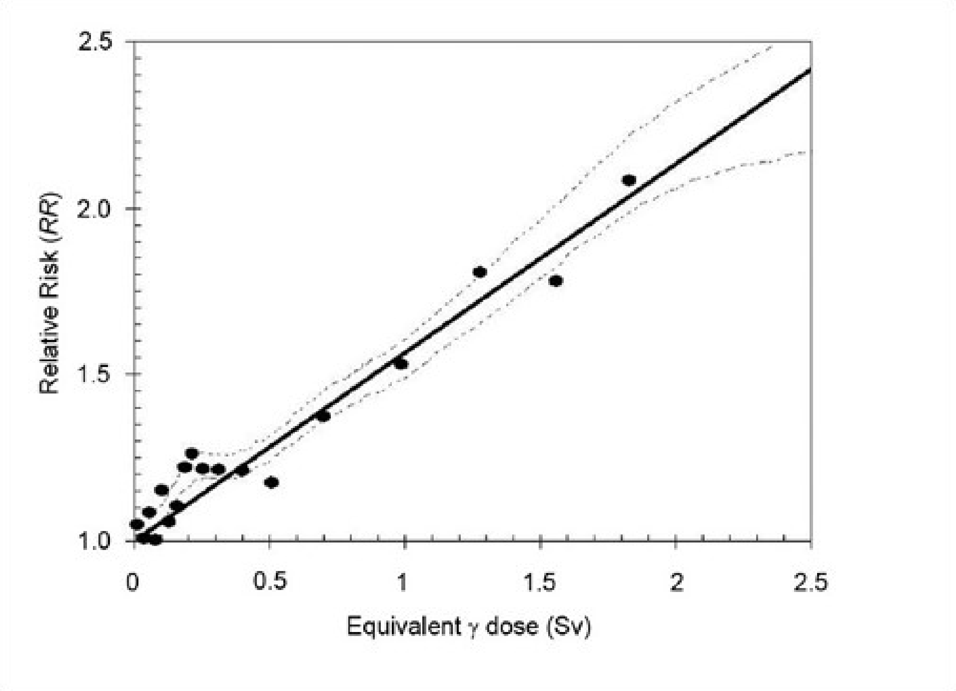
Figure 6-III. Smoothed Average Time-Course of Platelet Changes in Human Cases from Accidental Radiation Exposure as a Function of Dose

Embryo, fetus, germinal cells

- Pregnancy – fetal damage *in utero*
  - <3 weeks (blastogenesis)
    - “all or nothing”
      - genetic or chromosomal mutations usually lead into abortion
  - 3rd – 8th week (organogenesis)
    - retardation of development
    - teratogenic – birth defects
      - microcephalia, microphthalmia, spina bifida, clefts, …
  - 8th – 15th week (early fetal period)
    - mental retardation
    - increased susceptibility to oncological diseases (leucemia)
  - later
    - similar to after birth
- Sterility
    - spermatogenesis – transitory sterility in men (from cca 0.5 Sv, permanent from cca 5 Sv)
    - ovaries – in women, high dose of ionizing radiation (cca 5 Sv) is necessary to induce sterility, then the sterility is permanent
- Germinative mutations
  - Birth defects

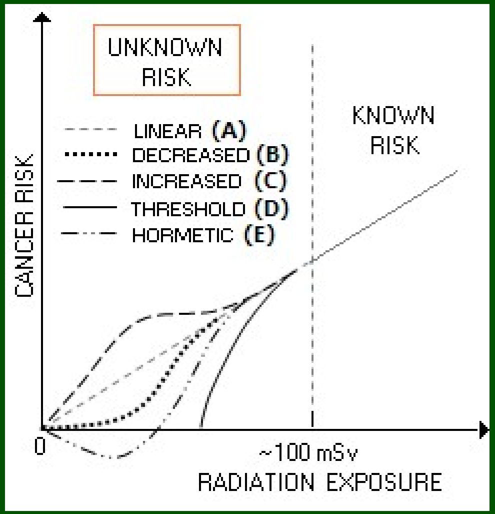
Risk of cancer

- in high doses, the risk increases linearly with life-long exposition
- approx. 1 new case of an oncological disease per 100 persons exposed to equivalent dose of 100 mSv (RR 1.024)
- the correlation is not clear below 100 mSv
- the risk is higher in children and women, around 40 years of age, the difference between both sexes ceases to be significant



Risk of cancer – low doses

- Little empirical data for human population
- „linear no-threshold model“: supposed linear effect also in low doses
- hormesis – supposed beneficial effects of radiation in very low doses (some evidence for the stimulation of antioxidant mechanisms and lower mortality from the animal studies - esp. in continuous irradiation)



