MPHY3892 Radiobiology

Lecture 5

Effects of Radiation on Tumours. Radiation Carcinogenesis.

Effects of Radiation on Tumours

- We need the balance between killing tumour cells and creating complications in surrounding tissues
- The only important tumour cells are clonogenic tumour cells which are able to multiply indefinitely
- Tumour control is achieved if all clonogenic tumour cells are killed
- In human tumours, the proportion of clonogenic cells varies between 0.01% and 1%

Tumour Control

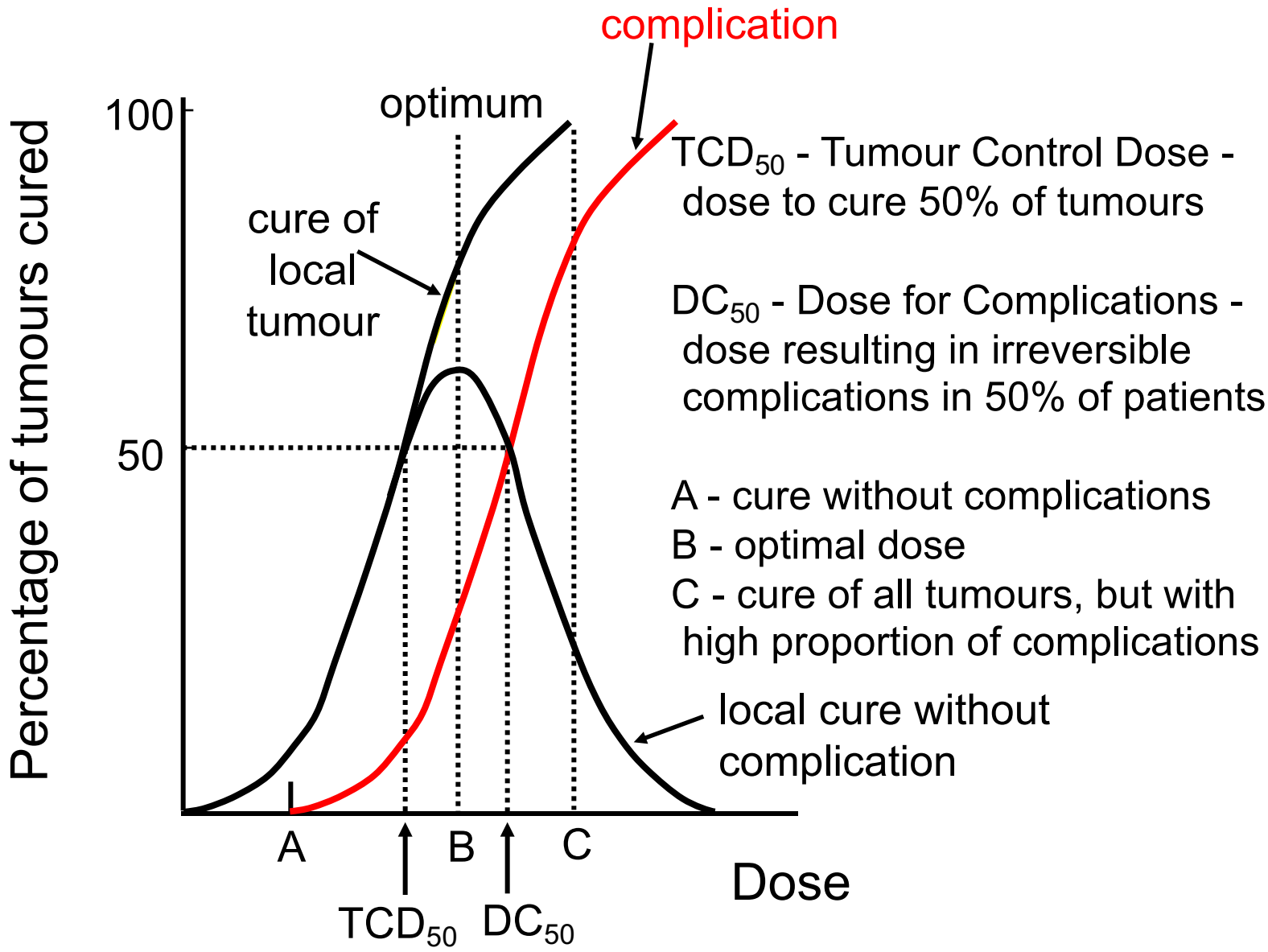
Probability of controlling the tumour depends on:

- number of clonogenic cells
- total dose D in N fractions of radiation
- proportion of cells surviving each fraction of radiation
  - radiosensitivity of clonogenic tumour cells
  - proliferation rate between the end of one irradiation session and the beginning of the next session

Example:

- A tumour of 100 g containing 10^{11} cells, of which 1% are clonogenic, contains 10^{9} clonogenic cells
- Assume that surviving fraction after each dose of radiation (2 Gy) amounts to 50%
- After 30 fractions (or total dose of 60 Gy) the proportion of surviving cells will be $0.5^{30} \approx 10^{-9} \Rightarrow$ there will remain on average one surviving clonogenic cell in the tumour

Tumour Control



TCD_{50} - Tumour Control Dose - dose to cure 50% of tumours

DC_{50} - Dose for Complications - dose resulting in irreversible complications in 50% of patients

A - cure without complications
B - optimal dose
C - cure of all tumours, but with high proportion of complications

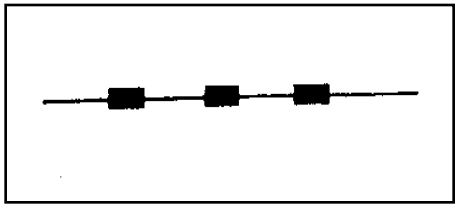
Tumour Control

- The severity of complications can be reduced by means of good technique and care of the patients
- Mean value of Dose for irreversible Complications DC_{50} for fractional treatment with x-rays = 68 Gy
- Mean value of Tumour Control Dose TCD_{50} = 62 Gy
- The difference DC_{50} - TCD_{50} varies with the type of cancer

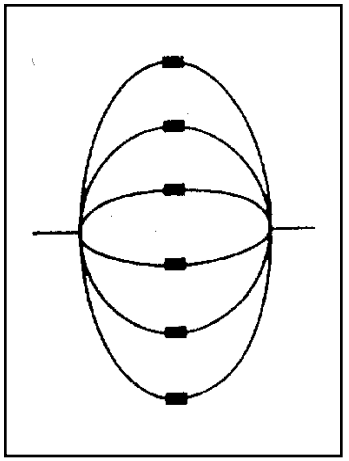
} for a large variety of cancers

Complications

- In serial organs (spinal cord, intestine, large arteries), a small volume irradiated above threshold may cause major incapacity, for example paralysis
- In organs arranged in parallel (e.g. lung and liver), the severity is related to the tissue volume irradiated above threshold



