MPHY3892 Radiobiology

Lecture 6

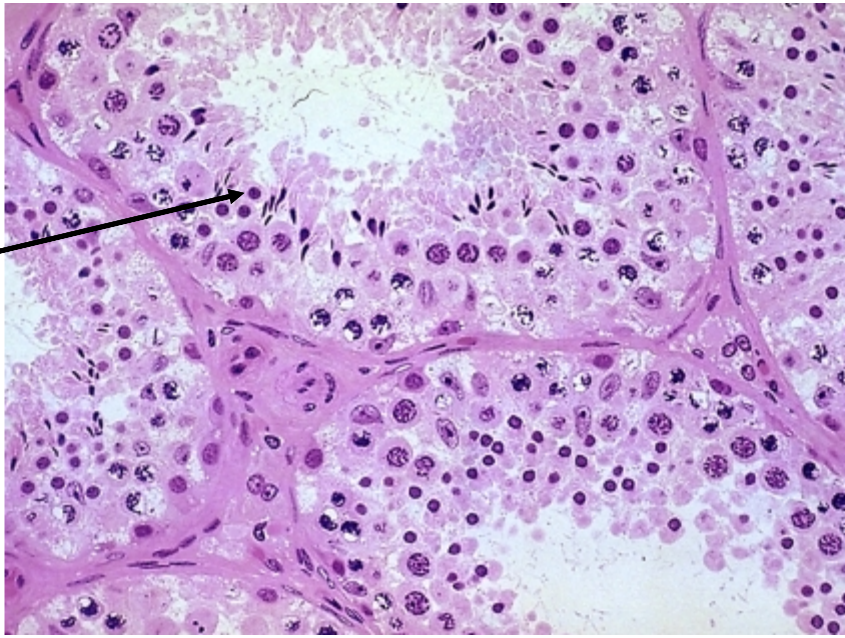
Genetic Effects of Ionising Radiation.

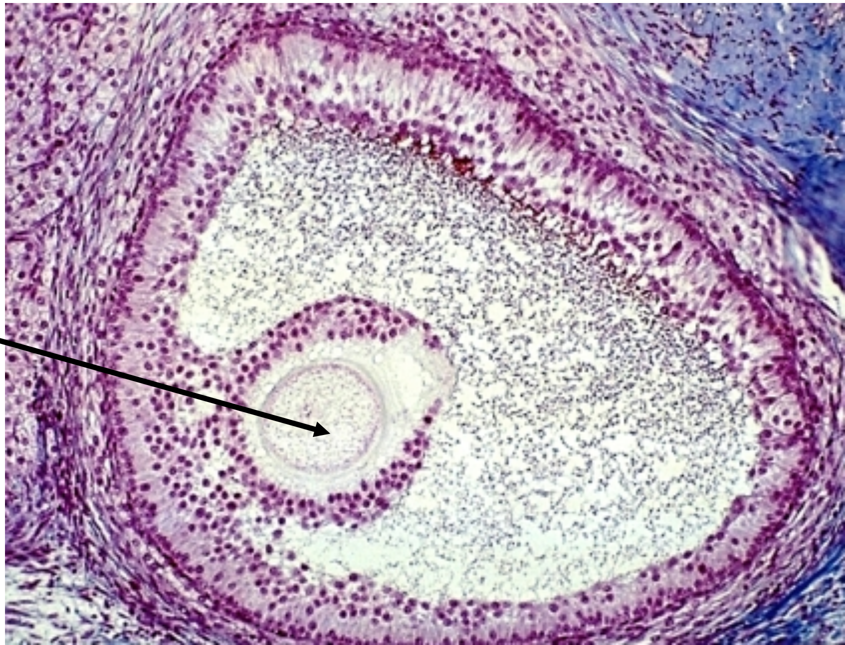
Natural Background Radiation.

Radiation Quantities.

Genetic Effects of Radiation

- Hereditary effects - result of lesions in the germinal cells
- In male mammals
  - dividing stem-cell spermatogonia constitute a permanent stem-cell population
  - continues to multiply throughout the reproductive lifespan of individual
- Female mammals
  - are born with a finite number of oocytes which are arrested in meiosis from prenatal life
  - shortly before ovulation these oocytes have to complete meiotic divisions





Genetic Effects of Radiation

- Mutability of germinal cells of the male is about 5 times greater than that of a female
- In female there are two periods which are sensitive to mutagenesis:
  - short period during fetal life before the seventh month
  - period of reproductive life after puberty
- In men spermatogonia is radiosensitive after puberty
- Mutants produced by man-made radiations cannot be recognised or identified as different, compared with natural spontaneous type