Deterministic effects develop approximately from…

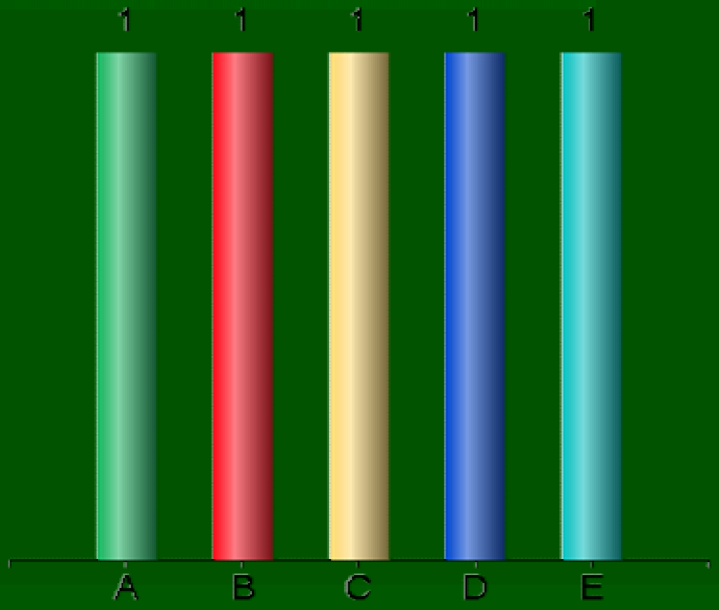
A. 100 mSv

✓ B. 500 mSv

C. 2 Sv

D. 5 Sv

E. 10 Sv



Radiation exposition in medicine – imaging methods

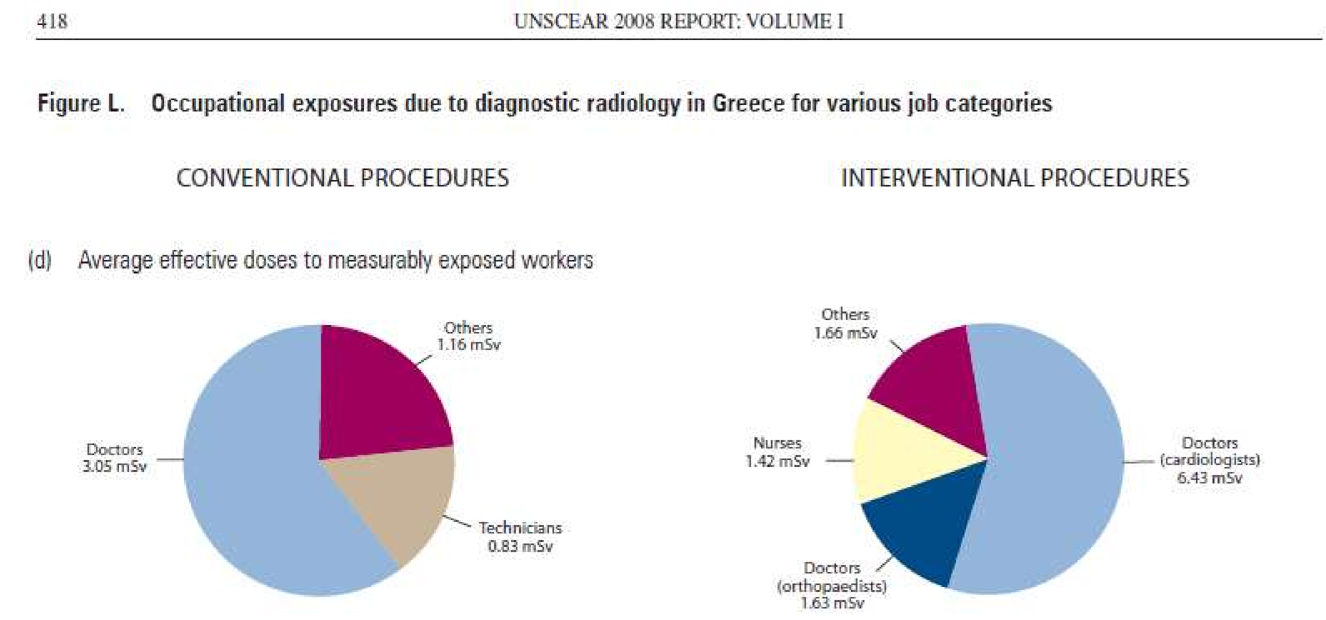
- X-rays, γ or β^+ (PET)
- chest X-ray 0.1 mSv
- lumbar spine X-ray 1.5 mSv
- head CT 2 mSv
- chest CT 7 mSv
- whole-body CT 10 mSv
- kidney scintigraphy 1.8-2.2 mSv
- bone scintigraphy 6.3 mSv
- brain PET 14 mSv
- heart stress test scintigraphy 9.4-41 mSv
- coronary angiography 20 mSv
- coronary angiography + PCI 30 mSv

Professional exposition (in medicine and elsewhere)

- Natural sources
  - uranium miners
  - coal miners
  - other miners
  - astronauts
  - aircrew

- Artificial sources
  - workers in nuclear facilities
  - military (nuclear weapons)
  - medical staff
    - interventional cardiologists
    - interventional radiologists
    - other radiologists
    - orthopaedists
    - nuclear medicine (doctors and nurses)
    - technicians

