Deterministic vs. Stochastic effects

- Deterministic effects:
  - has a threshold of dose
  - severity of the effect is dose-related

- Stochastic effects:
  - probability of an effect increases with dose
  - no dose threshold
  - severity of the effect is not dose related
Stem cells

- Hierarchy of stem cells and differentiated cells

- Skin: ~2Gy, 3w. lost of hair after, but regrowth
  ~5Gy, 1d. red skin, 2w. thin skin, >3 dry
  “derskvamering”
  >15Gy, >3w. wet “derskvamering”
- Bone marrow: ~5 Gy, 50% death after 2-4 week
- Intestinal: >7Gy, epithelium layer disappear,
  nosiness, diarrhea, bleeding and dehydration
- Brain: ~50Gy, death 1. day
- Lungs: ~10Gy, inflammation after 80-180d.
Effects in fetus period

Data from mice

- Brain most sensitive, as it develop most compare to other organs in this period
Biological foundation of radiation protection
Part 2: Stochastic effects

Audun Sanderud

Stochastic effects

- Radiation is proven to have a carcinogen effect, but is less associated to genetic effects
- *Stochastic effects:* A change in cells *can* lead to:
  - Cancer
  - Genetic effects

Can happen independent of dose, but probability increase with dose

- Survivors of Hiroshima and Nagasaki constitute the most important material in the study of this effects
The bombing of H&N

- Population: 330,000 and 250,000
- >100,000 dead immediately from the shock wave of the bombs
- Gamma and neutrons gave the radiation doses to the survivors
- The survivors have amongst other been check for:
  - Cancer and deadliness
  - Genetic effects expressed in the descendants

Cancer

- Complicated diseases which depend on among other things:
  - Age
  - Sex
  - Nutrition
  - Genes
  - Intake of cancer developing substances
- Large differences between Europe and Asia
- Cancer develop through several stages (multi-step process)
• Generation of cancer takes long time – often 20-30 years from starting point to detection (Latency time)
• Exception: f. ex. Leukemia (cancer in the Hamatopoietic system) and Thyroid cancer
• Studies of the cause of cancer depend of nice historical data
• Generally difficult to separate single factors responsible for the disease

Population studies
• Epidemiology most be used in studies of a population
• H & N: f. ex. Cohort studies of cancer frequency

- By comparing the exposed population and the control population risk estimates is composted
• Models of radiation induced cancer (example):

\[
\text{Risk} = \text{Background risk} \times (1 + \text{Excess Relative Risk})
\]
\[
R = R_0 \times (1 + \text{ERR})
\]

↑  ↑  ↑
Dependent on sex, age and radiation dose

\[
\text{ERR} = a \times \text{dose}, \ a = \text{constant}
\]

↑
Additional risk is assumed to increase linearly with the radiation dose

Calculations of radiation dose

- Radiation spectra and strength of the bombs
- Radiation transport in air and attenuation in buildings
- Absorption in organs
Dose and risk

Database of survivors

- City, distance from g.c.
- Position in house or street
- Sex, age, position
- Unattenuated radiation
- Attenuation from house
- Absorption in body
- Dose

RISK

Medical history

Cancer in H & N

<table>
<thead>
<tr>
<th></th>
<th>H&amp;N (1950-1987)</th>
<th>Japan (comparable population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>80114</td>
<td>80114</td>
</tr>
<tr>
<td>Cancer as cause of dead</td>
<td>5859</td>
<td>6343</td>
</tr>
</tbody>
</table>

- The survivors of H&N must be evaluated as a statistical isolated population
- Control is survivors whom was > 2500m from hypocenter during the bomb detonation
  → Excess cancer deaths due to radiation(1950-1990) among the survivors of H&N : 420
Risk of cancer – solid tumours

Exposition

If the x-axis is cigarettes smoked per day, can the y-axis be divided by 1-2

Risk = Background risk \times (1 + ERR(D))

ERR(D) = constant \times D

Cancer risk 2)

- Different types of cancer have different radiation risk factors – ERR

Different types of cancer have different radiation risk factors, with ERR indicating the excess relative risk for each type.
Cancer risk – leukaemia 3)

The influence of age at exposition:

- Breast
- Thyroid
Cancer risk 5)

• Other studies (from therapy and similar) show that the data from H&N are possible overestimating the risk:

Cancer risk – error estimates

• The errors in the risk factors can origin from amongst other things:
  - Errors: in the radiation estimates, cancer frequency and the models from H&N
  - Small verses large doses
  - Dose distributed over a period verses acute radiation
  - Age and sex
  - Joint effects of other factors with radiation
Other studies