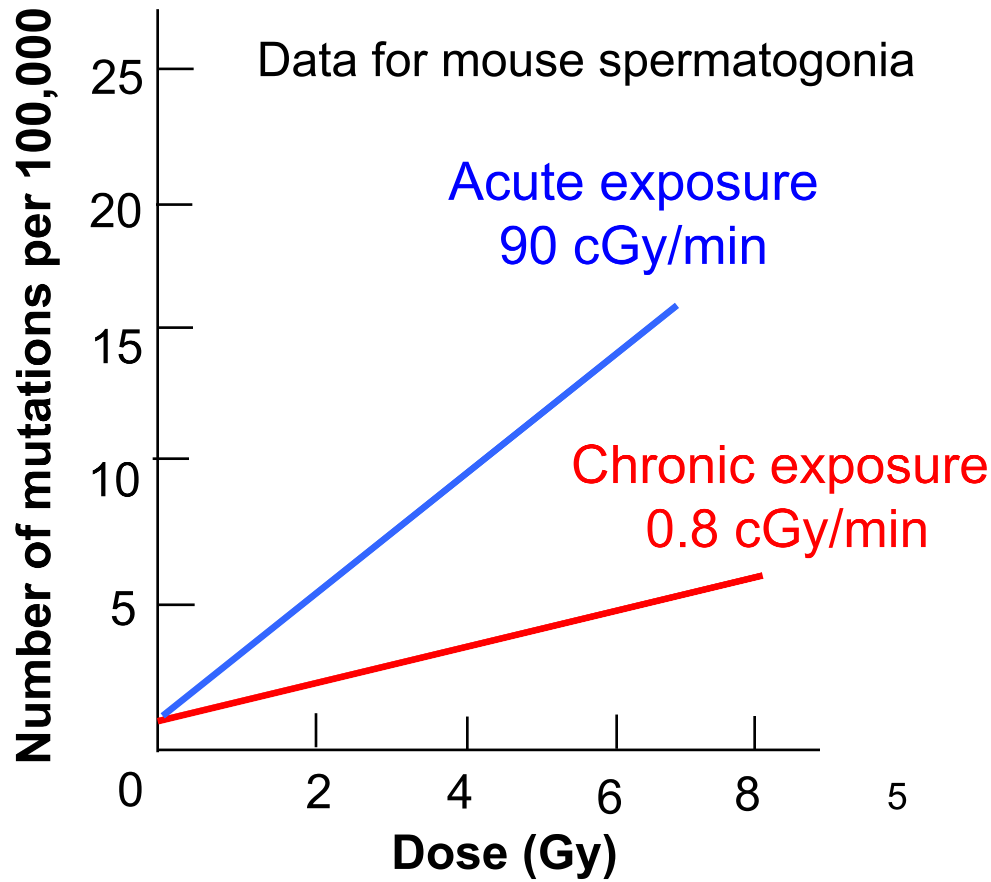
Studies of Genetic Mutations in Mice: "Megamouse" Project (1947-1967)

- 7 million mice (about 1000 mice per day for 20 years!) were irradiated at Oak Ridge National Laboratory (USA) with a range of doses and dose rates
- Six specific mutations involving change of coat colour and one mutation involving the shape of the ear were followed
- These mutations occur spontaneously, but their incidence can be increased by radiation

Examples of 3 studied mutations involving change of coat colour in mice

Megamouse Project: Conclusions

- In mammals males are much more radiosensitive to genetic effects than females, particularly at low dose rate $\Rightarrow$ almost all radiation-induced genetic burden in a population is carried by the males
- The number of mutations is proportional to the dose
- Spreading radiation over a period of time results in fewer mutations.
- Genetic consequences of a given dose can be greatly reduced if a time interval (at least 6 months for humans) is allowed between irradiation and conception



Other Studies of Genetic Mutations in Mice

- 80 generations of mice were exposed at the rate of 2 Gy per generation
  - No detectable changes to viability and fertility of their descendants were observed
  - But impairment of intellectual capacity cannot be demonstrated in studies in mice
- Estimate of the first-generation incidence of mutations from mouse skeletal deformities (Oak Ridge National Laboratory, USA)
  - 37 skeletal abnormalities (including an extra rib) resulting from mutations were studied

Other Studies of Genetic Mutations in Mice

- Study of radiation-induced dominant mutations producing cataracts in mice
- Data on mice living close to the damaged Chernobyl nuclear reactor for many generations since 1986. They have the highest levels of radioactivity recorded in the bodies of animals outside a scientific laboratory

Mice living at Chernobyl reactor

Epidemiological Studies of Genetic Effect

- Little information to directly estimate the genetic risk in man
- Studies of descendants of subjects irradiated at Hiroshima and Nagasaki:
  - Parents of children studied came from low-dose (0.01-0.09Gy) and high-dose (>1Gy) groups
  - NO statistically significant evidence of genetic effects:
    - frequency of birth defects
    - characteristics of blood proteins
    - activity of erythrocyte enzymes
    - morphology and life expectancy

  in comparison with children of non-irradiated control group
  - This absence of any detectable effect can be only explained if mutagenic effect is at least 4 times lower in man than in mouse

Epidemiological Studies of Genetic Effect

- Surveys of descendants of patients treated by radiotherapy have revealed NO increase in frequency of congenital defects.
- However:
  - epidemiological surveys are of limited precision
  - there is lack of understanding of the genetics of pathology
- Therefore
  - experts are continuing to extrapolate genetic effect from animal experiments in a deliberately pessimistic way
  - estimation of genetic risk in humans is based on animal data