Professional exposition in medicine



418 UNSCEAR 2008 REPORT: VOLUME I

Figure L. **Occupational exposures due to diagnostic radiology in Greece for various job categories**

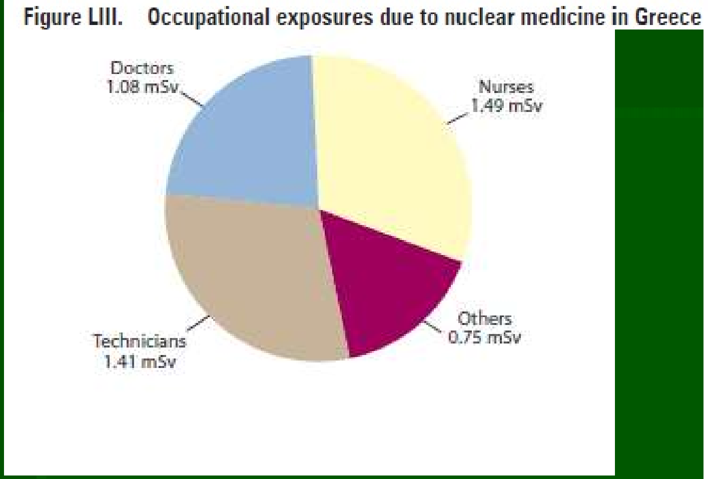


Figure LIII. **Occupational exposures due to nuclear medicine in Greece**

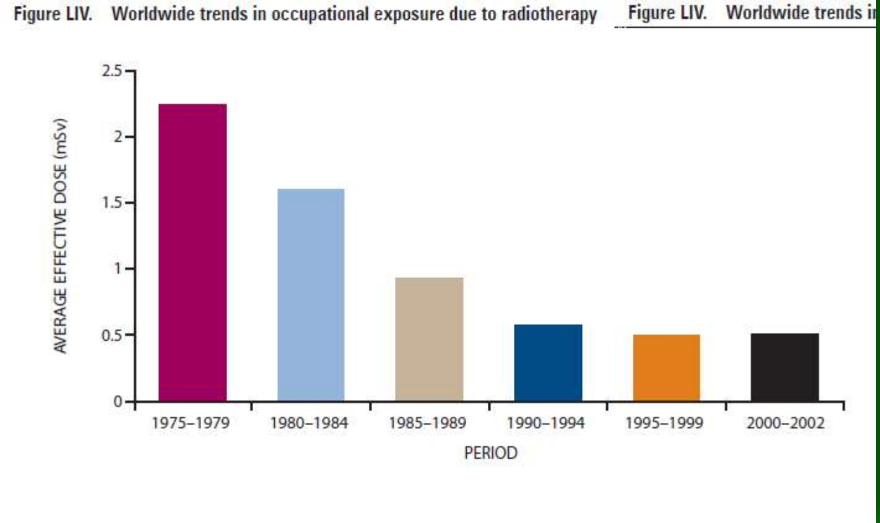
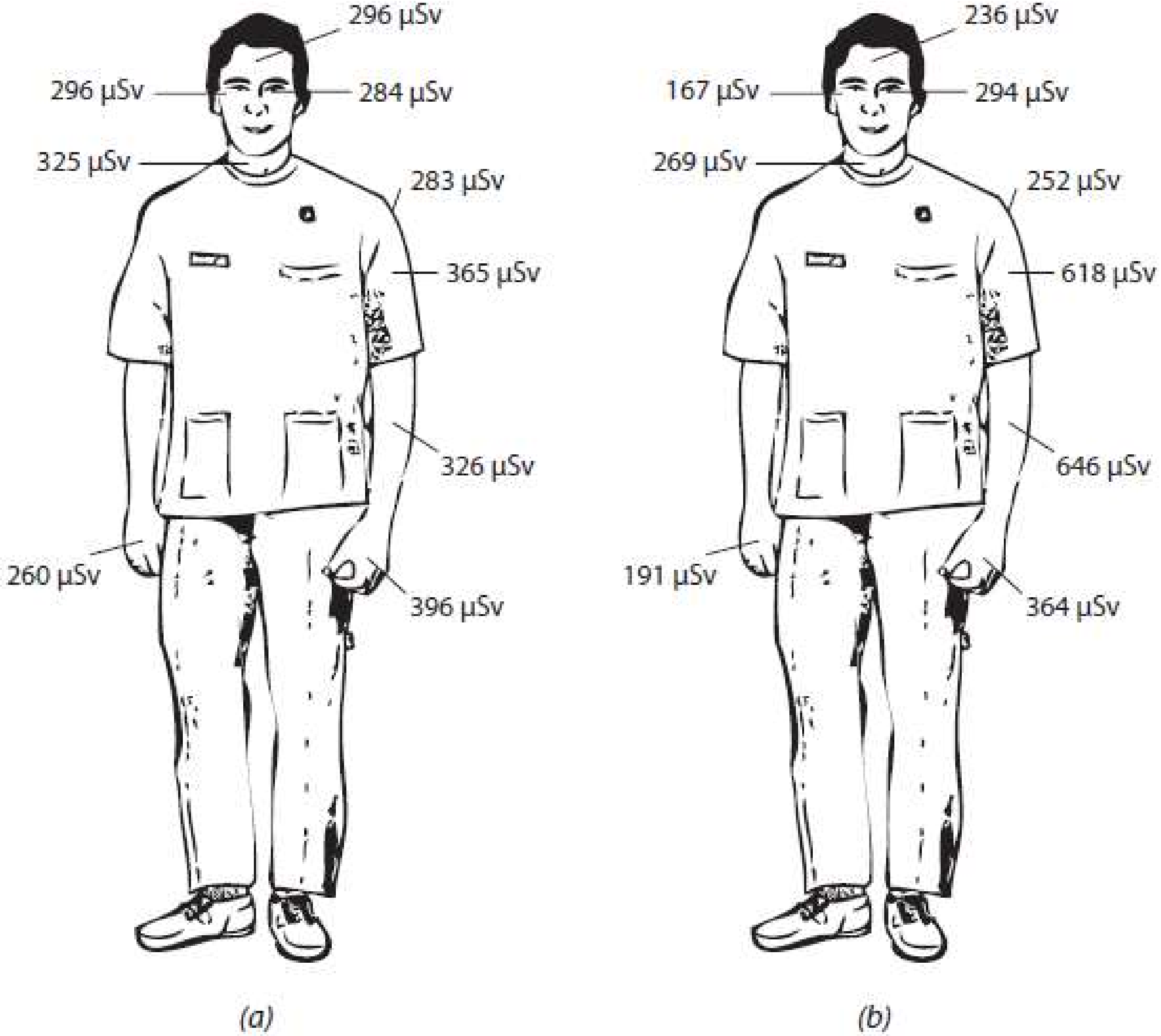