Organs with serial arrangement (for example, spinal cord)



Organs with parallel arrangement (for example, liver)

Tumour Control

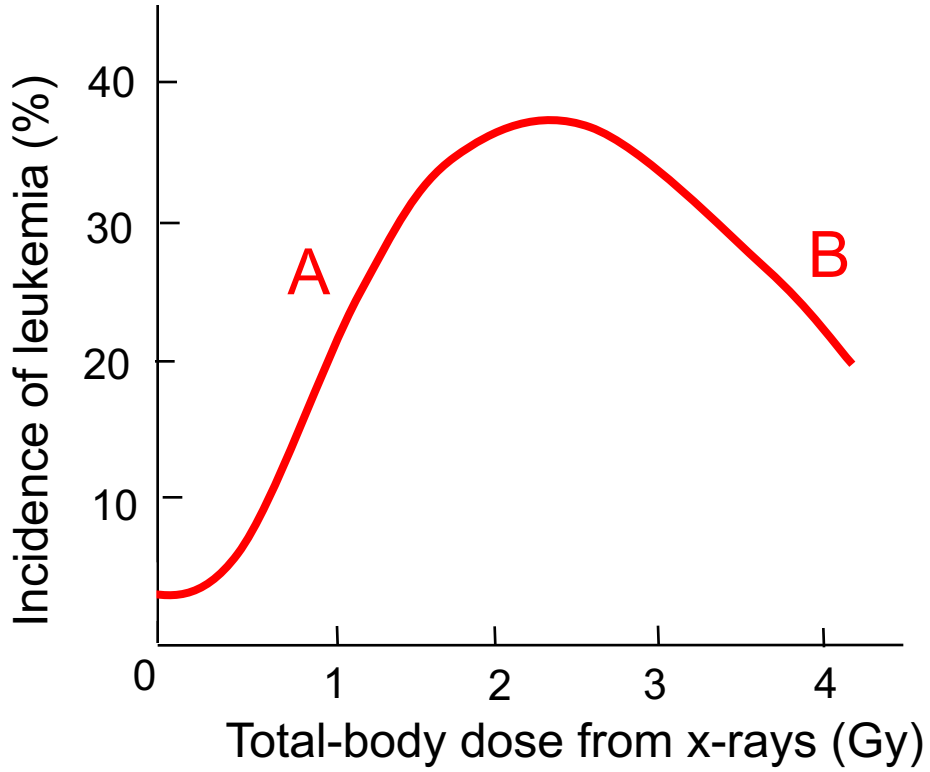
- Large tumours are harder to cure than small ones as cure depends on a number of surviving cells, not on Surviving Fraction
- Must therefore use higher doses for larger tumours
- There is also better repair of potentially lethal damage in large tumours due to hypoxia and tumour heterogeneity (with the presence of cell lines of decreased radiosensitivity)
- Birth rate of malignant cells can increase after radiation (recruitment of G_0 cells) $\Rightarrow$ failure of radiotherapy??

Radiation Carcinogenesis

Sources of information on carcinogenesis

- *in-vitro* cell studies
- animal experiments
- epidemiological studies in man

Laboratory Animal Experiments



Data for male mice

Presence of two phenomena:

A - dose-related increase of the proportion of normal cells that are transformed into malignant cells

B - dose-related decrease of probability that such cells may survive the radiation exposure ⇒ the fraction of transformed cells is reduced exponentially at high doses

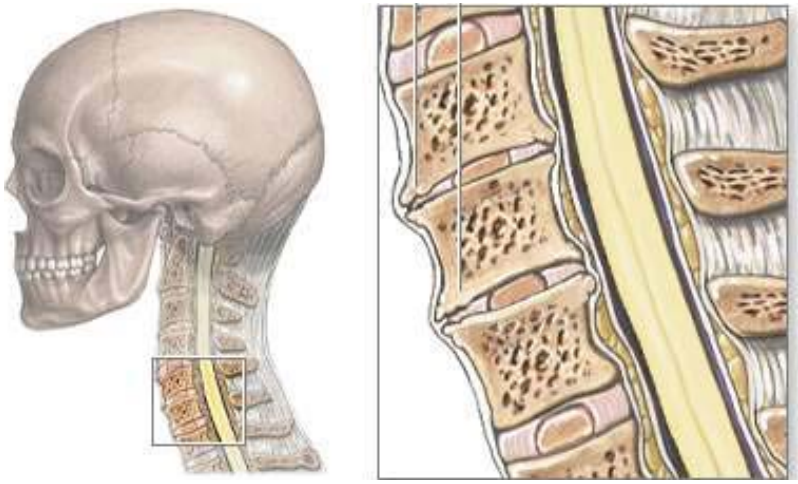
Epidemiology

Main sources of data are:

- Patients irradiated for medical reasons
- Survivors of Hiroshima and Nagasaki atomic bombing
- Occupationally exposed workers

Ankylosing Spondylitis Patients

- Ankylosing spondylitis is a disease characterised by inflammation and immobility of a part of spinal column, causing severe pains
- 14,000 sufferers in Britain between 1933 and 1954 were given radiotherapy to various regions of their spine to relieve pain
- These patients were followed thereafter
- Total bone marrow dose 2 - 6 Gy