Mutated Genes

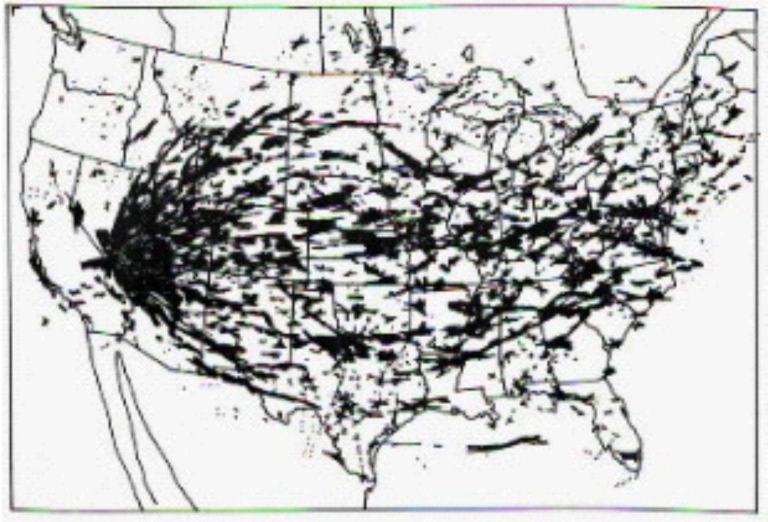
- In a human cell each gene is double: one from the paternal chromosome, the other from maternal chromosome
- If they are identical, they are called homozygotes, if not heterozygotes
- A heterozygotic gene is effective in the first generation only if it is dominant
- Usually a mutated gene is recessive and is not immediately manifest. It must be inherited from each parent $\Rightarrow$ many generations may pass before it is expressed

Dose to the Whole Population

A recessive gene becomes diluted in the genome of the population:

- Normally in this genome there are a large number of recessive genes resulting from spontaneous mutations
- It is necessary to consider the population dose
- <u>Population dose</u> is the sum of the doses received by the gonads of all the individuals composing the population
- However, irradiation of 60% of subjects of all ages will have no genetic consequence as these individuals will bear no more children

Dose to the Whole Population

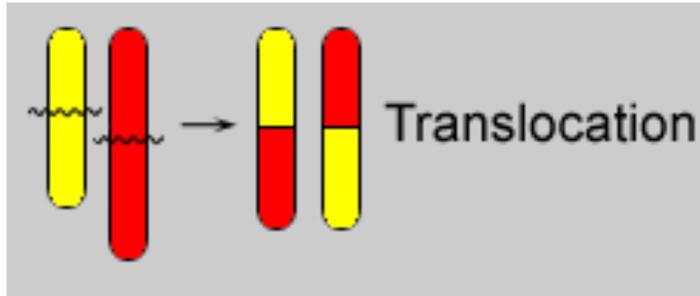


Areas crossed by nuclear clouds from Nevada atomic bomb testing in 1950-s

Nevada nuclear field exercises with troops ← (1952)

The glow of atomic bomb test (1953) in Nevada as seen from Las Vegas →

Chromosome Abnormalities



- In normal population, chromosomal abnormalities are associated with at least 40% of the spontaneous abortions that occur from the 5th to the 28th week of gestation and with about 6% of stillbirths
- Chromosome translocation (exchange of parts between two or more chromosomes without loss of genes) is an example of recessive mutation. When it is expressed and it does not cause the death of the embryo, it typically leads to physical abnormalities and mental deficiency
- This kind of chromosome error is not strongly influenced by radiation, particularly at low doses

Methods of Assessing Genetic Effects: Doubling Dose Method

- Doubling dose method - expresses the risk in relation to natural prevalence of genetic diseases in the general population
- The doubling dose is the amount of radiation necessary to produce as many mutations as those occurring spontaneously in a generation
- A doubling dose of 1Gy for low dose-rate exposure was adopted in 1962 in the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) report
- This value of doubling dose is still used although the lack of detectable effect in the descendants of the population of Hiroshima and Nagasaki suggests that it must be much higher