Figure LIV. **Worldwide trends in occupational exposure due to radiotherapy**

Figure LIV. **Worldwide trends i**

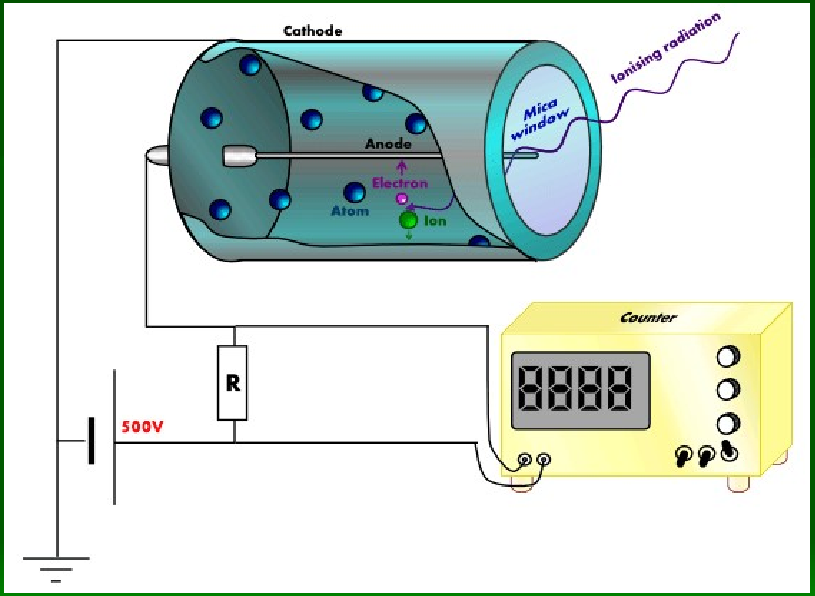
Figure XLVIII. Dose levels for *(a)* interventional radiologist and *(b)* interventional cardiologist

Average values of 83 procedures performed by ten specialists in six laboratories [V7]



Detection of ionizing radiation

- Geiger-Müller counter
  - Its detector part consist of a tube filled by a gas (noble gas + halogen)
  - The wall serves as a cathode, the rod inside as an anode,
  - The ionization of a gas create a short-circuit, which is then registered by a counter
  - GM counter measures counts per a minute (dose per a minute may be estimated based on the counts)



Dosimeters

- Measure overall absorbed **dose** of the ionizing radiation
- Film badge dosimeters – use a change of the film color by the effect of ionizing radiation
- Thermoluminescent dosimeters (TLD) – electrons released by the ionizing radiation bind to the lattice, after heating they get back and getting to the lower potential energy level, they release the visible or UV light
- Optically stimulated luminescence (OSL) – similar principle, green light is used instead of the heating – suitable for automatized detection

Anti-radiation measures

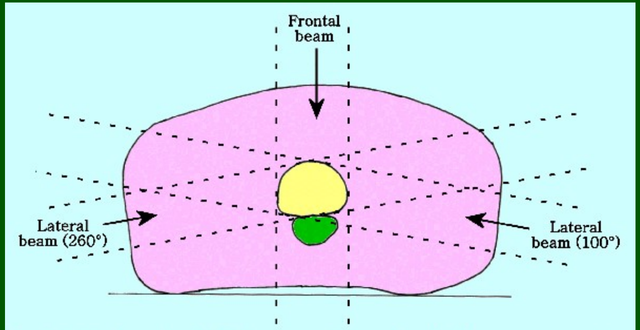
Hygienic limits: 20 mSv/year for the radiation workers, 1 mSv/year for the others („bystanders“)