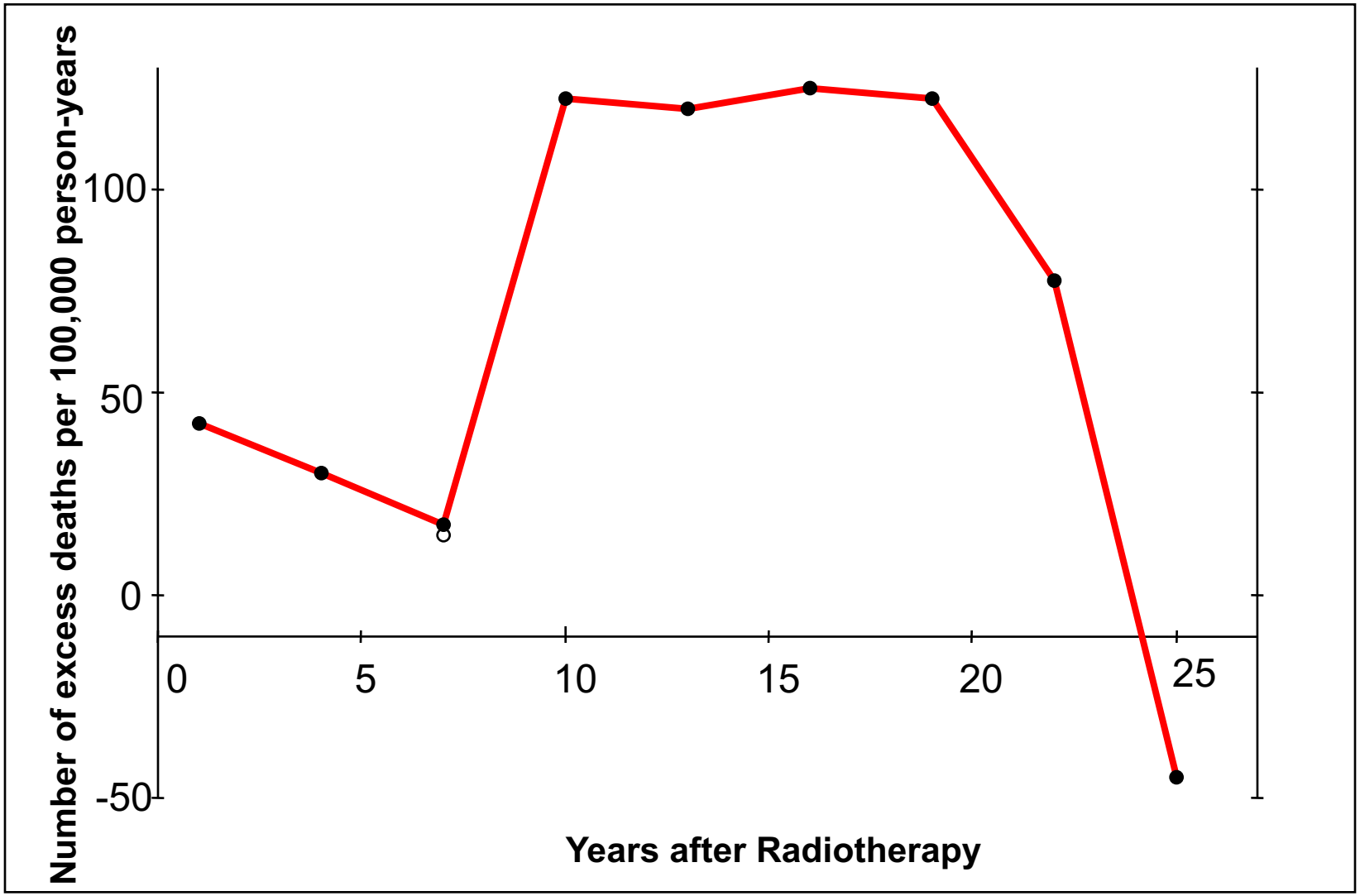


Servical spodylitis

Ankylosing Spondylitis Patients

- Overall leukaemia incidence increased 3 times
- Leukaemia peaked 3 - 5 years post-irradiation
- Approximately 2 cases of leukaemia per 1000 for a dose of 3 Gy to the whole spine
- Proportional increase of solid tumours peaked at 10 -12 years post irradiation then declined
- Risk of cancer of oesophagus was significantly raised
- This study is not ideal because:
  - it lacks a proper control group consisting of patients with the same disease who did not receive x-ray therapy, but whose treatment was otherwise the same
  - possible contribution of carcinogenic drugs to tumour incidence

Ankylosing Spondylitis Patients

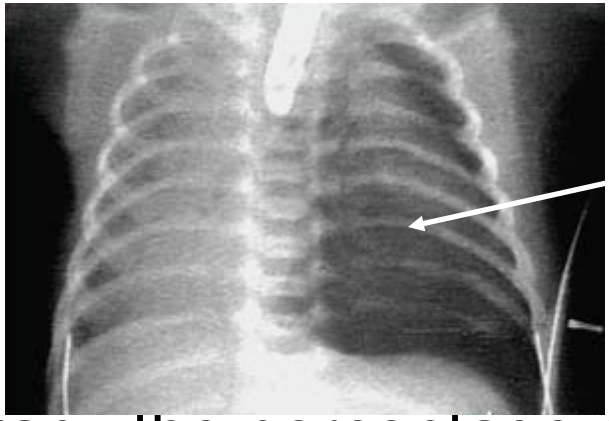


Cervical Cancer Patients

- 82,000 women were given external beam and/or intracavity radiotherapy for cancer of the uterine cervix
- Followed for 5 - 20 years
- 260 excess cancers compared with control population of women of same age
- A similar study was made on women treated by surgery alone: found excess lung cancer in both groups due to increased use of tobacco by cervical cancer sufferers
- After excluding lung cancer, excess of other cancers attributed to radiation was only 125, lower than expected
- 10 years after irradiation incidence of cancer was increased in organs that received doses > 1 Gy, mostly in the bladder and rectum

Other Patients

- Two studies, in Canada and New England, on women with pulmonary tuberculosis receiving artificial pneumothorax - introduction of air into pleural cavity to collapse the lung
  - This procedure was done under high dose fluoroscopy every 15 days, total dose 0.8-0.9 Gy
  - Increase in breast cancer noted, but no increase in leukaemia or skin cancer



Pneumothrorax of the right lung as seen on the radiograph

- After other types of radiotherapy the percentage of second radiogenic cancers increased by 0.5-2% (mostly bone tumours and soft tissue sarcomas). In children this increase is larger (4%).

Hiroshima and Nagasaki: Survivors

This is the most important single-group study:

- large number of persons exposed
- care with which they are followed
- persons of all ages and both sexes received a wide range of whole-body doses from γ-rays