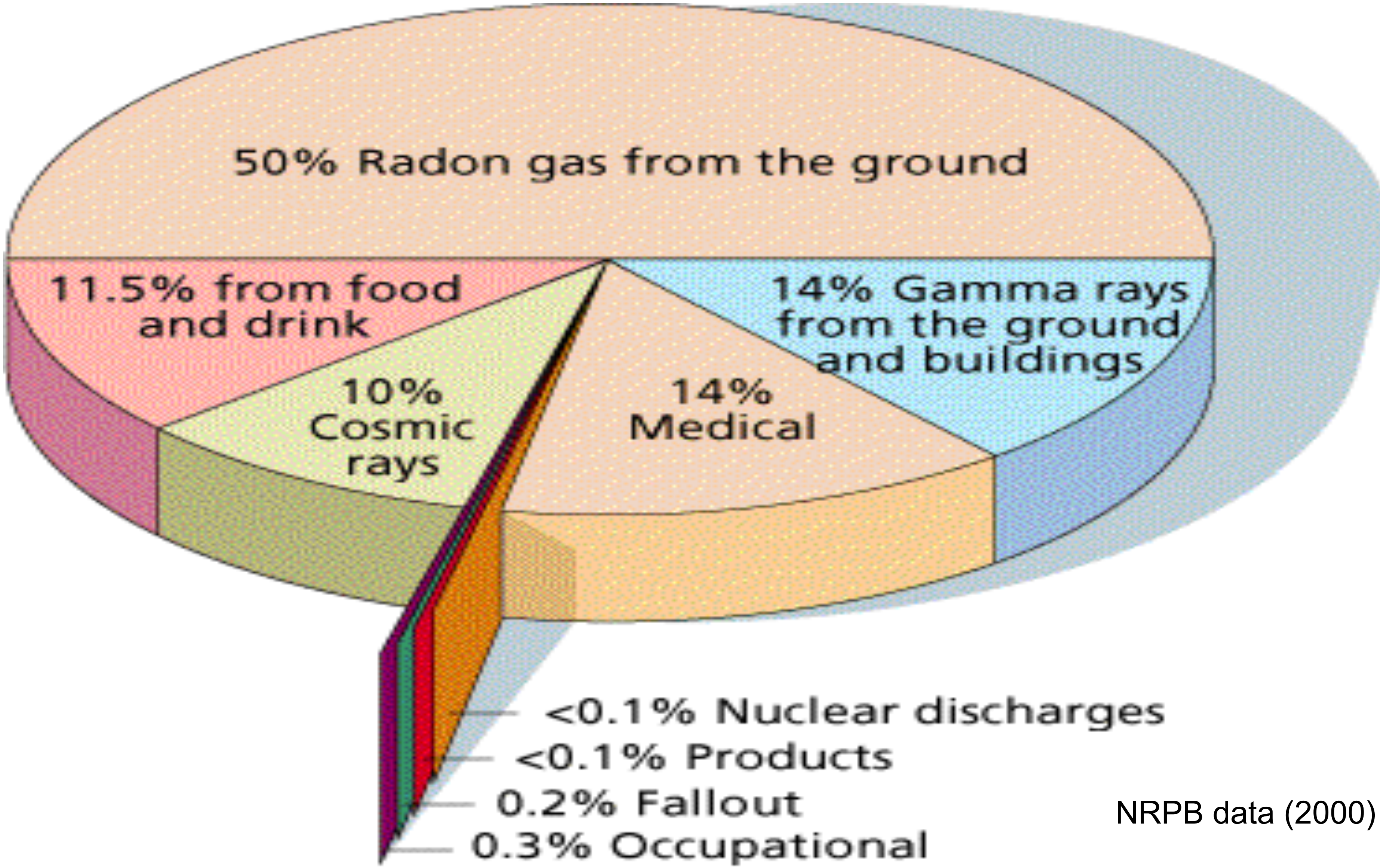
Genetic Effects: Conclusions

- Most of the embryos carrying serious genetic defects are eliminated at the beginning of pregnancy
- The probability of serious hereditary disorders in all future generations due to radiation exposure is about 10 times less than probability of fatal cancer for the same dose of irradiation
- The number of mutations produced is proportional to the dose
- It is safer to evaluate the risk with a pessimistic hypothesis

Natural Background Radiation

- Ionising radiation is naturally present in the environment
- We are all constantly exposed to a certain level of natural background radiation
- Natural background radiation has great variations in different regions
- Average dose for the UK population (mainly from natural background radiation) is **2.6 mSv per year**

Average Exposure to Ionising Radiation in the UK



NRPB data (2000)