Radiation exposition in medicine – radiotherapy

- various sorts of ionizing radiation
- tens of grays (sieverts) – **deterministic damage of the tissue is actually the goal of the therapy**
- teletherapy
- brachytherapy
- radiopharmaceuticals
- risks: damage of healthy tissue, secondary cancers
- risk reduction strategies: fractioning (one dose approx. 2 grays), exact focusing

Tumour radiosensitivity

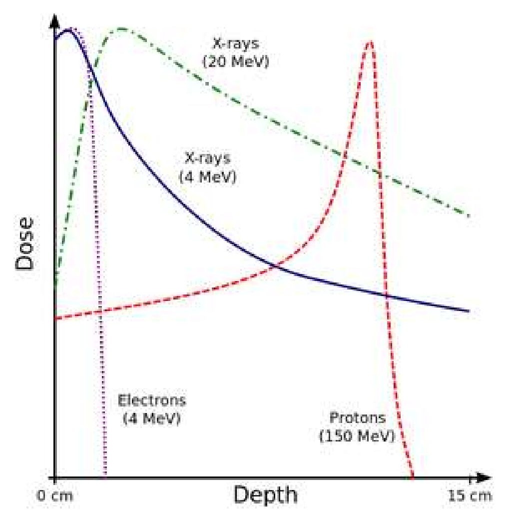
- Roughly corresponds to their parent tissue
  - high: lymphoma, seminoma, medulloblastoma
  - moderate: most carcinomas
  - low: sarcoma, glioma, malignant melanoma
- Other factors:
  - hypoxia (decreases radiosensitivity)
  - phase of the cell cycle (radiosensitivity in M > G2 > G1 > S > G0)
    - fractioning allows the consecutive irradiation of tumour cells in vulnerable phases of the cell cycle
  - production of p53 (increases radiosensitivity), growth factors (decreases radiosensitivity)



A sketch of a simple 3-beam conformal radiotherapy geometry.

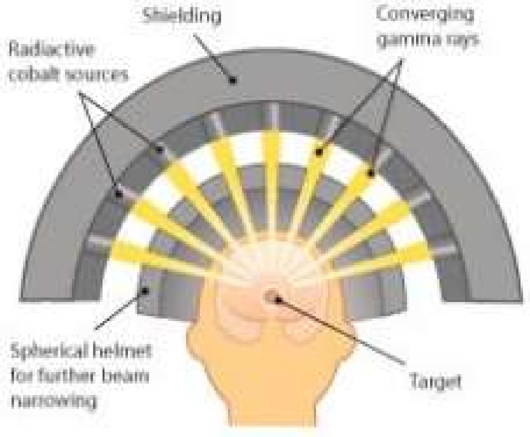
Teletherapy – X-rays vs. protons

- Electromagnetic rays are captured closer to the body surface, protons more deeply („Bragg peak“ – depth, where most protons are captured)
- The penetration of electromagnetic rays is deeper in higher energies (= shorter wavelengths)
- Besides the protons, accelerated bigger nuclei can be used (e.g. carbon)
- Electron teletherapy – skin tumours
- Neutron capture therapy – non-radioactive boron ${}^{10}_{5}B$ is administered to a patient, after its uptake by a tumour, it is irradiated by neutrons: ${}^{10}_{5}B + {}^{1}_{0}n \rightarrow {}^{11}_{5}B \rightarrow {}^{7}_{3}Li + {}^{4}_{2}\alpha$



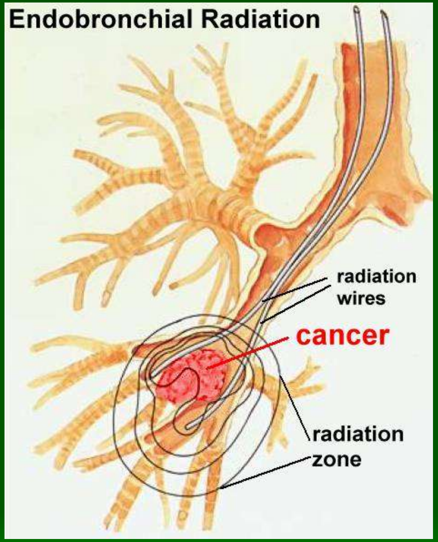
Gamma knife

- = stereotacic radiosurgery
- Specific form of teletherapy used in brain tumours
- A helmet with collimators is surgically attached to the skull
- The patient‘s head enters the radiation unit containing 201 $^{60}_{27}$Co sources with collimated beams
- Focusing prevents the damage of surrounding tissue