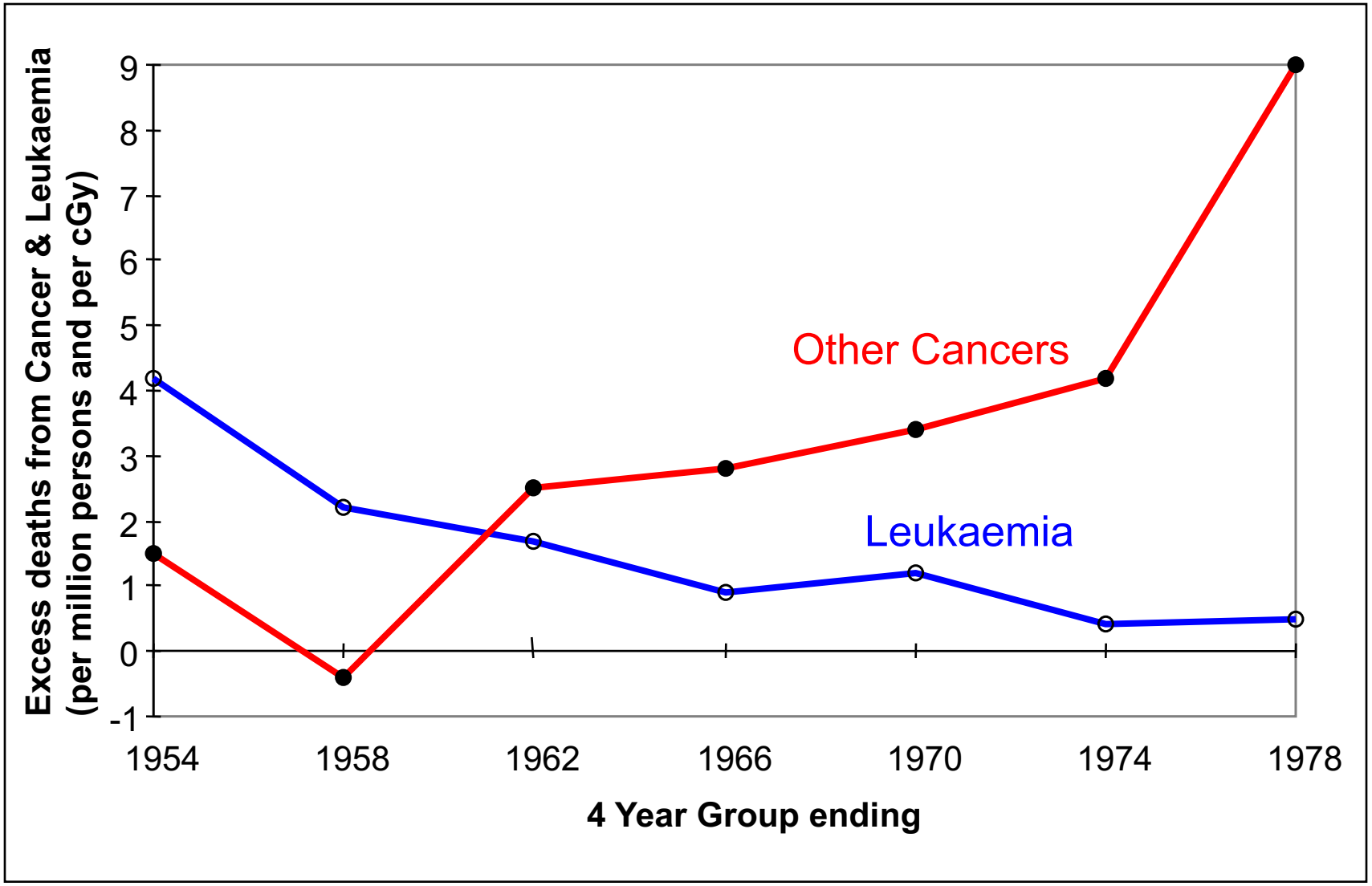
- 120,000 survivors were followed for more than 50 years
- 80,000 died from natural causes in 1945-1978, by 1990 there were 6000 deaths from cancer
- Whole-body doses for γ-ray irradiation are carefully calculated for 76,000 survivors who were at distances <2.5 km from the hypocenter at the time of the bombing
- Shielding of γ-rays by Japanese-style earthquake-proof houses was taken into account when calculating doses

Hiroshima and Nagasaki

- For these 76,000 people 260 excess solid cancers were observed in 1950 - 1985, also 90 excess leukaemias
- This gives probability of radiogenic cancer in a given organ
- Carcinogenic effect appears to be certain, but small
- Leukaemias peaked first (1952-1965) and then returned to normal while incidence of solid tumours increased
- Most solid tumours are thyroid, breast, lungs, stomach, oesophagus, ovary, bladder, central nervous system
- In children, the number of excess cancers has diminished with time
- No such effect observed in adults

Business centre in Hiroshima

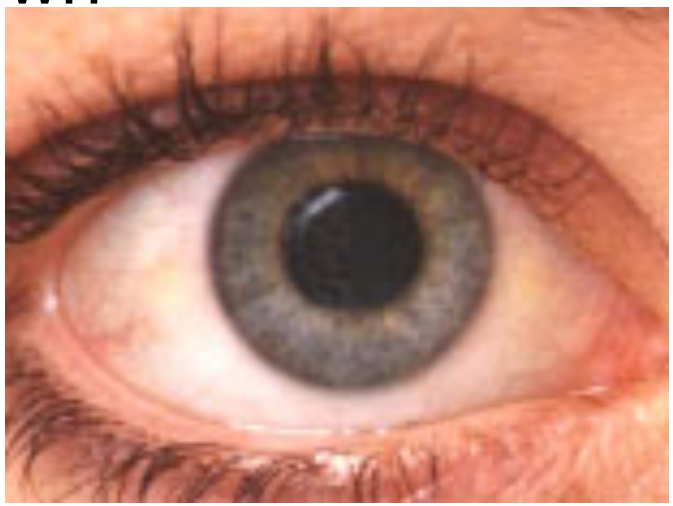
Hiroshima and Nagasaki



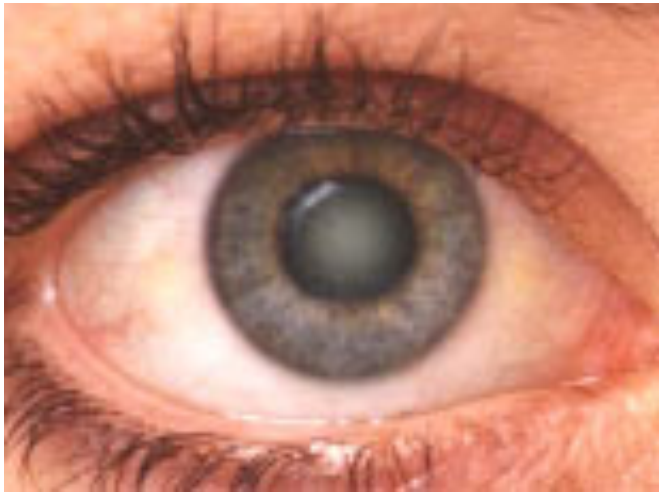
Hiroshima and Nagasaki

- Cataract formation and slight retardation of growth of children (who were exposed when very young) were shown