- Animal experiments have shown that the cancer risk decreases if the dose gets high enough:

- Radiation induced cancer are therefore seldom seen after cancer therapy

Other studies 2)

- Breast cancer studies:

100 rad = 1 Gy

0.04 Gy < Dose per fluoroscopy < 0.2 Gy
Other studies 3)

- Lung cancer among miners – radon levels:

![Graphs showing excess relative risk vs exposure for different locations.](image)

1 WLM (working level month) 0.05 Sv hmgedose

Genetic effects in offspring

- Search genetic independent distinctions in offspring which origin from (radiation induced) mutations in egg cells and sperm cells
- Mutations are changes in DNA
- Radiation is assumed to increase the frequency of natural mutations (which is low?) – expect also a low frequency of radiation induced mutations
Mendelian genetic on one page

- Humans have about 50,000 pairs of genes and each of these are located in a defined positions (locus) in a defined chromosome.
- Different versions of a gene (at the same locus) is called alleles (f. ex. alleles of blue and brown eyes).
- Dominative alleles: just one is needed to make a distinct feature to occur in the offspring.
- Recessive alleles: need two.
- Sex related recessive: if the X-chrom. mutated, males gets the feature (f. ex. red-green color blindness), while female only if both X mutated.

The mega mouse project

- Millions of mice used to examine genetic effects of radiation.
- Example: Mice with 7 pairs of recessive alleles; give 7 different features (6 give special colors, 1 short ears).
- Normal mice is radiated and matted with mice’s with such recessive alleles:

\[
\begin{array}{c}
\text{Normal mouse with two normal alleles} \\
\text{Recessive mouse} \\
\text{Radiation induced mutation in radiated normal mouse} \\
\text{Some of the offspring gets radiation f. ex. short ears}
\end{array}
\]

\[
\begin{array}{c}
\frac{N}{N} \times \frac{R}{R} = \frac{N}{N} \quad \text{If no mutations: Normal mouse, Offspring always normal}
\end{array}
\]

\[
\begin{array}{c}
\frac{R}{R} \times \frac{R}{R} = \frac{R}{N} \quad \text{If mutations: Radiation induced mutation in radiated normal mouse, Some of the offspring gets radiation f. ex. short ears}
\end{array}
\]
The mega mouse project 2)

- Important: *at which period in the generation of sperm or egg cells the exposition occur.*
- Male: continues spermatogenesis; 40/70 days (mice and men) to generate sperm cells
- Female: egg cells ready before birth; only matures
- If mice is radiated and mutations in sperm cells (spermatogenesis) is to be examined, most at leased wait for 40 days

The mega mouse project 3)

- The number of mutations observed in offspring increase almost linearly with dose, but at high doses the mutation rate decrease
- Reduction of the effect at low dose rate – indicate repair
- Dose Rate Effectiveness Factor - DREF
The mega mouse project 4)

- Matured sperm cells are more radiation sensitive (concerning mutations) than in spermatogenesis
- Egg cells not as sensitive to mutations
- Dominant mutations have also been examined:
  - Abnormalities in skeleton
  - Cataract (unclear eyes)
- Problem: the number of genes contributing to these effects are not known

Offspring off H & N

- Offspring (over 30,000) have been examined among other things for:
  - Natal mortality (< 2 weeks) and abnormalities (Untoward Pregnancy Outcome, UPO)
  - Mortality (from 2 weeks and 26 years of age)
  - Protein mutations
  - Cancer
  - XY-aneuploidi (f. ex. XXY)
- Problem: effect depends probably not of mutations in only one gene, but are multifactor effects
Offspring off H & N 2)

• The studies show a doubling dose about 2 Gy:

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency/dose(%/Sv)</th>
<th>Natural frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPO</td>
<td>0.264 (±0.277)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0.076 (±0.154)</td>
<td>0.330-0.530</td>
</tr>
<tr>
<td>Protein mutations</td>
<td>0.001 (±0.001)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>(-0.008) (±0.028)</td>
<td>0.002-0.005</td>
</tr>
<tr>
<td>XY aneuploidi</td>
<td>0.044 (±0.069)</td>
<td>0.030</td>
</tr>
<tr>
<td>Total</td>
<td>0.375</td>
<td>0.632-0.835</td>
</tr>
</tbody>
</table>

• Radiation is a weak mutagen