Biological foundation of radiation protection
Part 1: Acute, deterministic effects on tissue and fetus

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Deterministic effects

- Cells can lose their reproductive capacity (death) from radiation, which can lead to:
  - Disruption of tissue and organs
  - Loss of organ function
  - Damage on fetus
- *Will happen at a relative high radiation dose:* there is a threshold dose where the effect occurs
- The impact can increase with dose, in contrast to stochastic effects (next lecture)
• Useful to see acute deterministic effects in relation with *stem cells*

• (Omnipotent) stem cells is the origin cells which all other cells in an organ, but do not perform tissue specific tasks

• Stem cells divide and give rise new cells which does the tissue specific tasks: *differentiated cells*

• Some tissue types have highly effective stem cells (bone marrow), while other don’t (brain cells)
Stem cells (2)

• Hierarchy of stem cells and differentiated cells

- Stem cell
  - Asymmetrical cell division
    - Maturing partially differentiated cells
    - Maturing partially differentiated cells
- Fully differentiated cells without reproductive capacity. Limited life time

Cell division and differentiation is mostly a result of growth factors

Time, number and differentiation
Stem cells in skin

• Skin:

- Stratum Corneum “Hornlag” (0.01 mm)
- Epidermis “Overhuden” (0.1 mm)
- Melanocytes
- Capillaries
- Dermis “Underhuden” (1 mm)
- Death cells
- Basal layer of stem cells (~5% of total)
  Complete repopulation time: ~5-7 days
- Artery
- Vein
- Connective tissue and fat

• From stem cell to Stratum Corneum: ~21 days

• If the basal layer dies, several weeks will pass before cell death is observed on the skin surface
Radiation induced symptoms, skin

- Development of symptoms after a dose of \(~10\) Gy:
  \(~1\) day: Red skin (erythema) as a result of transient capillary expansion
  \(~14\) day: New skin response, the skin getting thinner as a result of cell death
  \(>21\) day: Dry “deskvaemering” skin lost and dryness from reduced tallow production

  At higher doses \( (>15\) Gy\) can also wet “deskvaemering” occur, skin detach

- If all stem cell die in a large area repopulation is not possible
Stem cells in bone marrow

- Bone marrow (Hematopoietic system) are located inside the “trabekulære” cavities:

- Are mostly located inside the pelvis and vertebral bones in adults
Stem cells in bone marrow (2)

- Just one type of stem cells gives rise to many types of blood cells:
Effects of radiation in bone marrow

- Radiation kills stem cells and spoil the cell division
- The mature processes (differentiation) is affected less
- Survived stem cells start to regenerate bone marrow by symmetrical cell division – no partly differential cells is produced – reduction in blood cell count
- 6 Gy gives ~1% survival: 4-6 weeks to completely regenerate the bone marrow
Quantification and symptoms

- Damage in blood forming tissue can be measured by counting lymphocytes.
- Lymphocytes are highly radiation sensitive + short lived.
- Granulocytes die slowly–has a delayed response of radiation and the minima occur 2-3 weeks after exposure.
- Infections, bleedings and reduced wound healing as a result.
Monitoring of blood cells

Lymphocytes
Gastro-intestinal effects

- Radiation of intestine lead to stem cell death
- Epithelium cells covering the inner of the intestine are in an unpleasant environment – short lifespan
- 5-6 cell divisions from stem cell to fully differenced epithelium cell – takes 4-5 days
- If the epithelium layer disappear nosiness, diarrhea, bleeding and dehydration occur
- Occur typical after 3-7 days
- Relatively high doses necessary ( >7Gy)
- Not to be mix up with late responses (fibroses, etc.)
Effects in central nervous system

- May lead to a sort of inflammation response with fluid assemblage in brain and spinal cord
- Will experience almost instant nosiness and dizziness, breathing problems and heart failure
- Will occur at very high doses (~50 Gy), and death after short time (<1 day)
Effects of radiation in lungs

• Lungs are a complex system of different cell types
• An inflammation (pneumonitt) in a lung can occur after exposition, but uncertain cellular cause
• Doses about 10 Gy cause 50 % probability of severe inflammation with death as result
• Happens very late, 80-180 days after exposition and may not be seen as an acute effect
Effects of radiation in lungs (2)

- Time from exposition to symptom has little dependents of dose
Response functions

- Cell and animal experiments and data from humans have shown that the cumulative probability of tissue function lost follows a sigmoid curve.