Without cataract



With cataract



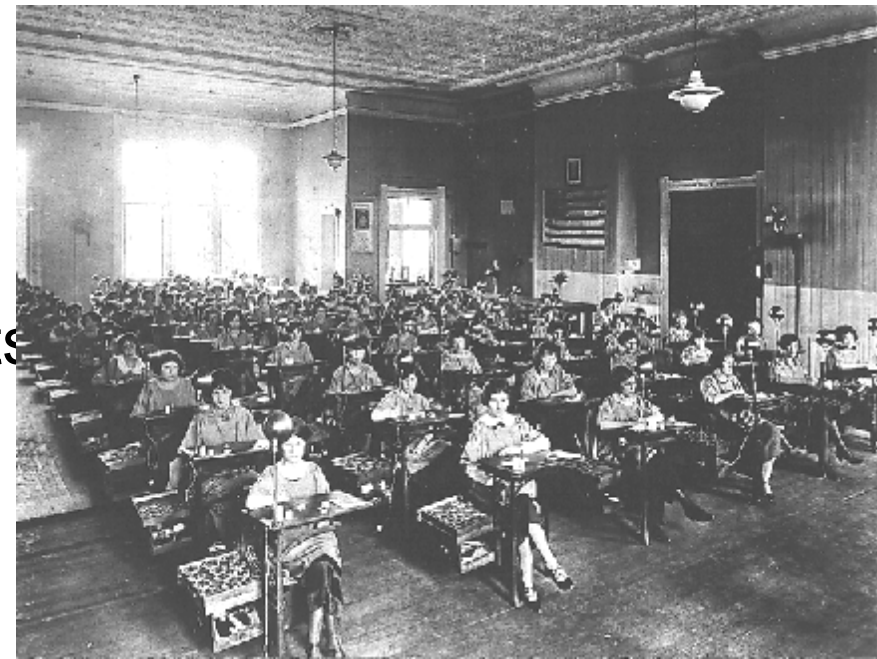
- NO evidence of any other effects due to radiation:
  - NO increase in morbidity
  - NO acceleration of ageing
  - NO life shortening
  - NO reduction in the number of children

Occupational Exposures

Radium Dial Painters

1,700 painters of luminous dials with paint containing Radium were exposed in 1920s to a mean skeletal dose 17 Gy (mostly due to α-irradiation)

- 48 died of osteosarcoma (bone cancer)
- no cases of bone cancer seen with low doses - dose-effect curve suggests a practical threshold

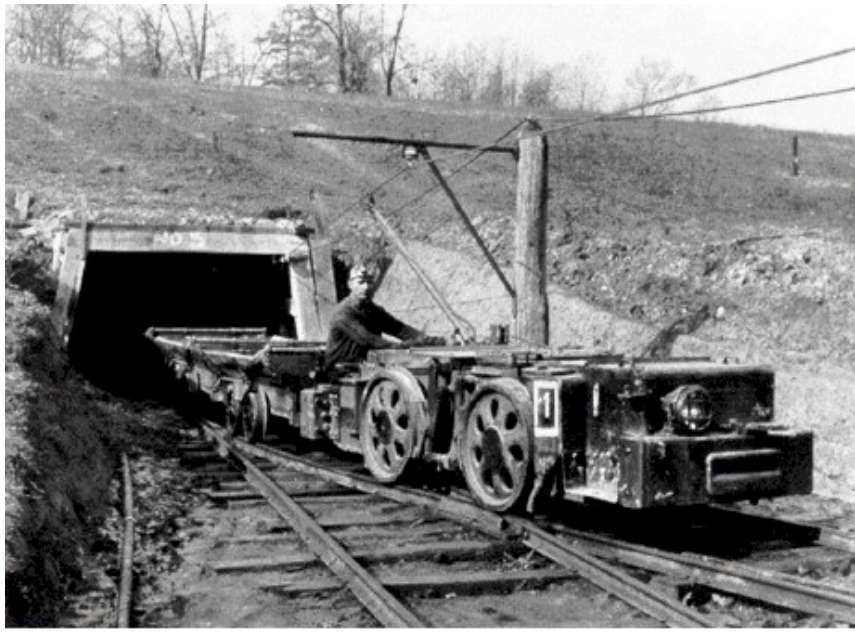


Occupational Exposures

Miners

Underground miners exposed to breathing Radon gas and its daughter products (α-emitters)

- many studies show excess lung cancers
  - appearing about 5 years after onset of exposure
  - peaking at 15 - 20 years after exposure
  - no longer significant 25 - 30 yeas after exposure
- large differences between smokers and non-smokers - worse in smokers



Epidemiology Conclusions

- If a dose is large enough either a single or a chronic exposure can be carcinogenic, acute exposures are more effective than chronic
- There is no cell type uniquely susceptible to radiogenic cancer
- Some malignancies (leukaemias, sarcomas) appear after a short latent period, peak rapidly and then decline, with some small excess risk persisting for several decades
- Latent period is the time interval between irradiation and the appearance of malignancy
- Leukamia has the shortest latent period: at least 2 years, mean value 8 years (all within 15 years)
- Solid tumours show longer latency periods 10 - 50 years, mean value 20 years
- Some cancers show shorter latency periods at higher doses

Epidemiology Conclusions

- On the basis of Japanese data:
  - the concept of a fixed time interval between irradiation and the appearance of cancer has been replaced by the concept of age at expression:
    - regardless of the age at the time of exposure, radiation-induced tumours tend to be expressed later in life, at the same time as spontaneous tumours of the same type
    - thus latency period can be very long, particularly in young subjects for whom radiogenic cancers may not appear until old age

Epidemiological Data Interpretation Problems

- Spontaneous risk of some solid tumours varies greatly with ethnic population
  - for example, breast cancer is more likely in Jewish population: carriers of genes related to breast cancer are
    * 1 in 833 for non-Jewish population
    * 1 in 107 in European Jews
    * are gene carriers more susceptible to radiation-induced cancer?
  - there are ethnic and geographical variations in spontaneous cancer rate
- A-bomb survival data gives much higher risk estimates (2 - 5 fold) than other data (e.g. from radiotherapy patients)

Relative Probability of Fatal Cancer in Organs for Males and Females

Organ	Males	Females
Colon	0.127	0.232
Bone marrow	0.106	0.040
Stomach	0.319	0.262
Oesophagus	0.031	0.044
Total probability ($10^{-2}\cdot Sv^{-1}$)	8.00	13.5

- The data is for Japanese population, age 0-90 yrs, for multiplicative risk projection model (ICRP, 1991)
- The total risk for all cancers is greater for females by about 40%

Relative Probability of Fatal Cancer in Organs for Different Population Types

Organ	National population				
	Japan	USA	Puerto Rico	UK	China
Oesophagus	0.038	0.014	0.098	0.030	0.269
Stomach	0.290	0.033	0.136	0.050	0.224
Breast	0.023	0.075	0.048	0.085	0.022
Total probability (10^{-2} Sv^{-1})	10.7	11.2	9.5	12.9	6.3