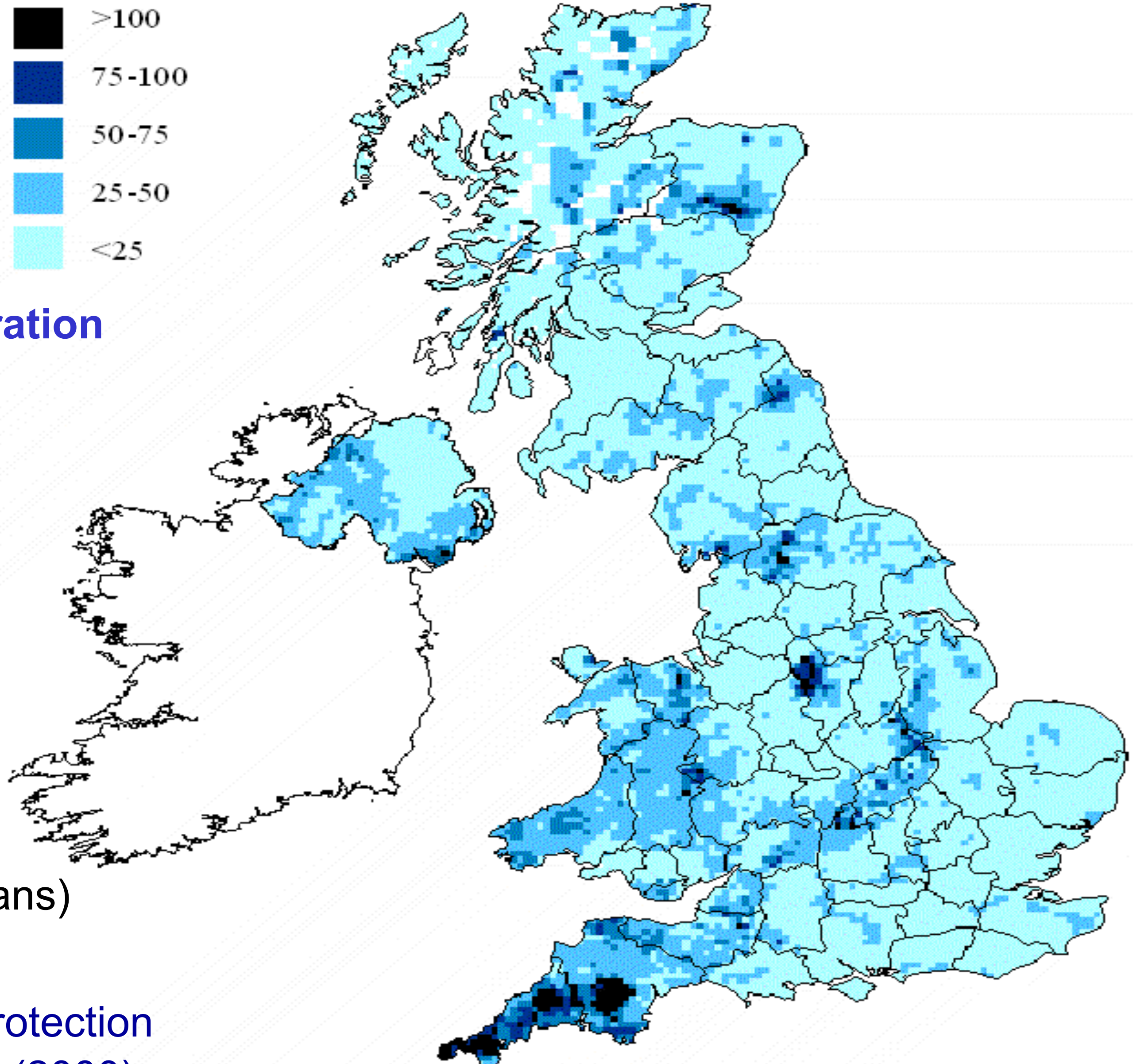
Natural Background Radiation

Naturally occurring radioactive minerals in the environment:

- Uranium ^{238}U ($T_{1/2} = 4.5 \cdot 10^9$ years), Thorium ^{232}Th ($T_{1/2} = 1.4 \cdot 10^{10}$ years) and Uranium ^{235}U ($T_{1/2} = 7 \cdot 10^8$ years) radioactive decay series
- Main contribution - from radioactive Radon gas (^{222}Rn) that is part of ^{238}U series and is formed by the decay of Radium ^{226}Ra. Radon has half-life 3.8 days and emits 5.5 MeV α-particles. When breathed, it causes damage to lungs. Most important of isotopes formed in Radon decay series are α-emitters Polonium ^{214}Po and ^{218}Po

Map of Indoor Levels of Radon in the UK

Average indoor Radon levels (Bq/m^3)



1 Bq is 1 disintegration per second

Action Radon level in the UK is 200 Bq/m^3, above which householder is advised to take remedial measures (e.g. install extractor fans)

National Radiation Protection Board (NRPB) data (2000)

Natural Background Radiation

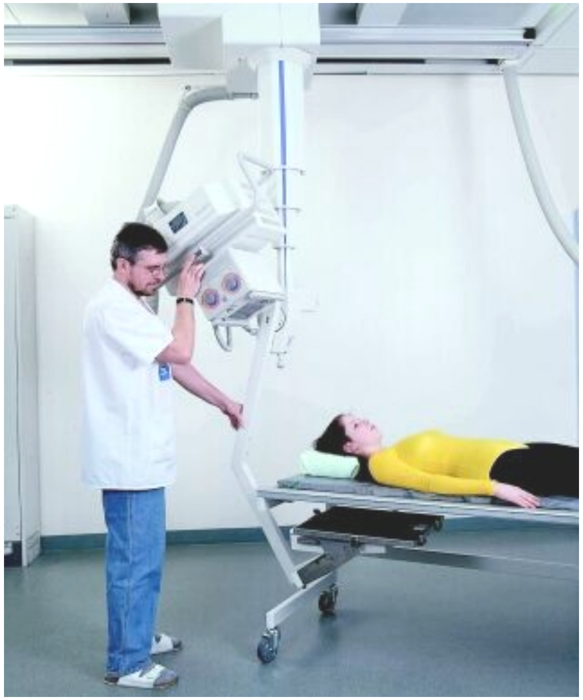
Radioactive materials in our food and drink. The main isotopes are:

- Potassium ^{40}K ($T_{1/2} = 1.25 \cdot 10^9$ years), β-emitter, decays to stable Argon ^{40}Ar. Human body contains about 0.03g of ^{40}K
- Carbon ^{14}C ($T_{1/2} = 5570$ years), β-emitter. Levels of ^{14}C are constantly renewed in the atmosphere by nuclear transformation of Nitrogen ^{14}N induced by cosmic bombardment

Risks of Radiation Exposures

Radiation doses are often compared to equivalent time of exposure to natural background radiation:

X-ray examination	Equivalent period of natural background radiation
Chest	3 days
Hip	7 weeks
Abdomen	4 months
Barium enema	3.2 years
CT abdomen	4.5 years

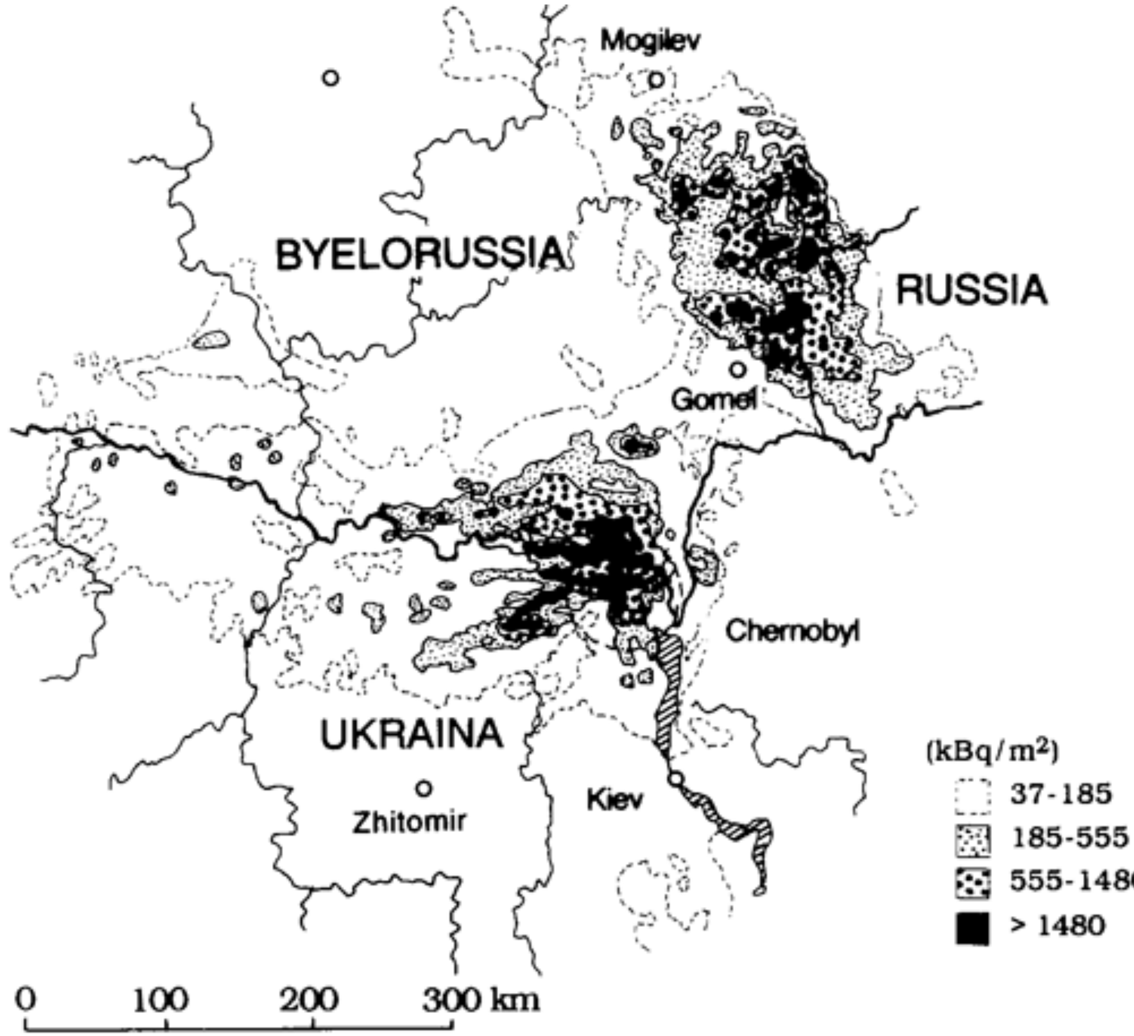


Chernobyl: Casualties

- 30 people were killed, including 28 from radiation exposure
- 134 people had acute radiation poisoning
- Nobody off-site suffered from acute radiation effects
- About 200,000 people ("liquidators") were involved in the recovery and clean up of the site:
  - they received doses around 100 mGy
  - some 20,000 of them received doses about 250-500 mGy (risk of fatal cancer up to 3%)

Chernobyl: Contamination Maps

- Vast surrounding areas were contaminated with Iodine ^{131}I and Caesium ^{137}Cs
- Contamination maps for ^{131}I are based on ^{137}Cs contamination maps which is debatable