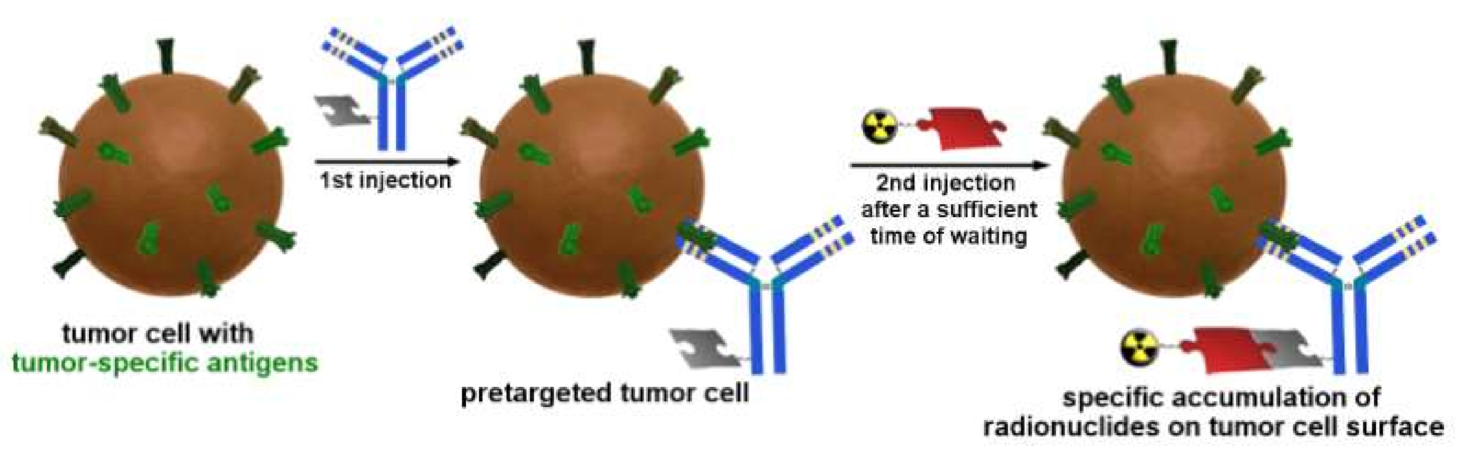
Brachytherapy

- Radiation source (β^-) is inserted locally to the site of tumour
- Advantages compared to teletherapy:
  - Higher dose with lower systemic effects
  - Lower irradiation of the surrounding tissues
- Disadvantages
  - Dose in the target tissue is not homogenous – high dose around the source, risk of insufficient effects at the tumour‘s periphery
- Diffusing α-emitters radiation therapy - radium $^{224}_{88}Ra$



Radiopharmaceuticals

- Are usually administered i.v. and specifically uptaken by tumour cells, which are then destroyed
- Radioiodine $^{131}_{53}I$ – thyroid cancer
- Strontium $^{89}_{38}Sr$, radium $^{223}_{88}Ra$ – bone metastases (they form deposits in the bone)
- Phosphorus $^{32}_{15}P$ (is locally injected into hollow brain tumours)
- Radiolabeled antibodies (e.g. $^{90}_{39}Y$) – targeted against lymphoma cells



Choose an effective teletherapy agent for deeply localized tumors

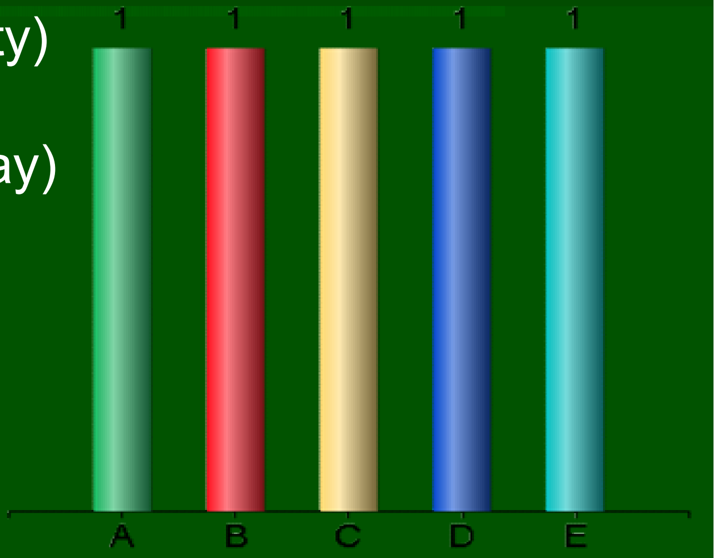
A. Pozitrons (because of their anihilation ability)

B. Muons (because of their spontaneous decay)

C. Electrons (because of the sharp border of ionization area)

✓ D. Protons (because of the Bragg peak)