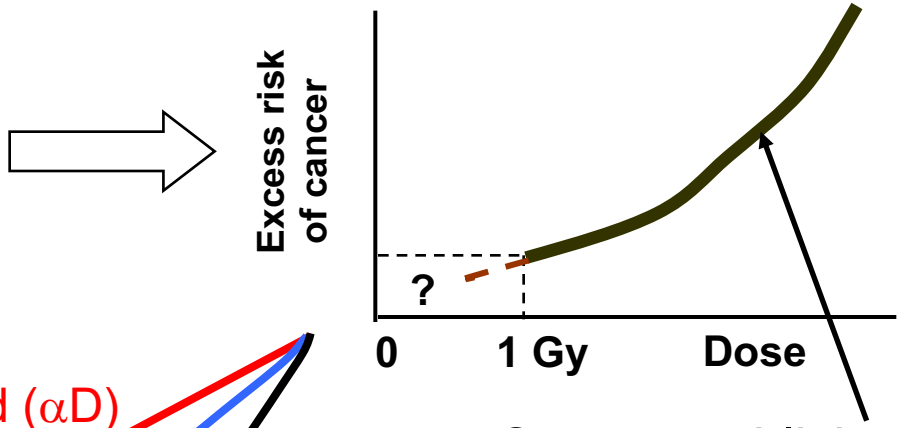
Differences up to a factor of 20 in relative probabilities of fatal cancer in organs can be observed for the five national populations

Interpretation Problems at Low Doses

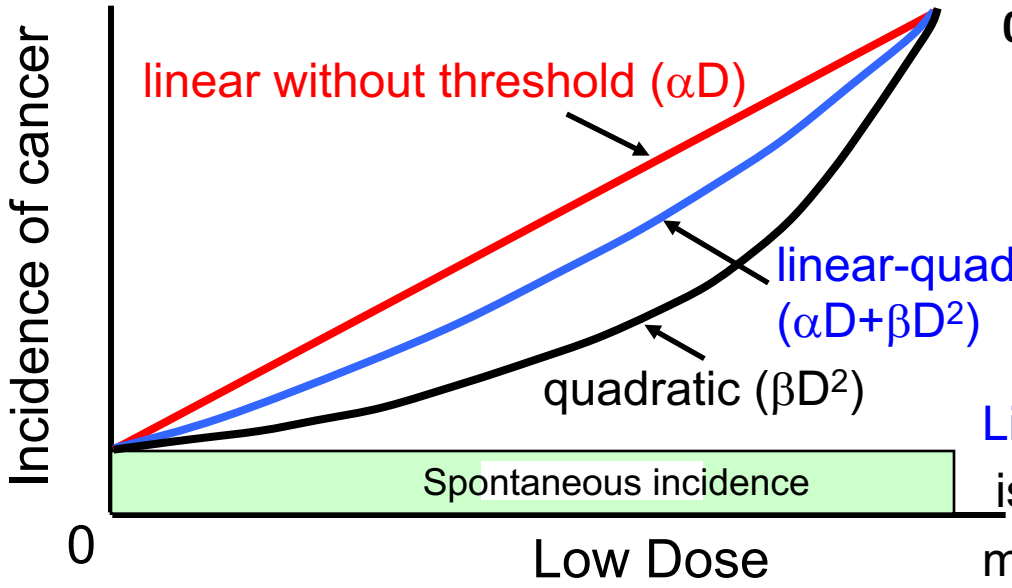
- To evaluate carcinogenic risk for occupational exposure or radiodiagnosis (total body doses < few cGy) there is NO reliable data
- Results of studies of subjects that received these doses are contradicting
- However these studies can provide some information on the upper limit of the risk coefficient
- It is necessary to obtain information on hundreds of thousands of individuals receiving annual doses 10-100 mGy to the whole body to obtain reliable estimate of effect (these studies are in progress now)

Low Dose Risk Estimation

Solution so far has been to extrapolate high dose data to low doses



Curve established after observations at high doses



Linear-quadratic relation is considered scientifically more plausible

Carcinogenesis Mechanism (*in vitro* studies)

At the cellular level, cancer is a molecular-genetic disease

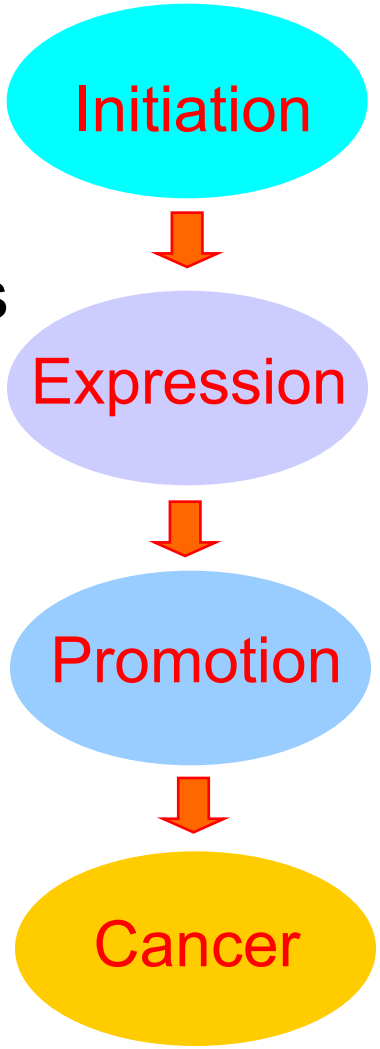
Multi-stage process:

Initiation: irreversible process when normal cell acquires pre-neoplastic characteristics following DNA modification. May remain in this state indefinitely

Expression of transformation leading to a transformed cell

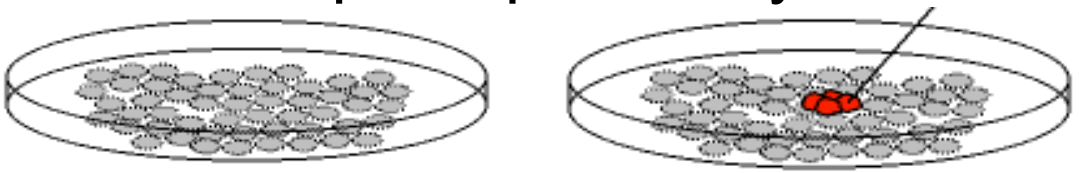
Promotion: transformed cell gives rise to malignant cells capable of multiplying and invading neighbouring tissues

– Promoters are physical or chemical agents with the property of stimulating cell proliferation, they also act on DNA
– Radiation is both an initiator and a promoter