Data from mice

- The curve shows a cumulative distribution of radiation sensitivity inside a population.

1000 R = 8.8 Gy
Response functions, example

- Pneumonitis:

Data from radiation therapy
Response functions

- Each individual has a certain response one radiation
- The distribution of radiation sensitivity may be a Gauss-function - \( \mu \) being the mean tolerance dose, while \( \sigma \) is the deviation of this
Response; dose and time

The time denotes the period between radiation and response
LD_{50}

- LD_{50}: dose which with 50% probability is deathly
- Very difficult to define, as treatment will effect the result
- Without treatment LD_{50} will denote a dose equal to 50% bone marrow syndrome (~4-5 Gy)
- With treatment LD_{50} may be 10 Gy
- **Important:** Fractionated doses or low dose rate will increase LD_{50}
Effects in fetus

- The fetus develop trough many steps, in which the radiation sensibility varies
- Expositor in different stages of developing fetus will thereby give different result
- The fetus is much more sensitive to radiation than an adult
- Much information are derived from studies of mice
- A threshold dose of an effect to occur
Fertilized egg (zygote) develop and divide – 128 cells defined as a blastocyst ($2^7$)
The blastocyst embedded in the uterus

“Ability” of organs forms: Starting points of each organ is initiated
Organ development

Growth and maturing – steps from embryo to fetus
Important period of brain development in humans

Fetus stage: 84% of the pregnancy of human, 32% mice
Effects in cell dividing period

- Embryo an assemblage of cells
- Small doses (> 0.05Gy) can give a “all-or-noting” effect: embryo dies or survive
- If survival, no effects is seen on the offspring
- Even if some cells die, the embryo can survive (Pluripotent stem cells)
- Lethal effects can be due to disturbance of the embryo so that it isn’t embedded to the uterus
- Can not rule out other effects (abnormalities), assumedly occurs at high doses (>1 Gy)
Effects in embryonic period

- Smaller litter (in mice) and fetus abnormalities leading to prenatal death; shapeless lumps

Threshold 0.8 Gy
Threshold 1.8 Gy

Effect of different radiation doses on the number of normally developed fetuses per litter in mice after
Irradiation on the 5th day of gestation (×)
Irradiation on the 8th day of gestation (○)
[according to Krieger, Langendorff and Shibata [1962a]]

Complex development of radiation sensitivity
Effects in embryonic period (2)

- Increased deathliness after birth at higher doses (>1Gy)
- Abnormalities; includes anencephaly (lack of brain), exencephaly (enlarged head/brain), spinal bifida (abnormal spine cord)
Effects in embryonic period (3)

- Exencephaly and other abnormalities can occur at doses >0.2Gy (applies to mice, humans have probable a higher value)
- Abnormalities in eyes also possible
- Growth reduction (>0.5Gy)

Data from exposed in Hiroshima and Nagasaki:

Embryonic period is part of 1. trimester
Hiroshima and Nagasaki:

- 62 of 1473 radiated in uterus had reduced head size (criteria: $<\mu - 2\sigma$)
- 26 were mentally retarded (low IQ)
- Dependence of trimester not distinct:

Just one case in 3. trimester
Effects in fetus period

- Growth- and maturing processes, but death and large abnormalities almost absent:

- Doses above 0.5Gy necessary to observe the effect
- Brain most sensitive, as it develop most compare to other organs in this period

Data from mice