E. α-particles (because of high kinetic energy)



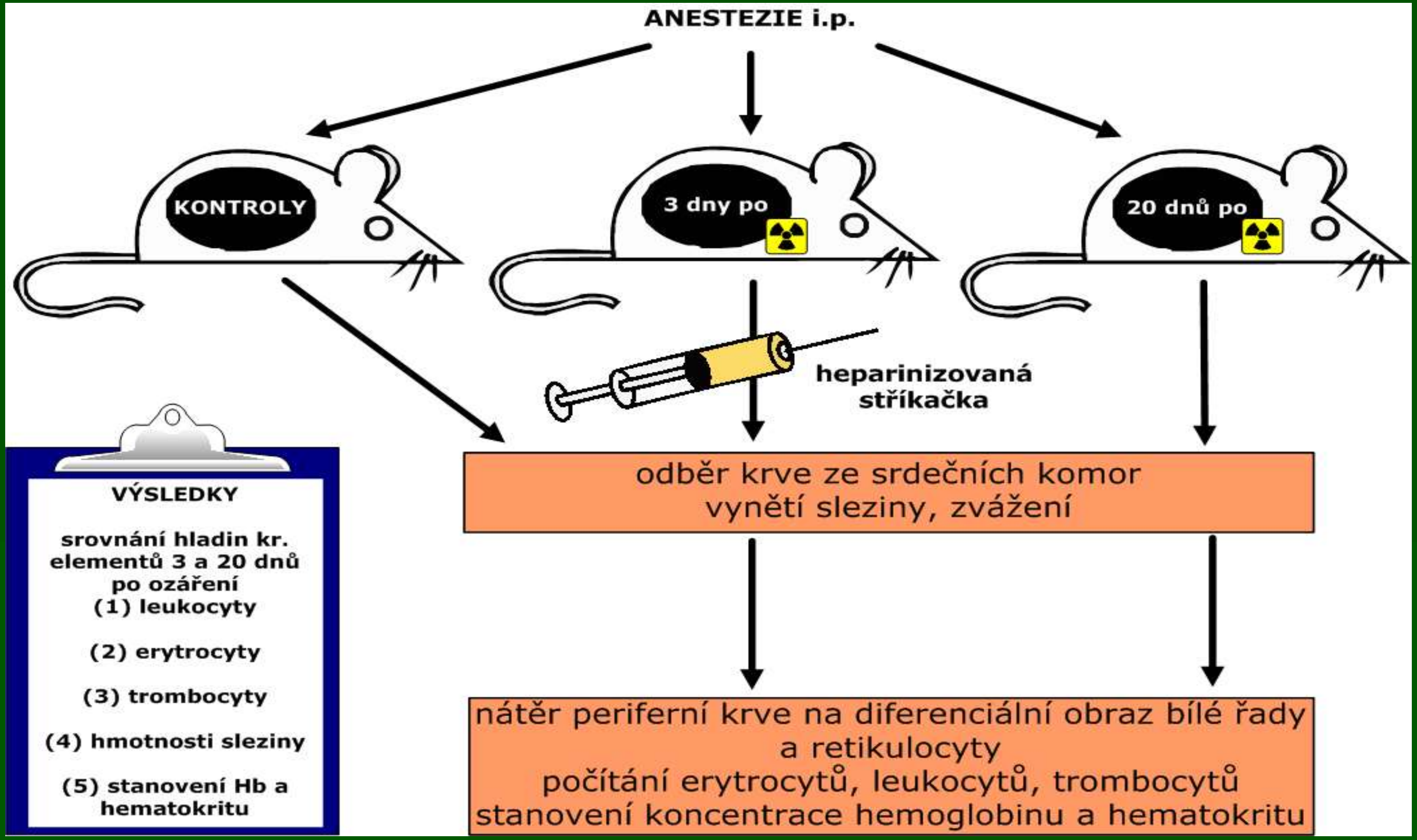
Practical:

Experimentally induced acute radiation syndrome in laboratory animal

Aim of the practical

- to demonstrate the deterministic effects of ionizing radiation on hematological parameters
- to observe the dynamics of peripheral blood count changes resulting from the changes in the blood marrow
- acute radiation syndrome is a model situation, helping us to understand the hematopoiesis

Practical I - design



odběr krve ze srdečních komor
vynětí sleziny, zvážení

nátěr periferní krve na diferenciální obraz bílé řady a retikulocyty
počítání erytrocytů, leukocytů, trombocytů
stanovení koncentrace hemoglobinu a hematokritu