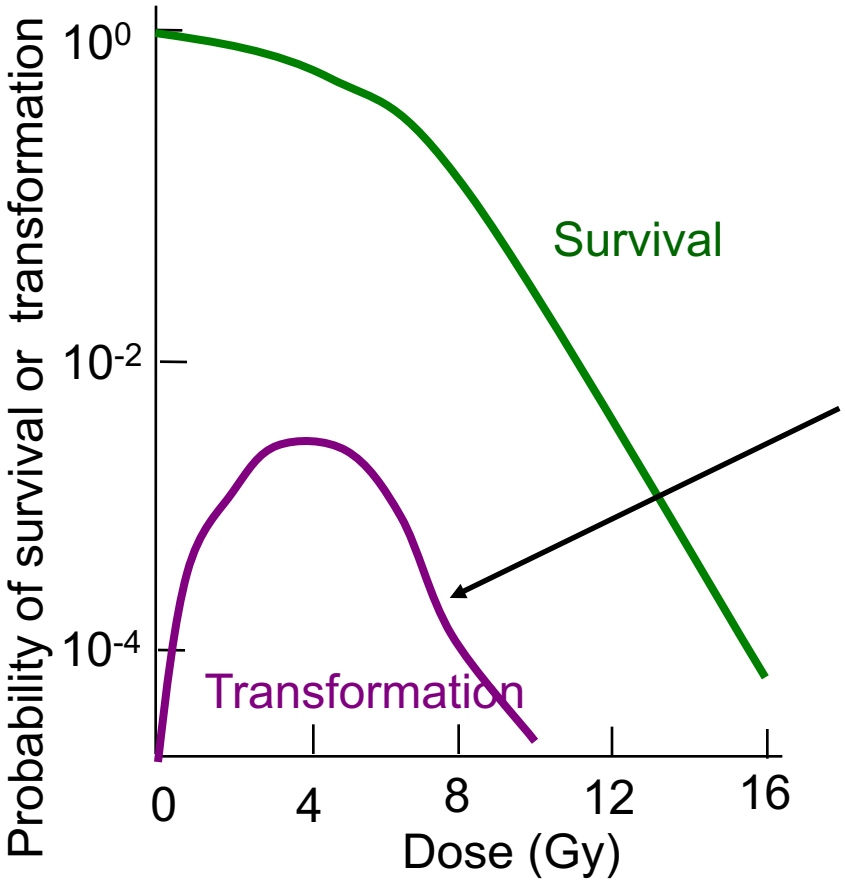
Transformed Cells (*in vitro* studies)

- Irradiation of cells transforms some of them, giving rise to new features:
  - Immortalisation: transformed cells are “immortal” (i.e. divide indefinitely). Normal stem cells can divide < 60 times
  - Morphological changes, particularly in cell membrane
  - Loss of contact inhibition: on a Petri dish normal cells remain in a monocellular layer whereas the transformed cells infiltrate among their neighbours and give rise to a small heap composed of superimposed layers ⇒ easy to count them



- When colonies of transformed cells are injected into another animal, they may give rise to a malignant tumour
- Proportion of transformed cells increases with dose

Transformations (*in vitro* studies)



Data for cells *in vitro* irradiated by Cobalt γ-rays

With γ-rays

At high doses the number of transformed cells peaks near 4 Gy with subsequent decline due to cell killing

This decrease is because transformed cells have the same radiosensitivity and can be killed as normal cells

The number of transformed cells, expressed as a proportion of surviving cells, remains small (≈0.1%)

Transformed Cells: Repair

- If cells are left in a quiescent (inactive) state without division, the number of transformed cells falls over 24 hours, implying repair
- Even though DNA was damaged, its repair can prevent development of tumour
- Time between DNA damage and mitosis is critical. 4 - 6 mitoses are necessary to produce a fixed transformation and the first mitosis must take place within the 1st day
- Proliferation after exposure results in higher number of transformed cells (due to shorter time available for repair before the lesion is fixed during mitosis)

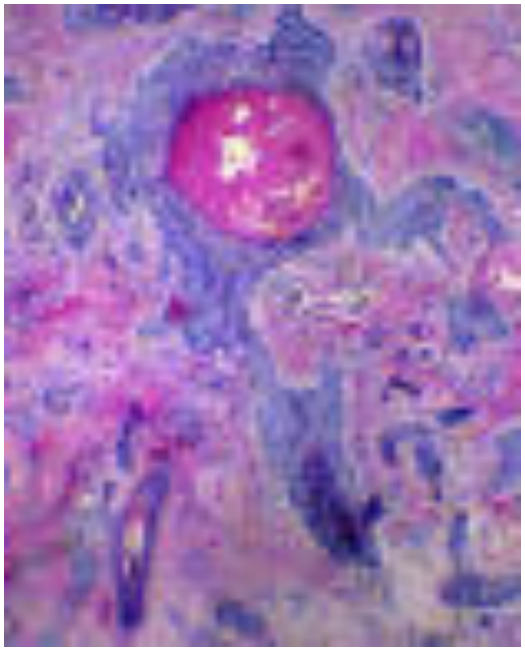
Expression of Transformation

- Experiments suggest that expression of transformation is a much rarer phenomenon than initiation and depends more on number of mitoses than radiation dose
- This suggests that expression of transformation requires a second event which occurs at random, but infrequently (with probability $\approx 10^{-6}$) during mitosis
- The greater the number of divisions, the greater the number of transformed cells
- Expression can be inhibited if cell division is blocked

Mechanism of Initiation

- Initiation can be due to point mutations or a chromosomal rearrangement
- In some experiments carcinogenesis is related to lesions leading to chromosome breaks and symmetrical chromosome translocations without loss of chromosome material
- Malignant cells contain oncogenes. These are also present in normal cells as proto-oncogenes, but they are not activated
- Activation of oncogene can be caused by gene mutation (transformation of a proto-oncogene into oncogene) or by disturbance in the mechanism how the gene is regulated (for example, this may be due to insertion, next to the proto-oncogene, of an activator gene)
- Most of initiated cells never result in a tumour. *In vivo*, several mechanisms ensure that most potentially carcinogenic cells do not cause cancer (e.g. for dose of 3 Gy less than 1 cell in 10^{14} cells *in vivo* gives rise to leukaemia)

Clinical Emergence of a Tumour



Is a result of series of successive stages.