^{137}Cs contamination map for Chernobyl accident

Chernobyl: Evacuation

- 340,000 people were evacuated from heavily contaminated zones. Each of them:
  - received external radiation doses averaging 20 mGy with a maximum of 380 mGy
  - also received internal contamination doses averaging 10 mGy
- 7 million people are still living in the areas contaminated by ^{137}Cs ($T_{1/2}$ = 30 years)
  - they presently receive various doses (ranging from 1 to 40 mGy/year) depending on soil contamination

Chernobyl: Thyroid Cancer in Children

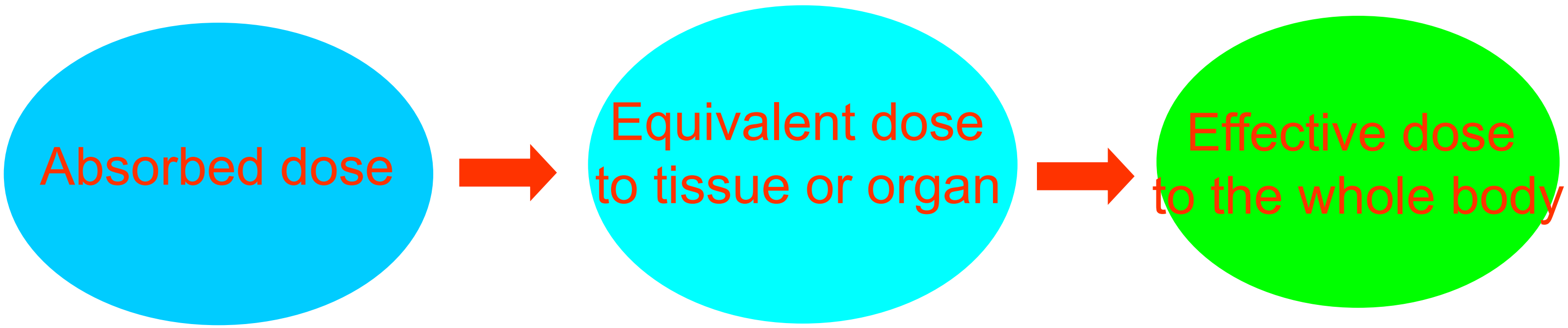
Thyroid monitoring

- 270,000 children were exposed:
  - 17,000 children received a thyroid dose from radioiodine greater than 1Gy
  - 6,000 greater than 2Gy
  - 500 greater than 10Gy
- A rising incidence of thyroid cancer in children:
  - 2000 cases of thyroid cancer are considered to be radiation induced
  - among these 10 deaths can <u>possibly</u> be attributed to radiation
  - these cancers are the least serious kind of thyroid cancer with a recovery rate of 95% after an early and appropriate treatment

Chernobyl: Conclusions

- Doses to the different organs are very poorly known for Chernobyl accident
- Apart from thyroid cancer in children, there is NO evidence of a major public health impact attributable to radiation
- NO statistically significant increase in: leukaemia, cancers other than thyroid cancer in children, congenital abnormalities, adverse pregnancy outcomes
- A study of the dose-effect relationship in “liquidators” shows that the risk of thyroid cancer decreases when the dose to the thyroid increases

Radiation Quantities



Absorbed Dose (D)

- Energy imparted by ionising radiation per unit mass of matter
- Units: $J \cdot kg^{-1}$
- Special Name: Gray (Gy)

Equivalent Dose to Tissue or Organ (H_t)

- Absorbed dose to tissue or organ weighted for harmfulness of different radiations
- SI Unit: $J \cdot kg^{-1}$
- Name: Sievert (Sv)

$$H_t = \sum_R W_R \cdot D_{tR}$$

- D_{tR} is the average absorbed dose to tissue or organ t from radiation R
- W_R is a radiation weighting factor reflecting the probability of detriment arising from radiation R

Radiation Weighting Factors w_R

Type & energy range		$\mathbf{w_R}$
Photons, all energies		1
Electrons, all energies		1
Neutrons, energy	< 10keV	5
	10keV-100keV	10
	>100keV-2MeV	20
	>2MeV-20MeV	10
	>20MeV	5
Protons (other than recoil)		
	energy >2MeV	5
Alpha-particles, fission fragments,		
	heavy nuclei	20

ICRP data, 2007

Effective Dose to the Whole Body (E)

- Equivalent dose weighted for susceptibility to harm of different tissues
- The sum of equivalent doses in all tissues and organs of the body weighted according to the relative detriment associated with the irradiation of that organ or tissue
- Name: Sievert (Sv)