VÝSLEDKY

srovnání hladin kr. elementů 3 a 20 dnů po ozáření
(1) leukocyty

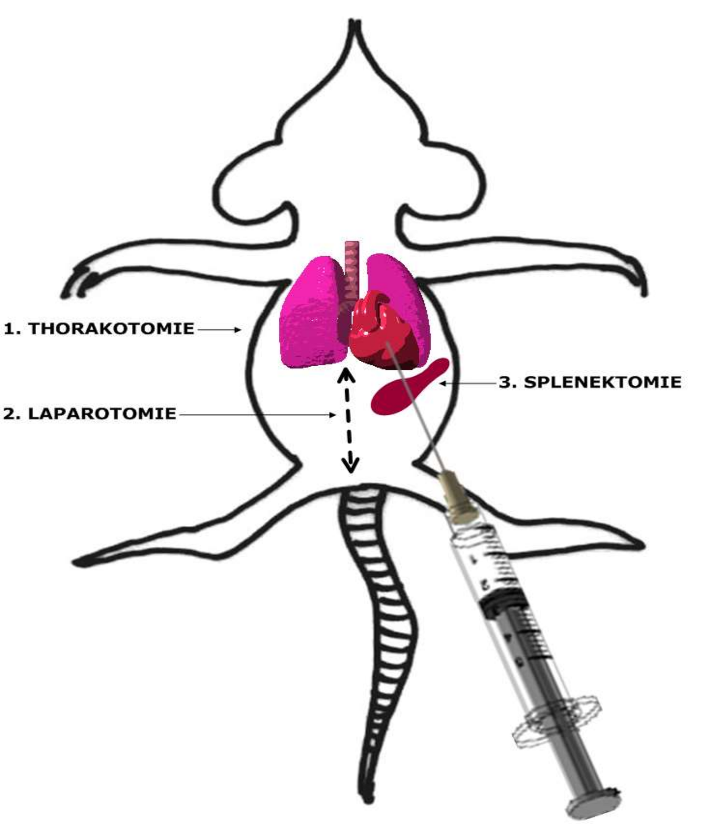
(2) erytrocyty

(3) trombocyty

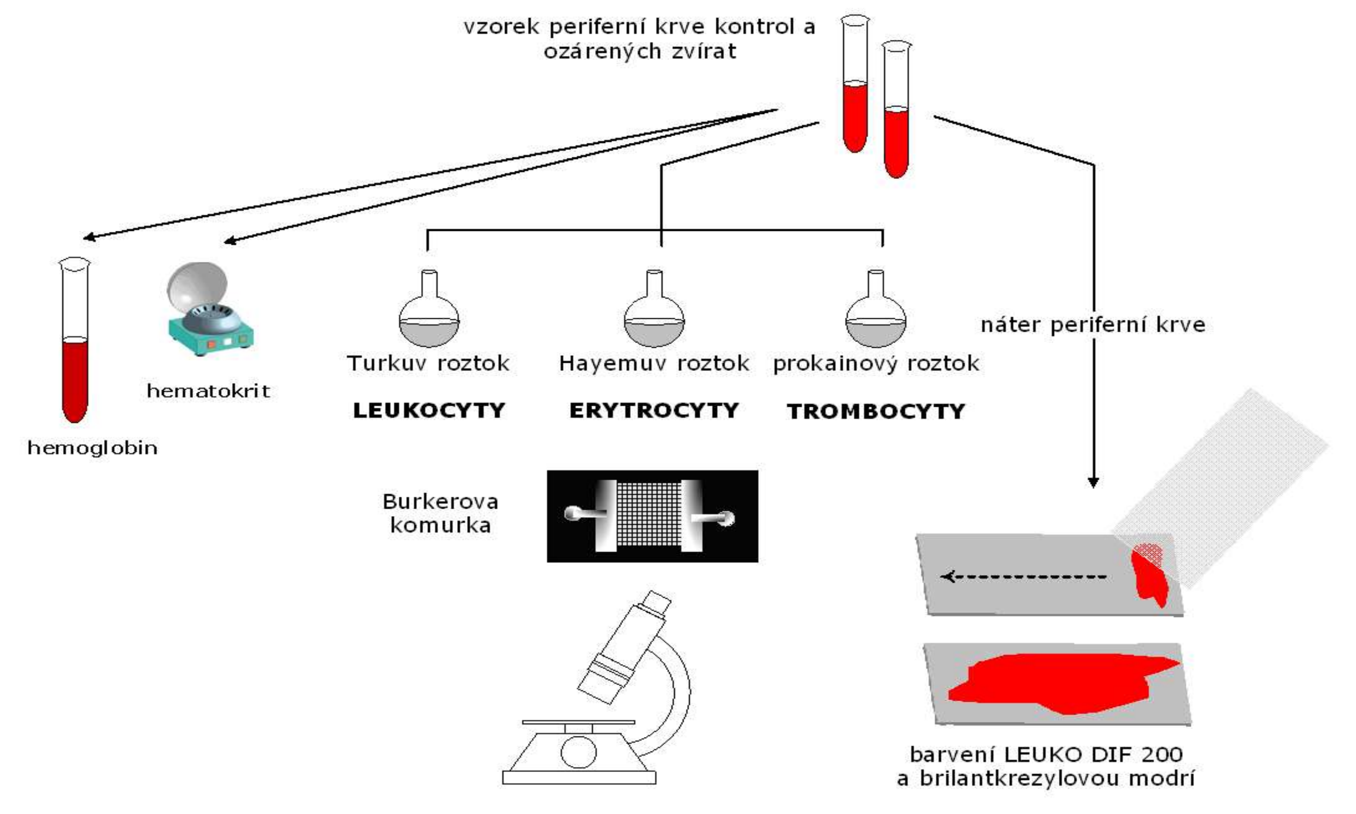
(4) hmotnosti sleziny

(5) stanovení Hb a hematokritu

Practical I – operation



Practical I - evaluation



Effects of ionizing radiation to the blood forming tissue

Practical II – peripheral blood smear evaluation