E.g. <u>for cancer of uterine cervix</u>:

- the first pre-cancerous lesions appear at about 25 years of age
- followed by more malignant lesions at the age of 40
- followed by invasive cancer at the age of about 50
- there are 10 times more pre-cancerous lesions as there are invasive tumours

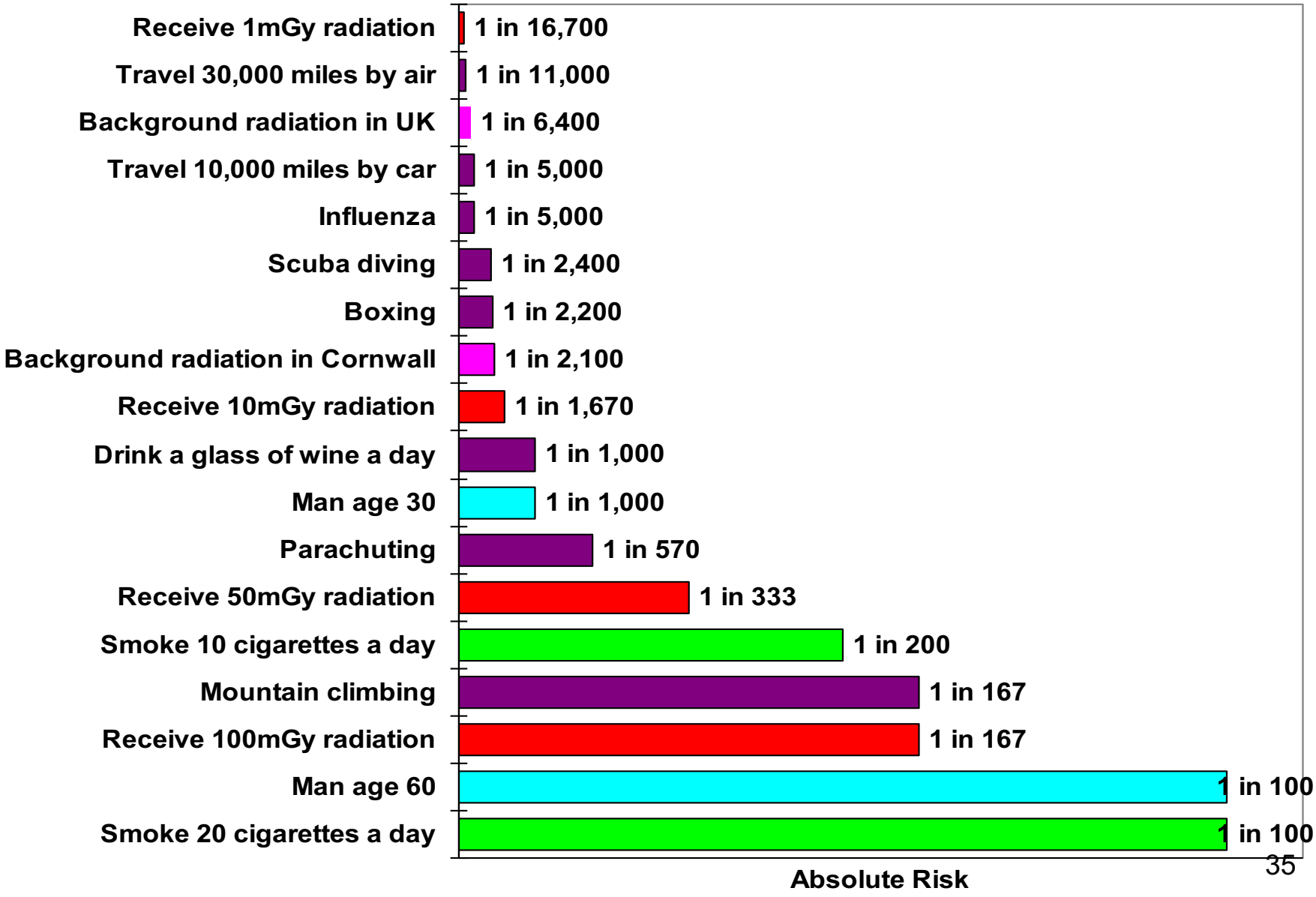
Stochastic Effects

- Cell modification $\Rightarrow$ stochastic (random) effects
- Repair of radiation damage may not be error free (e.g. chromosomal translocation)
- Modified cells may remain viable and, after some latency period, develop a malignant condition
- Probability of malignancy is proportional to dose
- As repair is not totally effective, even at low doses, there is no threshold dose
- Cancers induced by radiation are identical to those induced by other causes

Risk of Radiation Induced Cancer

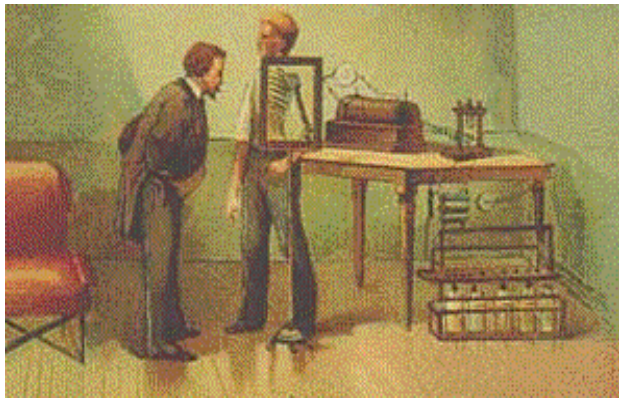
- Epidemiological studies (mainly data on Japanese survivors) can be used to estimate risk associated with radiation doses $\geq$ 1Gy
- United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in 1988 report concluded that after a high dose of low LET radiation delivered at high dose rate, the lifetime risk coefficient for death due to radiation induced cancer for the whole world population is $4 - 11 \cdot 10^{-2}\ Gy^{-1}$
- The wide range of lifetime risk coefficient is due to lack of information on children
- Adult population risk coefficient for death due to radiation induced cancer: $5 - 6 \cdot 10^{-2}\ Gy^{-1}$

UK Mortality Risk (per year)

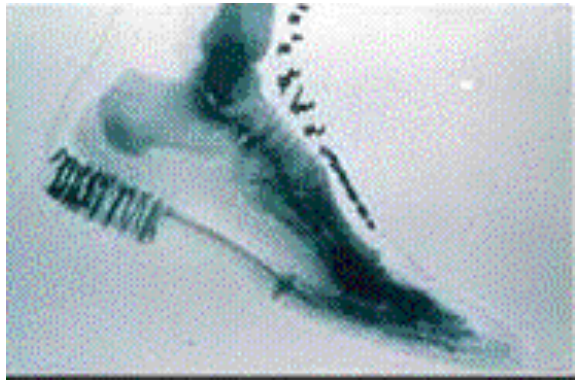


Radiation Risks During Early Years of X-rays

- After x-rays were discovered they were considered harmless for several years
- At that time people were sometimes x-rayed for hours
- In 1900-s there were coin operated amusement machines "*See the bones of your hand for a nickel!"*
- X-ray studios took 'bone portraits'
- About 50,000 of fluoroscopic machines were installed in department stores for fitting shoes. This practice continued until early 1950-s!



Roentgen at his x-ray laboratory



Radiograph of a foot in a high-button shoe