$$E = \sum_t W_t \cdot H_t$$

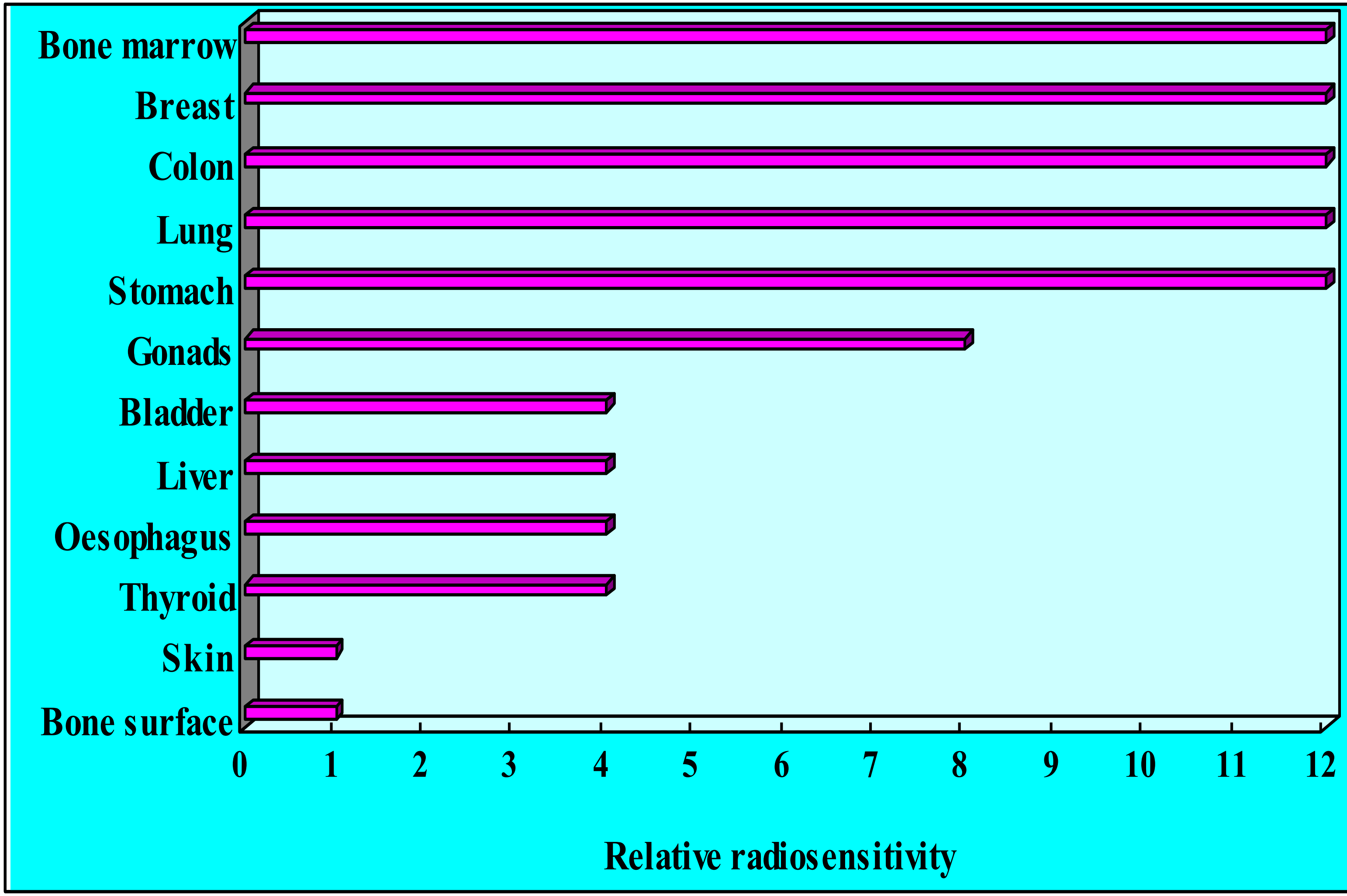
- $\mathbf{W_t}$ are tissue weighting factors reflecting radiosensitivity of different tissues **t** of the body
- $\mathbf{H_t}$ is equivalent dose to tissue **t**

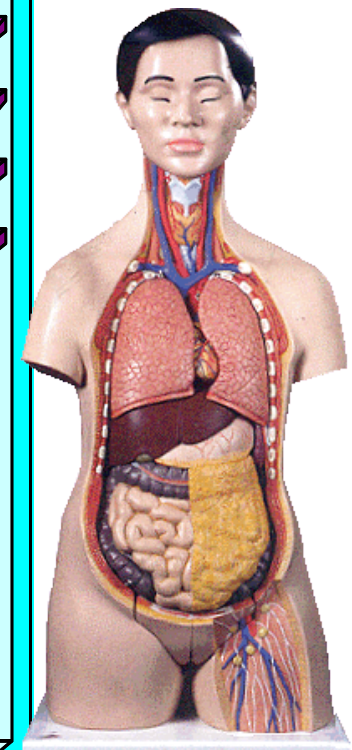
Tissue Weighting Factors W_T

Tissue or organ	$\mathbf{w_T}$
Bone Marrow (red)	0.12
Colon	0.12
Lung	0.12
Stomach	0.12
Breast	0.12
Gonads	0.08
Bladder	0.04
Liver	0.04
Oesophagus	0.04
Thyroid	0.04
Skin	0.01
Bone Surface	0.01
Brain	0.01
Salivary Glands	0.01
Remainder	0.12

ICRP data, 2007

Radiosensitivity of Organs





ICRP data, 2007